Diabetic neuropathy

Neuropatia diabética

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ABSTRACT

BACKGROUND AND OBJECTIVES: Diabetic neuropathy is a major cause of neuropathy worldwide and may lead to amputations and incapacity. This study aimed at a detailed and updated review on diabetic neuropathy, focusing on its classification, diagnostic investigation and treatment.

CONTENTS: It is estimated that 371 million people aged from 20 to 79 years, worldwide, have diabetes mellitus and that at least half of them are unware of the diagnosis. Its prevalence in Central and South America was estimated in 26.4 million people, corresponding to approximately 6.5% of the population. Among microvascular complications, diabetic neuropathy is the most prevalent, leading to the highest rates of hospitalization, atraumatic amputations and incapacity. Diabetic neuropathy may have different clinical presentations, being distal symmetric polyneuropathy its most frequent presentation and major mechanism to the development of diabetic foot. Predominantly it presents with positive (burning, tingling) and negative (numbness, loss of sensitivity) sensory symptoms. In general it is associated to autonomic signs and symptoms and seldom there is motor manifestation. Approximately 20% of patients with distal symmetric polyneuropathy have neuropathic pain, which sometimes becomes chronic and disabling.

CONCLUSION: Early and accurate diagnosis allows for adequate treatment, preventing progression of neuropathy and severe complications. For such, it is necessary to obtain an acurate clinical history, in addition to thorough neurological tests and additional tests, to identify signs of nervous fibers involvement. Its treatment depends on adequate glycemic control and neuropathic pain treatment, when present.

Keywords: Diabetes mellitus, Diabetic neuropathy, Neuropathic pain, Peripheral neuropathy.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A neuropatia diabética constitui uma das principais causas de neuropatia no mundo, podendo levar a amputacoes e incapacidade. O objetivo deste estudo foi fazer uma revisão detalhada e atualizada sobre neuropatia diabética, focando em sua classificação, investigação diagnóstica e tratamento.

CONTEÚDO: Estima-se que 371 milhões de pessoas, entre 20 e 79 anos, em todo o mundo apresentem diabetes *mellitus* e que pelo menos metade destas desconheça o diagnóstico. Sua prevalência na América Central e do Sul foi estimada em 26,4 milhões de pessoas e projetada para 40 milhões, em 2030. O Brasil ocupa a 4ª posição mundial com maior prevalência de diabetes *mellitus* com 13.4 milhões de pessoas com a doença, correspondendo a aproximadamente 6,5% da população. Dentre as complicações microvasculares, a neuropatia diabética apresenta maior prevalência, levando a maiores taxas de internações hospitalares, amputações não traumáticas e incapacidade. A neuropatia diabética pode se manifestar de diferentes formas clínicas, sendo a polineuropatia simétrica distal sua apresentação mais frequente e principal mecanismo de desenvolvimento do pé diabético. Predominantemente, apresenta-se com sintomas sensitivos positivos (queimação, formigamento) e negativos (dormência, perda de sensibilidade); porém, pode se desenvolver de maneira assintomática. Geralmente associa-se a sinais e sintomas autonômicos e raramente há manifestação motora. Aproximadamente, 20% dos pacientes com polineuropatia simétrica distal apresentam dor neuropática que, por vezes, torna-se crônica e incapacitante.

CONCLUSAO: O diagnóstico realizado precoce e corretamente possibilita o adequado tratamento, evitando-se a progressão da neuropatia e complicações graves. Para isso, é necessária a obtenção de cuidadosa história clínica, além de minucioso exame neurológico e exames complementares, a fim de identificar sinais de comprometimento de fibras nervosas. Seu tratamento depende do adequado controle glicêmico e quando presente, tratamento da dor neuropática.

Descritores: Diabetes *mellitus*, Dor neuropática, Neuropatia diabética, Neuropatia periférica.

INTRODUCTION

Diabetic neuropathy (DN) is a heterogeneous set of clinical or subclinical manifestations affecting the peripheral nervous system (PNS) as complication of diabetes *mellitus* (DM). It may have different clinical manifestations, pathophysiologic mechanisms, onset and evolution[1,2].

It was only in 1864 that DM was recognized as cause of peripheral neuropathy (PN). Some years later, the involvement of cranial nerves of diabetic patients has been observed[3]. The loss of tendinous reflexes in lower limbs (LLll) was described by Bouchard in 1884[4] and the presence of spontaneous symptoms such as pain and hyperesthesia was described by Pavy in 1885[5]. Motor manifestations were documented by Buzzard in 1890[6].

