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Case report

Peripheral and Autonomic Neuropathy in an Adolescent with Type 1 Diabetes Mellitus: Evidence of Symptom Reversibility after Successful Correction of Hyperglycemia

Joselyn Rojas, Mervin Chávez-Castillo, Wheeler Torres, Carmen Chávez, Vanessa Apruzzese, Mayela Cabrera and Valmore Bermúdez

Endocrine and Metabolic Diseases Research Center, Medicine School,
Zulia University, Maracaibo, Venezuela

Correspondence should be addressed to: Valmore Bermúdez; valmore@gmail.com

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Abstract

Introduction: Diabetic neuropathy is the most frequent chronic complication of Diabetes Mellitus (DM), currently considered an irreversible end-organ damage complication. The present case concerns a teenage patient, who after effective glycemic control, was shown to regain sensitive and autonomic nerve function. **Case Report:** An 18-year-old female patient with Type 1 DM with 6 years of evolution since diagnosis and poor metabolic control (HbA1c 13%) presents to our outpatient clinic with severe sock-pattern burning pain sensation in both lower limbs, which is perceived to have worsened in the previous 6 months despite receiving gabapentin and pregabalin, prescribed in another health center. At physical examination, orthostatic hypotension was evidenced after a fast transition to standing position, tachycardia, muscular hypotrophy of both quadriceps and sural triceps, with a negative Rydel-Seiffert test and a positive Romberg test. Patellar and calcaneal osteotendinous hyporreflexia were found, while hyperalgesia and allodynia to palpation of both feet were present. The RINES-VALCARDI test yielded 8 points at first consultation. She was given patient education concerning her disease and started a strict diet as well as an appropriate insulin therapy to achieve metabolic control. She was treated with duloxetine and capsaicin cream, treatments which she abandoned 6 months later with no observable or measurable relapse of her nerve dysfunctional symptoms; not even one year afterwards. **Discussion:** This case is unique due to several aspects: The severity of hyperalgesia, and the reversibility of both peripheral and autonomic symptoms after glycemic control and patient education. These elements are fundamental pertaining to reversion of nerve damage.

Keywords: Diabetes mellitus, diabetic neuropathy, peripheral diabetic neuropathy, autonomic diabetic neuropathy.

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Introduction

Chronic complications of Diabetes Mellitus (DM) represent the greatest source of deterioration of lifestyle quality of affected subjects (Shrestha & Ghimire, 2012). These entities are also linked to most of the expenses associated with DM management, constituting a heavy economic burden for public health systems worldwide (van Dieren et al, 2010). Within the broad spectrum of chronic complications of DM, Diabetic Neuropathy (DN) has the highest prevalence, being present in approximately 50% of all cases of DM (Boulton et al, 2005), especially those with Type 1 DM (DM1) (van Dieren et al, 2010; Boulton et al, 2005).

Distal Symmetric Polyneuropathy (DSP) is the most prevalent neuropathic disorder, found in 30% of all patients with DM, and reaching up to 60-70% in those with long lasting DM since diagnosis (Boulton et al, 2005; Hilz, Marthol & Neudörfer, 2000). This alteration is progressively disabling, not only due to the pain it generates but because of the risks it imposes on patients, such as the development of foot ulcers, recurrent skin and soft tissues infections (Boulton et al, 2005; Centers for Disease Control, 2011), and the degeneration of osteoarticular structures (Centers for Disease Control, 2011); moreover, the diabetic foot is responsible for up to 75% of non-traumatic amputations worldwide (Clayton & Elasy, 2009). On the other hand, Diabetic Autonomic Neuropathy (DAN) comprehends a heterogeneous group of manifestations secondary to the dysregulation of the Autonomic Nervous System (Said, 2007). Although less common than DSP (14-50% of patients with DM), it implies a high risk of mortality –approximately 50% within the first 5 years after diagnosis– particularly when autonomic cardiovascular regulation is compromised (Kuehl & Stevens, 2012; Kamenov & Traylov, 2012; Karayannis et al, 2012).

