DIABETIC NEUROPATHY. ELEMENTS OF EPIDEMIOLOGY AND PATHOPHYSIOLOGY

LUIGI RAMPELLO*, IGNAZIO VECCHIO**, GIUSEPPE BATTAGLIA***, GIULIA MALAGUARNERA****, LIBORIO RAMPELLO*
*"G.F. Ingrassia" Department, Neurosciences Unit, University of Catania, Azienda Policlinico Vittorio Emanuele, **Department of Medical and Pediatric Sciences, ***Istituto Neurologico Mediterraneo, Venafro (IS), ****Research Centre The Great Senescence, University of Catania

[Neuropatia diabetica. Elementi di epidemiologia e fisiopatologia]

ABSTRACT

Diabetic neuropathy is a common complication of diabetes, especially in cases of poor control or long duration, which is characterized by its clinical polymorphism whose most common form is distal symmetric polyneuropathy. This brief review outlines the prevailing views on the epidemiology and pathogenesis.

Key words: Diabetes, diabetic neuropathy, polyneuropathy, diabetic physiopathology, diabetic complications.

Received *September 11, 2012;* ***Accepted*** *September 26, 2012*

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 whose most common form 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 also be said that diabetic neuropathy is an increasingly spreading pathology correlated with incorrect lifestyles typical of modern society.

Neurophysiology of the peripheral nervous system

The PNS consists of all the neural structures that are outside the pial membrane of the spinal cord and brainstem. The portions that must be considered are the roots of the spinal nerves: the posterior sensory (or afferent) roots, formed by the axonal extensions of the cells of the spinal and cranial ganglia; the anterior motor (or efferent) roots, formed by axons that exit the anterior and lateral horns and by the motor nuclei of the brainstem. The larger fibers reach the muscle fibers, while smaller ones reach the sympathetic and parasympathetic ganglia. The axons branch out of these, terminate in the smooth muscles, heart and glands, and form the autonomic system.

The myelinated nerve fibers are covered by a nerve sheath, which takes the name of myelin, which has a different composition in the PNS, as it is formed by Schwann cells, compared to the CNS, where it consists instead of oligodendrocytes. The unmyelinated fibers, quantitatively greater than

myelinated ones in the peripheral nerves, also originate from the cells of the dorsal root and from the ganglia of the autonomic nervous system.

The peripheral nerves include the cranial nerves, spinal nerves, the ganglia attached to the dorsal roots, the peripheral nerve trunks and their terminal branches, and autonomic nervous system.

The nerves are divided into:

• wide and myelinated axons (motor axons and axons responsible for vibration, proprioception and, in part, tactile perception);

• small and myelinated axons (fibers of the autonomic nervous system and sensory axons responsible for tactile, thermal and pain perception);

• small unmyelinated axons (sensory axons, specialized in conveying some subtypes of pain and thermal information).

Each damaged cell shows a specific vulnerability to various pathological processes so that some toxins selectively damage the membranes that form the myelin sheaths and cause demyelination leaving the axons relatively intact (demyelinating neuropathies), while others, conversely, cause specific damage to the axons or cell body with the formation of axonal neuropathies or neuronopathies. In certain cases, there may be instead so-called Wallerian degeneration, in which there is degeneration of both the axon and myelin distally to the breakpoint of the axon.

The functional recovery time can be rapid, as in the case of segmental demyelination, because the axon is intact and only needs to be remyelinated, or it can be very slow, as in the case of Wallerian degeneration in which months or even years may be needed because in this case it is the axon that must regenerate (1 mm a day).

Depending on the lesion site, the causal factors, duration of action of the pathogenic agent, individual susceptibility, coexistence of multiple causal factors, the symptoms typical of PNS diseases can be motor, sensory, reflex, vegetative and trophic.

The sensory symptoms most commonly reported by patients are described as tingling, numbness, bites, pangs, pinching, itching, and electric shock. In some neuropathies (like diabetic neuropathy) there is pain that is described in different ways and expressed as burning, stinging or even stabbing as in tabes dorsalis.

Another important category of symptoms consists of vegetative disorders including anhidrosis and orthostatic hypotension; other vegetative symptoms are: abnormal pupillary reactivity, disorders of sweating, erectile dysfunction and sphincter disturbances.