The first DN classification was suggested by Leyden (1893)[7] who subdivided it in sensory and motor manifestations. Jordon and Crabtree (1935)[8] in turn, were the first to mention pathophysiologic DN mechanisms.

After the discovery of insulin in the 1930s to treat DM, the prevalence of DN has significantly increased since diabetic patients started to have longer life expectation.

Studies by Fagerberg[9], Mulder et al.[10] and Pirart, Lauvaux and Rey[11], have proven the correlation of DN with other microvascular complications such as diabetic nephropathy and retinopathy[12].

In face of an alarming number of DM patients, the prevalence of DN is following this growth and is already appearing as major cause of NP in developed countries. One should stress that for being the most prevalent microvascular complication, it is estimated that at least half the diabetic patients shall develop this neuropathy in some moment of their clinical evolution[13].

Distal symmetrical polyneuropathy is its most frequent clinical presentation, being in general asymptomatic[14]. Less than half the patients have some type of neuropathic symptom, being mostly sensory symptoms[15]. Among DN patients, approximately 20% have neuropathic pain, implying significant decrease in quality of life and functional capacity[16].

In addition, DN is a major risk factor for LLII ulcers, deformities and amputations and for the development of other microvascular complications. In addition, it increases hospitalization and cardiovascular mortality rates in diabetic patients due to autonomic involvement.

In 2003, it has been estimated in the USA an annual cost directly related to DN and its complications of US$ 10.9 billion, being even higher in patients with painful presentation[17].

CONTENTS

Since the first classification suggested by Leyden in 1893[7], many other classifications were proposed and currently the most widely accepted are the classification based on clinical presentations published by Thomas[18] and the classification according to its pathophysiologic mechanism proposed by Dyck and Giannini[19] (Figure 1; Table 1).

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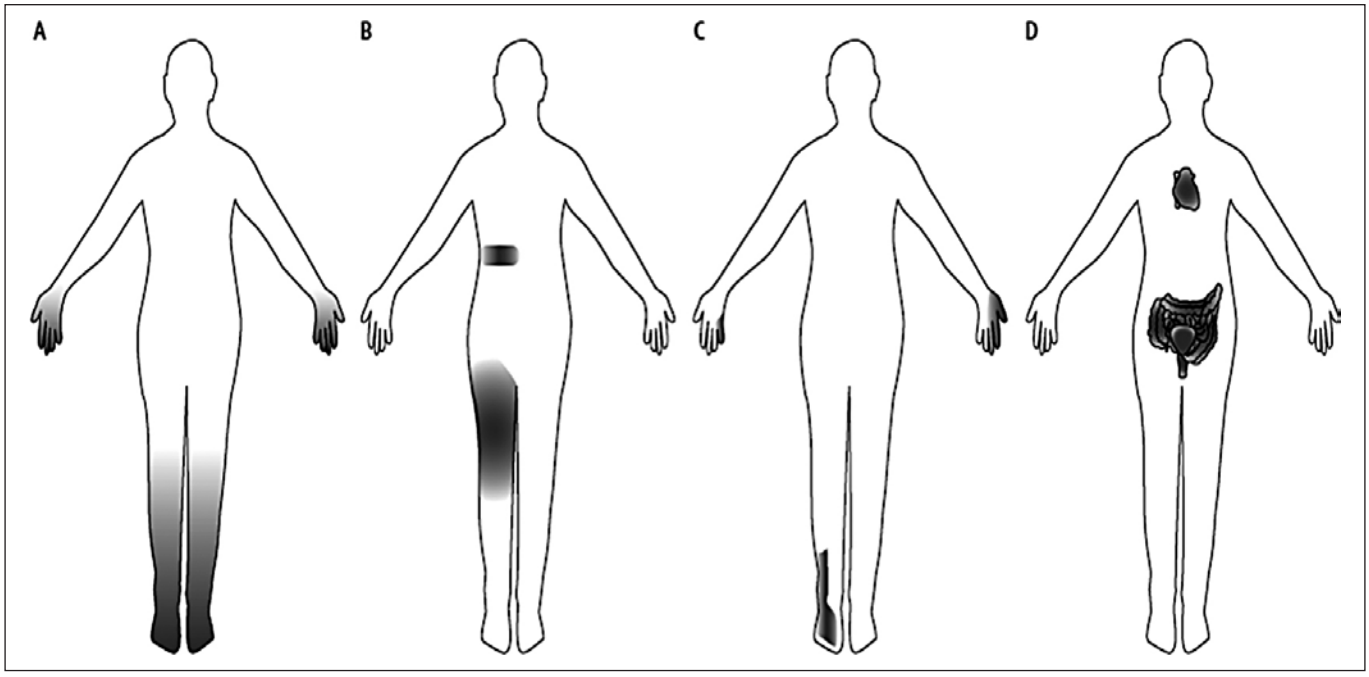