The development of diabetic neuropathy relies on the two aspects: hyperglycemia –which represents poor metabolic control– and genetic susceptibility. It has been suggested that this kind of end-organ damage is proportional to the duration and severity of hyperglycemia (Rogus, Warram & Krolewski, 2002), yet it is not always the case. Heesom et al. (1998) reported that polymorphisms of the Aldose Reductase gene were involved in the pathogenesis of neuropathy in type 1 DM, even in those without long term disease (χ^2 17.3; $p<0.00001$). Through the years, other genes have been postulated to exacerbate and accelerate diabetic neuropathy, such as Methylenetetrahydrofolate reductase (Yigit, Karakus & Inanir, 201313), Catalase (Chistiakov et al, 2006), Glutathione peroxidase 1 (Chistiakov et al, 2006), polymorphisms in the 2B adrenoreceptor (Papanas et al, 2007), Poly ADP ribose polymerase (Nikitin et al, 2008), Mn Superoxide Dismutase (Hovnik et al, 2009), and finally, the 4 ApoE allele is associated with a 5-fold risk for severe neuropathy (Monastiriotis et al, 2013). Moreover, several epigenetic modifications have been related to microvascular complications, which also participate during the development and amplification phase of neuropathy (Rafehi, El-Osta & Karagiannis, 2012), and even influence the capacity for wound healing (Rafehi, El-Osta & Karagiannis, 2011).

Clinical evaluation of nerve function has been classically done using the Ewing battery of tests (Ewing & Clarke, 1982), which consists of a series of maneuvers aimed to assess cardiovascular autonomic function. However, other evaluation protocols, such as the RINES-VALCARDI test (Chacín, Jatem & Rojas, 2009) are applied locally, with good sensitivity when evaluating diabetic neuropathy (Chacín, Jatem & Rojas, 2009).

Classically, both entities are most prevalent in adult patients, due to the greater possibility of extended DM evolution and a prolonged impaired metabolic control in older patients (Blankenburg et al, 2012). However, the onset of these disorders in an adolescent patient with a relatively short DM personal history since diagnosis highlights the importance of appropriate glycemic management (Nalysnyk, Hernández-Medina & Krishnarajah, 2010; Soedamah-Muthu, Abbring & Toeller, 2011). The following case concerns a

teenage patient with long term DM1 with poor metabolic control, who presents with distal polyneuropathy and autonomic neuropathy.

Case Report

An 18-year-old female patient, with past medical history of DM1 with six years of evolution since diagnosis and poor metabolic control (HbA1c 13%), presents to our outpatient clinic with severe sock-pattern burning pain in both lower limbs which is perceived to have worsened in the past six months despite receiving gabapentin (400 mg/day) and pregabalin (150 mg/day), prescribed in another health center. Insulin therapy in this patient consisted in a bolus/basal regimen, with insulin Glulisine, 3 IU SC 15 minutes prior main meals, and a basal insulin Glargine component, 16 UI SC at 9 pm, referring to poor glycemic control during the last two years, with fasting blood glucose levels around 220 mg/dL, 2-H post-prandial glycemia between 280-320 mg/dL and HbA1c of 13%. It is noteworthy to mention that the insulin therapy dosage was never completely adjusted, which would explain the chronically worsening of metabolic control during puberty. Additionally, in the last 4 months, she developed weakness and frequent dizziness crisis that worsened with sudden postural changes, and intolerance to cold-room environments. In regards to gastrointestinal symptoms, she referred to post-prandial fullness with occasional vomits with alimentary content, constipation and profuse sweating of the face, scalp, and neck after food ingestion.