Typically, in all neuropathies, the reduction or absence of the osteotendon reflexes is observed as generic signs of disease of the peripheral nerve. Alterations in trophism are finally due to denervation in case of interruption of the motor nerve trunks and often are associated with analgesia in the distal districts of the limbs, which makes them susceptible to burns, pressure sores and other forms of traumatic injury .

Epidemiology

Given that diabetic neuropathy may complicate any type of diabetes[1], the incidence of neuropathy increases with the duration of diabetes, especially when it exceeds five years[2] in non-insulin-dependent diabetes. No evidence of neuropathy has been found in 8% of patients, at the time of diagnosis of diabetes and in 50% of patients re-examined twenty-five years later[3]. The main risk factors identified are: duration of diabetes, its poor control, male sex, and weight of the patient. In addition to these, there is the role of individual susceptibility, as neuropathy may also occur in 2-3 years that follow the appearance of insulin-dependent diabetes poorly compensated in particularly predisposed individuals[4,5].

In a recent American study conducted by Harris on 2,405 diabetic subjects out of a sample of 85,000 people aged over 18 years, 28.2% of the patients felt distal numbness, 26.8% pain or tingling and 9.8% decreased sensitivity to hot or cold. It should be emphasized that the incidence of each of these symptoms increased with the duration of non-insulin dependent diabetes[6].

The incidence of new cases of diabetic neuropathy is about six cases a year every 100 patients with diabetes mellitus of both type 1 and type 2. Probably, however, this is an underestimate, since about 1/3 of the cases of diabetes remains undiagnosed.

Diabetic neuropathy also has significant economic costs for society. The high rate of diabetic neuropathy causes a substantial morbidity due to recurrent infections of the lower limbs, ulcers and amputations. Diabetic patients with foot problems spend more days in hospital than those with any other diabetic complication.

The cumulative risk of lower extremity amputation is 11% twenty-five years after the diagnosis of diabetes.

A prevalence study conducted in Sicily also highlighted the relatively high frequency of peripheral neuropathies and in particular diabetic neuropathy: 7% of the population responded positively to the initial screening exams and diabetic neuropathy was diagnosed in 0.3% of the population[7]. In some retrospective studies, it has been noted that 4% of diabetics developed peripheral neuropathy within 5 years of diagnosis, after twenty years, the prevalence rose to 15%[8].

Another study based on sensory symptom criteria in the hands and feet, and on reduced/no tendon reflexes in patients with insulin-dependent diabetes found a prevalence of distal symmetrical polyneuropathy of 34%, which increased to 58% in diabetic patients for over 30 years[9]. The same study in patients with non-insulin-dependent diabetes, combining criteria based on decreased or absent thermal sensitivity, found a prevalence of 26%[10].

Nerve conduction velocity was also measured in over 1000 at the beginning of a recent study and five years later, and a comparison was made between patients receiving conventional and intensive treatment: the intensive treatment of diabetes lowered the risk of developing neuropathy by more than 60%[11]. As regards nerve conduction velocity, significant differences were found between the intensive and conventional treatment groups: the intensively treated group showed a greater sensory and motor conduction velocity and less F wave latency than the conventional treatment group. Moreover, while most of the neurophysiological variables worsened over time in patients receiving conventional therapy, these remained stable or showed a modest improvement in the intensive treatment group[12].

Etiopathogenesis

The causes that lead to the development of neuropathy in diabetic patients have not been defined yet. Therefore, various hypotheses have been formulated which provide a good representation of the multifactorial nature of the process. One of the most accredited among these is the polyol pathway: hyperglycemia and the resulting increased levels of intracellular glucose in the nerves leads to saturation of the normal glycolytic pathway.

Then, the excess glucose is deflected towards the polyol pathway and converted into sorbitol and fructose by aldose-reductase and sorbitol dehydrogenase, which, in excessive doses, lead to an alteration of the ion transport function of the membrane resulting in a reduction of Na+/K+-ATPase activity with consequent reduced axonal transport (due to alteration of the processes of depolarization/repolarization), structural decomposition of the nerves and abnormal propagation of the action potential[13].

A second hypothesis to be considered is the formation of advanced glycosylation end products (AGE): the advanced glycosylation triggered by the non-enzymatic reaction of excess glucose with proteins, nucleotides and lipids may play a role in altering neuronal integrity and in repair mechanisms interfering with the metabolism of the nerve cells and with axonal transport[14].