Figure 1. Schematic drawing – different clinical patterns of diabetic neuropathy. Modified[20]
A) Distal symmetrical polyneuropathy, B) Radiculoplexus neuropathies, C) compressive focal neuropathies, D) Autonomic neuropathy.

Table 1. Clinical classification of diabetic neuropathies. Modified[21,22]

I- Symmetrical polyneuropathies:
Relatively stable conditions:
Symmetrical distal sensory polyneuropathy (SDSP)
Variants: acute, severe SDSP in beginning of diabetes, pseudosyringomyelia neuropathy, pseudodiabetic neuropathy, autonomic neuropathies.
Episodic (transient) symptoms:
Diabetic cachexia neuropathy
Hyperglycemic neuropathy
Treatment-induced diabetic neuropathy or insulinic neuritis
Chronic inflammatory demyelinating polyneuropathy (CIDP-plus)
Hypoglycemic neuropathy
Symmetrical distal sensory polyneuropathy (SDSP)
Variants: acute, severe SDSP in beginning of diabetes, pseudosyringomyelia neuropathy, pseudodiabetic neuropathy, autonomic neuropathies.
II - Asymmetrical/focal and multifocal neuropathies:
Diabetic lumbosacral radiculoplexus neuropathy (DLSRN; Bruns-Garland syndrome, diabetic amyotrophy, proximal diabetic neuropathy).
Cervicobrachial radiculoplexus neuropathy
Trunk neuropathies (thoracic/abdominal radiculopathy)
Cranial neuropathies
Mononeuropathies (median, ulnar, fibular)

It is important to highlight that, although didactically subdivided in different clinical presentations, these presentations may coexist in a same patient during disease evolution.

ASYMMETRICAL OR FOCAL AND MULTIFOCAL PRESENTATIONS

Acute mononeuropathies
They refer to acute onset of the affection of one or more nerves, in general associated to sensory (pain and paresthesia) and motor symptoms in the territory supplied by such nerve. It is more prevalent in older patients, having as major cause vascular obstruction with consequent nervous fibers ischemia. In general it presents with self-limited course and good clinical evolution, with recovery within six to eight weeks. It is more frequent in cranial nerves such as oculomotor, trochlear and facial, and in peripheral nerves, such as ulnar and fibular[23].

Chronic compressive mononeuropathies
They have insidious onset with sensory symptoms and in their most severe form with motor involvement in specific compression sites such as wrist median nerve (Carpal Tunnel syndrome – CTS), elbow ulnar, common fibular in fibular head and lateral and medial plantar nerves in tarsal tunnel syndrome. Their prevalence is three times higher than in general population, having as pathogenesis the participation of micro traumas associated to perineural edema secondary to DM metabolic changes, which peak in nerve compression. Its course is in general progressive, and may have severe motor presentations which often need surgical interventions[23].

Radiculoplexus neuropathies (RPNP)
RPNP are asymmetrical sensory-motor presentations of acute onset, involving proximal and distal segments. In general they evolve with severe and disabling painful symptoms and may present autonomic symptoms in up to 50% of cases[24]. They may affect cervico-brachial, thoracic, abdominal or lumbosacral segments in isolation or even concomitantly[25]. Their pathophysiology seems to be closely related to immunopathic mechanisms, and signs of microvasculitis and consequent ischemic injury were shown by Said et al.[26] and Dyck, Norell and Dyck[25] in LLll peripheral nerve biopsies.
Is spite of the severity of nervous fibers involvement, prognosis is in general favorable, even without therapeutic intervention. However, it is still not clear in the literature whether treatment with immunomodulators such as steroids, intravenous human immunoglobulin (IgIV) or plasmapheresis might be effective[24].

SYMMETRICAL OR DIFFUSE PRESENTATIONS

Insulinic neuritis
This was firstly described by Carvati[27], who has observed patients with distal sensory symptoms in LLII after starting insulin therapy. Its pathophysiologic mechanism is unknown and its course is in general benign.