Her diabetic debut was an episode of diabetic ketoacidosis, with five successive incidents over the following two years, associated with intentional omission of insulin administration. On the other hand, she also refers to an episode of tonic-clonic seizures due to severe hypoglycemia as a result of insulin overmedication and a lack of nutritional regimen compliance. In the past few years, she was referred to an outpatient gastroenterology consult for acute erosive gastritis and multi-parasitic colitis. Concerning infectious diseases, she referred to 3 episodes of soft tissue infection and 1 urinary tract infection, which required hospitalization for antibiotics and glycemic control. A history of recurrent allergic rhinitis and bacterial otitis media was also documented. In regards to her gynecological history, the patient reported her menarche at age 12, with 4-day cycles every 28-30 days without dysmenorrhea. At the moment of consultation, she was undergoing psychological therapy due to anxiety and depressive disorders associated with her diagnosis of DM1. The mother denies any relevant first-grade family medical history.

During her physical examination, the patient was observed to be in great pain with evident *"facies dolorosa"*, having a difficult time standing and walking around the examination room. In the general examination protocol, the patient was found conscious, afebrile, with moderate pale. The thorax was normal-sized and expanded without effort, normal vesicular murmur and a respiratory frequency of 20 r.p.m. Breasts were anatomically normal, without nipple discharge. On cardiovascular exploration, heart rate was 100 b.p.m., without murmurs, and associated with orthostatic hypotension (110/70 mmHg lying down, 95/60 mmHg standing, 110/80 mmHg sitting). Pedial and tibial pulses were present and normal on both limbs. The abdomen was slightly painful to palpation in the epigastric region; no visceromegalia was detected by palpation. Genitalia were normal. Regarding anthropometry, weight was measured at 43.2 kg, height 150 cm, and Body Mass Index (BMI) 19.2 kg/m^2.

Neurological examination presented an alert patient oriented in time, place and person. There is no gross evidence of aphasia, apraxia or agnosia. The recent and the remote memory appear normal with good fund of knowledge. Cranial nerves: Pupils are 4 mm, reacting briskly to 2 mm without afferent pupillary defect. Visual fields are intact to confrontation testing. Funduscopic examination reveals sharp disk margins with normal vasculature. No papilledema, hemorrhages or exudates. Extraocular movements are full and smooth with normal pursuits and saccades. No nystagmus was noted. The face was symmetric and the remaining cranial

nerves were intact and symmetrical. Lower limbs were further examined, observing discreet muscular hypotrophy with diminished muscle strength (III/V), especially in the *quadriceps femoris* and *triceps surae* muscle groups, accompanied by hyperalgesia, hypersensitivity and allodynia (mainly in the feet). Reflexes are 4/4 and symmetrical in the upper extremities, 2/4 and symmetrical at the knees and at the Achilles tendon. Plantar responses were normal bilaterally, but painful. No involuntary movements were noted. Sensation: Intact sensation to gross pinprick with hyperalgesia exacerbation, and mild diminished perception to light touch, vibration (The Rydel-Seiffer tuning fork test was negative) and proprioception (Kästenbauer, 2004) and Semmes-Weinstein monofilament test (Lee et al, 2003) was not performed due to severe pain and allodynia found at the moment of consultation. Coordination: The patient accomplishes finger-nose-to-finger, heel-to-knee-to-shin and rapid alternating movements in a symmetrical fashion without effort, but Romberg's test was positive. Gait and station: The patient walks with a broad-based antialgic gait leaning on the outer edge of the foot (Figure 1). Additionally, the electrocardiographic RINES-VALCARDI test (Chacín, Jatem & Rojas, 2009) was performed to assess autonomic cardiovascular function, yielding a score of 8 points (Figure 2). Finally, the LANSS pain scale questionnaire was applied, obtaining 19 points.

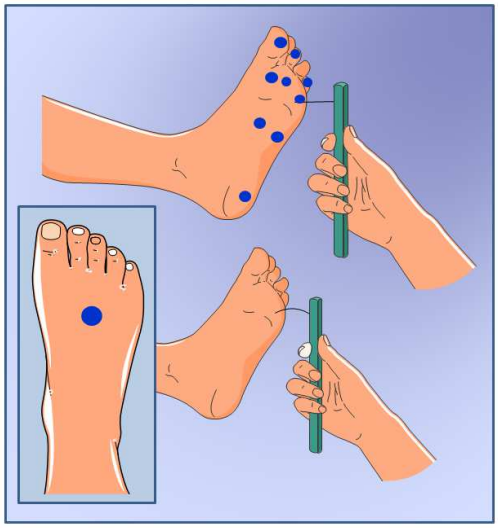


Figure 1: Semmes-Weinstein monofilament test.