Another mechanism that contributes to nerve damage and is the third pathogenetic hypothesis is that of oxidative stress: it would result from increased production of free radicals. In fact, the process by which they damage the nerve is not well known, but it is known with certainty that there is a direct damage to the blood vessels leading to ischemia of the nerve and the facilitation of AGE reactions[15].

Other possible contributing mechanisms consist of alterations in gene expression and altered cellular phenotypes, some alterations of cellular structures such as the composition of the cytoskeleton or cellular transport, and finally the ischemic phenomena of the nerve.

Genetic factors also have a significant importance in the genesis of damage: these could explain how some diabetic patients, despite good glycemic control, develop microvascular complications, while others with poor glycemic control do not. Similarly, also the cardiovascular risk factors, such as hyperglycemia, hypertension, hyperlipidemia, smoking and obesity, contribute to the microangiopathy, which is also affected by coagulation and hematological factors[16].

The loss of nerve fibers is the cause of the reduced sensitivity that is observed characteristically in patients with diabetic neuropathy[17] and this can be confirmed by sural nerve biopsy, which, in addition to this reduction, also shows microvascular alterations in the endoneural vessels as a substantial thickening of the basal membrane, endothelial cell proliferation and hypertrophy[16] in combination with reduced oxygen tension[18].

The reduction of blood flow results in the reduction of conduction velocity as is shown in some studies[19] in which nerve conduction velocity is measured after an activity that has led to an increase in cardiac output by 80%: this increase produced an improvement of more than 5 m/sec in the motor conduction velocity in healthy patients and 4 m/sec in diabetic patients without neuropathy. The same exercise does not increase the conduction velocity in patients with neuropathy because the nerve is not able to increase the blood flow in response to exercise.

A more recent study on the changes of the vessels of sural nerve in acute diabetic neuropathy has shown the possible onset of painful neuropathic symptoms as a result of acute insulin neuritis due to the rapid improvement of blood glucose levels[20]. This acute insulin neuritis was found to be associated with proliferative changes, which consist in the development of a dense neovascularization on the nerve surface, as happens in the retina of diabetic patients[20].

Ultimately, if we wish to classify the pathophysiology based on the main clinical presentations, it should be noted that ischemia is the main factor in focal and multifocal neuropathies, and metabolic disorders are dominant in the distal symmetrical forms of diabetic neuropathy.

In the light of inflammatory lesions detected in some nerve biopsies during proximal neuropathies, it is also possible that the inflammatory lesions, sometimes with vasculitis, are involved in a certain percentage of focal diabetic neuropathies[21]. Cases of cranial neuropathy are to be taken into account. These are sometimes due to demyelinating processes and rare forms of paroxysmal headache, of stabbing type, with which it is necessary to perform differential diagnosis[22-23].

There is also a recent pathogenic hypothesis, which involves matrix metalloproteases: in particular, metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9) would be overexpressed in diabetic patients with neuropathy and this would lead to an accelerated degradation of the extracellular matrix in the vessels with damage to the vascular bed and to the supply of nutrients to the sensory nerve fibers[24].

Finally, the different pathogenic, metabolic, and hypoxic hypotheses and the conduction disturbances must also take into account the prevalence of sensory and autonomic disorders over motor disorders in diabetic neuropathy.