Hypoglycemic neuropathy
Uncommon condition associated to prolonged and repeated hypoglycemic states, in general secondary to insulinomas (insulin-producing pancreatic tumor). It is presented with sensory-motor pattern, with predominance of upper limbs (UULL), with presence of atrophy, and may be reversible after treating the hypoglycemic condition[28,29].

Post-ketoacidosis polyneuropathy
CNS manifestations secondary to the state of ketoacidosis, acute complication of glycemic decompensation in general experienced by DM type 1 patients, are widely known. However, PNS involvement, in addition to being uncommon, is not totally understood. Case reports of these conditions show predominantly motor polyneuropathy with rapid and spontaneous recovery after reversion of this basic condition[24].

Acute painful sensory neuropathy
Also known as diabetic cachexia neuropathy, so called because it is in general developed after major weight loss secondary to uncontrolled DM glycemia. It evolves in a single-phase manner with acute onset of symptoms on LLll, predoninantly painful, severe and disabling. Due to a strong correlation between glycemic uncontrol and development of this neuropathy, it is especulated the participation of metabolic changes in its pathophysiology, however these mechanisms have not been totally explained. Its treatment is based on glycemia and pain control. It has good prognosis evolving with pain improvement and weight gain after glycemic control[30].

Glucose intolerance-associated neuropathy
This has remained as a questionable clinical entity for a long time until Lu et al.[31] have shown in a broad population study glucose intolerance as independent risk factor for PN. It is manifested by predominantly sensory and autonomic symptoms with further involvement of small fibers. It shares the same pathophysiologic mechanisms of DSP, suggesting that this is an early type of this clinical presentation with already established DM.

Autonomic neuropathy (AN)
Disorder affecting autonomic nervous system involving small PNS unmyelinated fibers (C fibers), resulting from chronic hyperglycemia metabolic changes. In few occasions, DM and pre-diabetes autonomic neuropathy is present in isolation. In its vast majority, it develops simultaneously with other DN types, more frequently with DSP and it is thought to be part of the same spectrum of chronic affection of DM[32].
In general asymptomatic and underdiagnosed, it is estimated that approximately 50% of patients with DM type 1 and 70% of patients with DM type2 have some autonomic involvement, although only 14% have moderate to severe disease[32].
AN may result in involvement of cardiovascular, gastrointestinal and urogenital system, sudomotor function and pupilary motility.
Autonomic cardiovascular dysfunction has been broadly recognized as an independent risk factor for mortality secondary to cardiovascular disease[33,34], increasing the risk of post-surgical complications and mortality[35,36]. Its major symptoms include postural hypotension, arrhythmias, silent myocardial ischemia, pressure lability and intolerance to exercise[33].
Sensory, motor and secretory functions of the gastrointestinal system may be involved in diabetic AN, producing symptoms such as nausea, early saciety, vomiting, alternance between diarrhea and constipation and, in more severe cases, postprandial hypotension and syncope[37].
Among autonomic DN changes, erectile dysfunction may be the first manifestation of the disease, however it shares other pathogenic mechanisms, such as internal pundendal artery atherosclerosis. It has major psychosocial impact, leading to severe decrease in quality of life[38].
Diabetic cytopathy involves urinary complications caused by changes in detrusor smooth muscles and urothelial dysfunction, secondary to autonomic involvement of the urogenital system. Its major symptoms are dysuria, polaciuria, nocturia, urinary urgency and incomplete bladder emptying. These factors, added to DM-related immunosuppression, increase the prevalence of repetitive urinary tract infections, contributing to the development of renal failure among these patients[39].
Sudomotor dysfunction in diabetic AN results in trophic changes in extremities, being associated to Charcot arthropathy, LLll ulcers and amputations. In general it presents with change in LLll color and distal temperature, added to hair loss, intolerance to heat, skin dryness, decreased sweating and perforating plantar disease[40].
Not uncommonly, there are pupilary changes, such as the presence of Argyll Robertson pupil, characterized at exam for becoming smaller and presenting dissociations between light and convergence reactions, that is, they react weakly or do not react to light, by react very well to proximity. This is due to the involvement of oculomotor nerve parasympathetic fibers[41].