This procedure is designed to evaluate the stimulus threshold required for touch perception. The patient must be in supine position and blindfolded. The subject should verbally indicate the moment the pressure from the monofilament is felt. Filaments should be utilized from shortest to longest, placed at a 90° angle relative to the surface of the assessed site (marked in blue in the illustration), and pressed against the skin for 1.5 seconds. In total, 5 filaments should be used: Lengh (cm) 2.83 and 3.61 are to be applied 3 times in each site; whereas 4.31, 4.56 and 6.65 filaments are applied once. If the patient reports perceiving the pressure, the site is considered "positive". The report should be filed in a specialized illustrative diagram documenting the first filament which was felt on each site, as per the following conventions: a) Green: 2.83; b) Blue: 3.61; c) Purple: 4.31; d) Red: 4.56; e) Red Lines: 6.65.

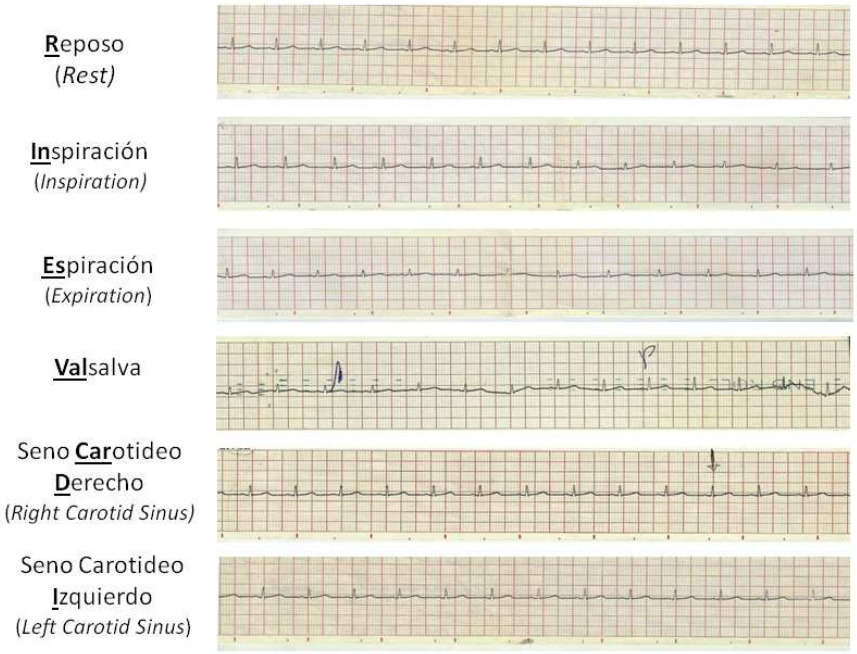


Figure 2: RINES-VALCARDI test.

The standardized lead used to perform test D-II at 10 mV/mm and 50 mm/s speed. After a 3-minute period of rest, the EKG monitoring is started. 15 QRS complexes are registered in each of 6 cycles –which alternate with 2-minute rest periods–, as follows:

- **Reposo (Rest): Basal heart rate.**
- **Inspiración (Inspiration): The patient is asked to perform one deep inspiration.**
- **Espiración (Expiration): The patient is asked to perform a deep expiration.**
- **VALsalva: The patient is asked to perform the Valsalva menuver, as follows: "Take a deep breath, keep it in, and push", maintaining the push for at least 10 seconds or as long as it may be tolerated.**
- **Seno CARotideo Derecho (Right Carotid Sinus): The examinator should gently massage the neck around the right submandibular angle with their second and third fingers.**
- **Seno carotideo Izquierdo (Left Carotid Sinus): The previous procedure is repeated in the left submandibular angle.**
- **All R-R' intervals in the EKG registry should be measured in milimeters. From each cycle, the difference between the longest and the shortest interval should be calculated. Finally, all 6 differences are added, yielding the final score. Scores ≤ 5 are compatible with Cardiac Diabetic Autonomic Neuropathy.**