References

1) Young MI, Boulton AI, MacLeod AF, Williams DR, Sonksen PH. *A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population*. Diabetologia 1993; 36: *150-154*.
2) Atsumi Y, Matsuoka K, Horiuchi A. *A statistical analysis of the neurological manifestations of Japanese diabetic patients*. Diabetic Microangiopathy, 1983.
3) Pirart J. *Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973*. Diabetes Care 1978; 1:168-188, *253-263*.
4) Said C, Bigo A, Améri A, Cayno lP, Eigrably F, Chanson P et al. *Uncommon early onset neuropathy in diabetic patients*. J Neurol 1998; 245: *61-68*.
5) Said C, Goulon-Goeau C, Slama C, Tchobroutsky G. *Severe early- onset polyneuropathy in insulin-dependent diabetes mellitus - a clinical and pathological study*. N Engl J Med 1992; 326: *1257-1263*.
6) Harris M, Eastman R, Cowie C. *Symptoms of sensory neuropathy in adults with NIDDM in the US population*. Diabetes Care 1993; 16: *1446-1452*.
7) Savettieri G, Rocca WA, Salemi G, et al. *Prevalence of diabetic neuropathy with somatic symptoms: a door-to-door survey in two Sicilian municipalities*. Neurology 1993; 43: *1115-20*.
8) Palumbo PJ, Elveback LR, Whisnant JP. *Neurological complications of diabetic mellitus: transient ischemic attack, stroke and peripheral neuropathy*. In: Schoenberg BS, ed. Neurological epidemiology: principles and clinical applications. New York: Raven Press, 1978: *593-601*.
9) Maser RE, Steenkiste AR, Dorman JS, et al. *Epidemiological correlates of diabetic neuropathy: report from Pittsburgh Epidemiology of Diabetes Complications Study*. Diabetes 1989; 38: *1456-61*.
10) Franklin GM, Kahn LB, Baxter J, Marshall JA, Hamman RF. *Sensory neuropathy in non-insulin-dependent diabetes mellitus: the San Luis Valley Diabetes Study*. Epidemiol 1990; 131: *633-43*.
11) DCCT Research Group. *The effect of intensive diabetes therapy on the development and progression of neuropathy*. Ann Intern Med 1995; 122: *561-8*.
12) Albers JW, Kenny DJ, Brown M, et al. *Effect of intensive diabetes treatment on nerve conduction in the diabetes control and complications trial*. Ann Neurol 1995; 38: *869-80*.
13) Greene DA, Arezzo JC, Brown MB. *Effect of aldose reductase inhibition on nerve conduction and morphometry in diabetic neuropathy*. Zenarestat Study Group. Neurology. Aug 11 1999; 53(3): *580-91*.
14) Ryle C, Donaghy M. *Non-enzymatic glycation of peripheral nerve proteins in human diabetics*. J Neurol Sci. Mar 1995;129(1):62-8.
15) Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA. *Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial*. Diabetes Care. Nov 2006; 29(11): *2365-70*.
16) Cameron NE, Eaton SE, Colter MA, Tesfaye S. *Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy*. Diabetologia.

2001; 44; *1973-1988*.
17) Malik RA, Tesfaye S, Thompson SD, et al. *Endoneurial localisation of microvascolar damage in human diabetic neuropathy*. Diabetologia. 1993; 36: *454-459*.
18) Newrick PG, Wilson AJ, Jakubowski J, et al. *Sural nerve oxygen tension in diabetes*. Br Med J (Clin Res Ed). 1986; 293: *1053-1054*.
19) Tesfaye S, Harris ND, Wilson RM, Ward JD. *Exercise-induced conduction velocity increment: a marker of impaired peripheral nerve blood flow in diabetic neuropathy*. Diabetologia. 1992; 35: *155-159*.
20) Tesfaye S, Malik R, Harris N, et al. *Arterio-venous shunting and proliferating new vessels in acute painful neuropathy of rapid glicaemic control (insulin neuritis)*. Diabetologia 1996; 39: *329-335*.
21) Said C, Goulon-Goeau C, Lacroix C, Moulonguet A. *Nerve biopsy findings in different patterns of proximal diabetic neuropathy*. Ann Neurol 1994; 35: *559-569*.
22) Rampello L, Casolla B, Rampello L, Pignatelli M, Battaglia G, Gradini R, Orzi F, Nicoletti F. *The conditioned eyeblink reflex: a potential tool for the detection of cerebellar dysfunction in multiple sclerosis*. Mult Scler. 2011 Oct; 17(10): *1155-61*.
23) Rampello L., Malaguarnera M., Rampello L., Nicoletti G., Battaglia G. *Stabbing headache in patients with autoimmune disorders*. Clinical Neurology and Neurosurgery 2012; 114: *751-753*.
24) Bhatt L. K., Addepalli Veeranjaneyulu. *Minocycline with aspirin: a therapeutic approach in the treatment of diabetic neuropathy*. Neurol Sci (2010) 31: *705-716*.

Request reprints from:
Prof. LIBORIO RAMPELLO
Direttore U.O.C. di Neurofisiopatologia
Padiglione 2 (Neurologia)
Policlinico dell'Università di Catania
V. Santa Sofia 78
95100 Catania
(Italy)