Distal symmetrical polyneuropathy (DSP)
Being the most common type of DN its prevalence is estimated in 50% of both type 1 and type 1 diabetec patients, being that it is already present in 20% of patients at the moment they are diagnosed with DM.
It remains subclinic in most cases, becoming symptomatic in less than half the patients with DSP[15].
It develops slowly, progressively and symmetrically, primarily presenting sensory and autonomic symptoms with predominant involvement of small fibers, evolving with the involvement of sensory large fibers and finally motor fibers in its more severe stages. Classically, it is distally distributed in LLll with length-dependent progression, then affecting upper limbs (UULL), central abdominal region and vortex, in a pattern known as “socks, gloves and apron”.
It may be associated to other types of DN, especially chronic compressive mononeuropathies such as CTS, however in some cases it may be associated to inflammatory neuropathies such as chronic inflammatory unmyelinating polyradiculopathy (CIUP). There is still no clear causality relation between both conditions, however chronic involvement of peripheral nerve by DM seems to be a risk factor for its development[30].

Pathogenesis
DSP pathogenesis is associated to multiple factors related to metabolic, vascular, inflammatory and neurodegenerative pathways.
Chronic hyperglycemia plays critical role and is the major triggering factor of DSP pathogenic pathways[42].

Metabolic pathway
Glucose penetrates in high levels in peripheral nerves and generates different pathologic metabolic reactions. An example is polyol pathway which transforms glucose into sorbitol by means of the aldose reductase enzyme. Build up of intracellular sorbitol and fructose decreases active transport of several metabolytes, among them myo-inositol
This process changes intracellular regulatory mechanisms decreasing Na/K pump activity with consequent build up of intracellular sodium. With this, intracellular osmolarity is increased, which generates oxidative stress. These abnormalities decrease nervous conduction velocity and produce the first and reversible structural changes in Ranvier nodes.
Another pathologic metabolic mechanism caused by chronic hyperglycemia comes from the formation of final advanced glycosylation products (FAGP), which are obtained by non-enzymatic reaction of groups of amino acids and glucose reduction products.
FAGP act changing intracellular function of several proteins, changing extracellular components such as laminin and fibronectin, which are essential for axonal regeneration and, finally, promoting irreversible binding in receptors of macrophages and endothelial cells. These changes result in oxidative stress, cytokines secretion and extracellular matrix degradation, peaking in cell apoptosis.
In addition, high glucose levels promote excessive protein C kinase activation, determining the production of nitric oxyde which leads to ischemic peripheral nerve injury[43].
Recently, due to high association rate between DM and dyslipidemia (DLD)[44] it has been observed the participation of excessive lipids as cofactor in DN pathogenesis[45]. It has been proven in vitro direct injury of free fatty acids in Schwann cells[46]. In addition, systemic DLP effects promote increased pro-inflammatory substances and oxidative stress.
Associated to all these metabolic pathways, there is the activation of hexosamine pathway which, induced by hyperglycemia, results in changes in the expression of some genes and on the functioning of intracellular proteins[47].
Oxidative stress leads to increased formation of free radicals, both by the polyol pathway and by FAGP and protein kinase C. This mechanism generates mytochondrial dysfunction, which when critically affected, activates cell apoptosis cascade[43].

Vascular pathway
Generalized nervous microvascular dysfunction has been proposed as pathogenic mechanism, based on the demonstration of blood flow decrease, increased vascular resistance and decreased oxygen tension. Numerous endoneural microvascular abnormalities have been observed, including basal membrane thickening and duplication, edema and endothelial and intimal smooth muscle proliferation, in addition to the presence of occlusive platelet clot[42].

Neurodegenerative pathway
Another mechanism possibly involved with DN pathophysiology is loss of cell neurotrophism. In DM, quantitative and qualitative decline of insulin also leads to partial reduction of activity of the insulin-like growth factor I and of the neuronal growth factor, with consequent decrease in production of proteins essential for the formation of neurofilaments and maintenance of axonal transport, indispensable for their growth and regeneration. This way, there is axonal degeneration and neuronal body apoptosis, making neuropathy to be gradually installed[43].

Inflammatory pathway
There are substantial evidences pointing to an immunopathic mechanism in the development of DN. The presence of pro-inflammatory agents has been proven in diabetic patients with neuropathy, promoting inflammatory cells recruitment, cytokines production and decreased blood flow[48]. In summary, these mechanisms increase peripheral nerve hypoxia and ischemia, making difficult its regeneration[49].

Histopathologic changes
Electronic microscopy has observed poorly oriented filaments in the subaxolemal region, reflecting the slowing down of axonal transport. These neurofilaments are later scavenged by Schwann cells which, added to decrease production capacity of cytoskeleton proteins, decrease axonoplasmatic volume determining axonal atrophy in a way that it peaks with Wallerian degeneration. Most common affection pattern is, then, compatible with dying-back axonal degeneration, which preferably affects longer fibers, determining the length-dependent clinical pattern.
These factors lead to most important DN histopathologic change: multifocal loss of nervous fibers, with axonal degeneration in activity and depending on its chronicity some level of regeneration, characterized by the presence of sproutings. In addition, there are obliterated blood vessels, with endothelial basal thickening and neoangiogenesis, revealing the participation of the ischemic component. It is also possible to observe segmentar demyelination and remyelination, which reflects the mixed neurophysiologic involvement pattern (axonal and unmyelinating) of this condition[50].

Risk factors
There are several risk factors associated to the development and progression of DSP, among them advanced age, male gender, non-hispanic blacks, longer DM duration, glycosilated hemoglobin (HbA1c) higher than 7%, insulin therapy and history of systemic hypertension (SH), DLP and albuminuria[51].

CLINICAL MANIFESTATIONS

Sensory signs and symptoms
Most symptomatic patients have positive sensory symptoms (excessive response to a stimulus or spontaneously), such as paresthesia and pain, and in some cases may present proprioceptive ataxia. These are referred as sensations of numbness, tingling, imbalance and falls, shocks, pricks and especially burning. They are distributed in LLll extremities and may evolve to UULL and characteristically patients refer worsening at night. In general these are mild symptoms, however they may be severe and disabling. Negative sensory symptoms (decreased response to a certain stimulus) are those referred as loss of sensitivity in involved segment.
At neurologic evaluation there is distal hypoesthesia/hyperesthesia in segments, initially in thermoalgesic sensitivity modalities. In the presence of severe painful neuropathy, there may be hyperesthesia (exaggerated response to tactile stimuli), hyperalgesia (exaggerated sensitivity to painful stimuli), hyperpathia (persistence of pain even afer painful stimulus removal) or even allodynia (painful sensation caused by painless stimuli). It may evolve to deep sensitivity hypo/anesthesia such as tactile, vibratory and proprioceptive. In addition, when there is large fibers sensory impairment, there is deep hypo/arreflexia, primarily in Achillean reflex, and there might be global arreflexia in very severe cases[30].

Autonomic signs and symptoms
Already described.

Motor signs and symptoms
Patients with this clinical presentation of neuropathy seldom refer motor symptoms. When present, they start in the most advanced phase of the disease with mild distal LLll weakness, and mild muscle atrophy of LLll and UULL extremities may be observed
In the presence of major motor signs and symptoms, one should investigate overlapping causes, such as PIDC or inflammatory radiculoplexus neuropathy[30].

Differential diagnosis
DSP secondary to DM is similar to a series of conditions eliciting distal sensory-motor polyneuropathy with axonal predominance. Among them, most frequent are those of toxic-metabolic etiology such as ethyl defficiency, uremic, hypothyroidism, etc. One should also rule out infectious, inflammatory and paraneoplastic causes as well as hereditary neuropathies. It is not uncommon the association of DM with other peripheral neuropathies, very often delaying its diagnosis and possible specific treatment.
Other clinical conditions, such as intermittent lameness, osteoarthritis and Morton's neuroma share painful symptoms which may simulate DSP.
For this reason it is necessary to obtain detailed clinical history, followed by careful neurological and physical evaluation, in addition to complementary investigation with neurophysiologic and laboratory tests[52].

Diagnostic tests
Several clinical scales and additional tests have been proposed along decades to early detect DPS and follow its progression with regard to the level of PNS involvement. Among additional tests, one should stress neurophysiologic, autonomic and morphologic tests.

Clinical scales
Clinical scales are based on questionnaires answered by patients about their symptoms and on scores regarding patients' neurological exams findings, filled by the examiner. Currently, most commonly used scales in population studies and clinical trials are the Michigan Neuropathy Screening Instrument[53] and the Neuropathic Involvement Score (NIS), Neuropathy Disability Scale (NDS) or Neuropathy Impairment Scale (NIS)[54,55].

NEUROPHYSIOLOGIC TESTS

Electroneuromyography (ENMG)
For years, ENMG has remained as the golden standard for DSP diagnosis. Still today, it is the diagnostic method most commonly used and available in Brazil. Notwithstanding the inability of the test to identify the early involvement of small fibers in this condition, it remains with major importance not only to document the involvement of large fibers but also to evaluate symmetry, severity and progression of the disease, ruling out other coexistent conditions, such as myopathy, motor plate or inferior motor neuron diseases, in addition to primary demyelinating diseases such as PIDC or hereditary neuropathies. By means of needle test (electromyography – EMG) it is possible to characterize both time of evolution (acute versus chronic) and the distribution of neurophysiologic changes.
The routine of neuroconduction study in diabetic patients with DSP involves motor evaluation of median, ulnar, tibial and fibular nerves and sensory evaluation of median, ulnar, radial and sural nerves. EMG should be performed when differential diagnosis with other etiologies is needed[56].
In general it presents as pure sensory or sensory-motor polyneuropathy or mixed polyneuropathy with axonal and distal predominance, preferably affecting LLll. Firs observed changes in the neuroconduction of DSP patients are sensory changes in distal LLll nerves with decreased sensory action potential amplitude in plantar, superficial fibular and sural nerves. The disease progresses with sensory UULL involvement and 10 to 30% decrease in conduction velocities (initially of LLll progressing to UULL) until, in its most advanced stages, present decreased compound muscle action potentials (CMAP) with predominance of LLll[57,58].
There is often focal slowdown of conduction velocity with possible presence of conduction blockade (more than 50% decrease in CMAP amplitude from a proximal stimulation point to a distal point) in some nerves susceptible to compression such as wrist median, elbow ulnar and common fibular nerves of fibular head[30].
Althoug being extremely useful, the limitations of this test are discomfort referred by patients, its low sensitivity to detect initial symptoms of the disease (small fibers), in addition to the demand for specialized professionals and equipment[59].

Quantitative sensitivity test (QST)
Method used to indentify and quantify sensory changes of polyneuropathy thermal, painful and vibratory modalities. It may be performed in different sites by applying thermal hot and cold stimuli and checking the temperature at the moment patients start to refer beginning of stimulus sensation and pain. It is also possible to check the level of vibration experienced by patients. It is a useful tool in the clinical practice for being a rapid, noninvasive and easy to perform test. However, this method has low repeatability rate because it depends on patients' cooperation, attention and motivation, being results vulnerable to emotional status. In addition, this test captures changes in any point of the neuraxis and may lead to error in the analysis[56].

Evoked potentials
Evoked potentials represent central nervous system electric responses to an external stimulus[60]. Of interest for the study of small fibers polyneuropathy are laser evoked potential stimulation (LEPS) and contact heat evoked potential stimulation (CHEPS). Such methods allow examining peripheral and central conduction of Aδ and C fibers. However, LEPS may cause skin injuries in laser-stimulated areas, while CHEPS, in addition to being more sensitive and specific, is noninvaise and able to generate reproducible evoked potentials. There is still no standardization for both methods for the clinical practice[61].

Autonomic tests
There are several autonomic tests to identify the involvement of C fibers. In clinical practice, most accessible tests for cardiac and sudomotor evaluation are, respectively: tilt test, Valsalva maneuver and R-R interval calculation at ECG and reflex sympathetic skin response and sudomotor reflex quantitative test (Table 2)[41].

Table 2. Signs, symptoms and autonomic tests. Modified[41]

Categories	Signs and symptoms	Diagnostic tests
Cardiovascular	Postural hypotension Arrhythmia Silent ischemia Intolerance to exercise	Variation of R-R interval at inspiration/ Valsalva maneuver Tilt test Myocardial cyntigraphy with MIBG
Gastrointestinal	Nausea Constipation/diarrhea Early saciety	Gastric emptying study Colonoscopy
Genitourinary	Erectile dysfunction Retrograde ejaculation Vaginal lubrication reduction Neurogenic bladder	Nocturnal penile pletismography Urodynamic study
Skin/sudomotor	Anhidrosis Skin dryness Intolerance to heat	Quantitative sudomotor reflex test Reflex sympathetic skin response

MORPHOLOGIC TESTS

Nerve biopsy
Peripheral nerve biopsy was used for a long time for morphologic and pathophysiologic study of nervous fibers involvement in DN[62]. Since this is an invasive exam with possibility of generating complications and sequelae, currently this method has been reserved for atypical situations of clinical presentations when there is doubt about the overlapping with other etiologies, such as inflammatory/infectious neuropathies and amyloidosis. In addition, this exam requires highly specialized material and qualified professionals to examine the blades[63]. In general, in research, fascicular biopsy of the superficial sensory nerve is used for being less harmful.

Skin biopsy
With a fragment of approximately 3mm of hairless skin, obtained by punch biopsy, it is possible to identify small epidermal nervous fibers, being a useful tool to diagnose small fibers neuropathy. This method is performed as from immune-hystochemical marking of PGP 9.5 – protein gene product, which is present throughout nervous fiber extension, allowing direct view of epidermal fibers.
Currently, intraepidermal fibers density quantification as from skin biopsy is suggested as diagnostic method for small fibers neuropathy, and its standardization for gender and age has been published. Its limitations include being an invasive process which does not add information about the etiology of the neuropathy[64].

Confocal corneal microscopy
Recently, human cornea sub-basal plexus, made up of small fibers, has been mapped by confocal microscopy in vivo allowing its characterization and distribution pattern of nervous fibers in healthy individuals of both genders and of different ages[65].
Malik et al.[66] have shown for the first time, in a series of 18 diabetic patients compared to controls, a significant decrease in sub-basal plexus fibers by means of corneal confocal microscopy (CCM) in vivo, highlighting this test as a rapid, noninvasive and reproducible diagnostic tool to identify DSP. Since then, this method has been pointed in different studies as able to identify neuropathy, as well as disease progression and possible improvement after treatment.

Treatment
A strict glycemic control seems to be critical for stabilization and even to improve DN[67]. This way, all effort should be done to maintain patients normoglycemic.
Many evidences indicate that oxidative stress is involved with DN genesis. So, antioxidant drugs would be an excellent therapeutic alternative. Intravenous α-lipoic acid (thioctacide^{MR}) (600mg/day for 3 weeks) is currently the only treatment based on disease mechanism with proven efficacy and amenable to be used in the clinical practice[68]. The same drug orally (600mg/day in fasting), the only presentation currently available in Brazil, still need further evidential studies, although evidences suggest its efficacy[67]. Other treatment modalities were proposed, but still lack data confirming that they are effective[67].
Among available drugs for symptomatic pain treatment, there is evidence level A supporting the use of tricyclic antidepressants, anticonvulsants gabapentin and pregabalin, and antidepressant duloxetine, selective dual inhibitor of serotonin and norepinephrine reuptake. There is also second line evidence for the use of opioids such as tramadol and oxicodone[67]. The combination of first line drugs should be considered before using opioids[67].
Tricyclic antidepressants have proven efficacy but their adverse effects are major limiting factors because they might be associated to cardiac conduction changes (A/V blocks, arrhythmias), xerostomy, sweating, dizziness, sedation, urinary retention and glaucoma. Above 100mg/day, their use seems to be associated to sudden death risk, reason why they should be carefully used in cardiopathic patients. It is recommended to start with 10 to 25mg/day and gradually increase the dose with careful follow up of patients. Although doses of up to 150mg/day are indicated, it is hard to go beyond 75mg/day. The choice of the specific drug should take into consideration patients' manifestations and drugs adverse effects[67].
Among anticonvulsants, gabapentin and pregabalin, both inhibitors of calcium channel alpha-2-delta subunit, are currently the best options for this group of patients[67]. Among dual antidepressants, serotonin and norepinephrine reuptake blockers, duloxetine, as compared to venlafaxine, have the best cost-benefit and control of painful neuropathy[69]. Duloxetine may be administered in the initial dose of 30mg/day, titrating in one week to 60mg/day as maintenance. Some patients need 120mg/day to control NP.
Whenever there is clinical and/or electromyographic evidence of significant arrest, with major motor involvement, decompressive surgeries are theoretically indicated, however the risk of no improvement or even of worsening is significant and should be explained to patients.
Maybe one of the most important functions of neurologists in managing DN is orienting prevention and treating diabetic foot, which basically results in insensitivity and autonomic dysfunction. Periodic exams, orientation for self-evaluation, and immediate rest at the onset of any injury, are simple but very important measures.

CONCLUSION

In face of increased prevalence of DM and as a consequence of its most frequent microvascular complication, DN, it has to be stressed the importance

of knowing its primary clinical manifestations, available investigation methods and proposed treatments to establish early diagnosis with possibility of preventing disease progression and its complications.

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