Diagnostic Work-up Analysis

Laboratory test results are summarized in Table 1. Concerning metabolic control, it was observed that the patient had a fasting glycemia of 143 mg/dL with HbA1c of 13%, hypertriacylglyceridemia and elevated pyruvic transaminase. Complementary imaging studies included hepatopancreatobiliary and renal echography with normal results. Ocular computed tomography and retinal fluorescein angiography were both found to be normal.

Table 1: Anthropometric and laboratory test values at first consultation.

Variable	Result
Weight	43.2 kg
Height	1.51 mt
Body Mass Index	18.9 kg/m^2
Total Cholesterol	243 mg/dL
LDL-C	151 mg/dL
HDL-C	32 mg/dL
Triacylglycerides	781 mg/dL
VLDL-C	24 mg/dL
Fasting Glycemia	143 mg/dL
Postprandial Glycemia	252 mg/dL
HbA1c	13%
Oxaloacetic Transaminase	25 U/mL
Pyruvic Transaminase	36 U/mL
Microalbuminuria	47 mg/dL
Urea	46 mg/dL
Creatinine	1.0 mg/dL
Creatinine Depuration	153.19 mL/min
Thyroid Profile	Normal

Given this personal history, clinical and laboratory findings, the following diagnoses were proposed: 1) Type 1 Diabetes Mellitus with poor metabolic control; 2) Distal Symmetric Diabetic Polyneuropathy; 3) Diabetic Autonomic Neuropathy, compromising cardiovascular apparatus, gastrointestinal system and the sudomotor complex; 4) Stage 2 Diabetic Nephropathy (microalbuminuria) (Zelmanovitz et al, 2009), and 5) Hypertriacylglyceridemia with Low HDL-C. On this basis, the following management protocol is started: a) Diet therapy according to the American Diabetes Association guidelines (American Diabetes Association, 2014), with increased sodium and water consumption in order to improve orthostatic hypotension; b) Adjustment of insulin therapy to insulin Glulisine (Apidra®) 7 UI SC 15 minutes prior to each meal, and insulin Glargine (Lantus®) 25 UI SC at 9 pm; with frequent capillary glucometric control (6 times per day) and detailed registry of all food consumption in order to readjust insulin doses depending on carbohydrate intake; c) Ciprofibrate (Hiperlipen®) 100 mg/day; d) Duloxetine (Cymbalta®) 30 mg/day; and e) 0.075% Capsaicin cream prepared in our research center, to be applied from the soles of the feet up to the knees twice per day. Rather impressively, the patient reported improvement of pain by day three after starting this plan, achieving complete pain relief at approximately 4 weeks into treatment.

During one of the successive evaluations (8 months after the first consultation), the patient reported having abandoned Duloxetine treatment after the sixth month, denying recrudescence of pain in this period. Likewise, she also denied feeling dizzy or weak with sudden posture changes. Laboratory tests revealed fasting capillary glycemia levels <110 mg/dL, with HbA1c at 6.5%; and BMI of 19.4 kg/m^2, performing daily physical activity without limitations. The Semmes-Weinstein monofilament test was performed with the 5.07 (10-g) filament for evaluation of protective sensation threshold in all 10 assessment sites, with normal results 8 months after starting this protocol. When repeating the RINES-VALCARDI test, results were also normal. At the moment of this publication, the patient presented improvement of microalbuminuria, reaching 18 mg/dL.

Discussion

DN is one of the most feared complications of DM, not only due to its inherent painful component (Vinik & Erbas, 2002), but also due to orthopedic complications such as Charcot's Osteoarthropathy (Papanas & Maltezos, 2013) which often requires hospital admissions and lower limb amputations (Casellini & Vinik, 2007). Although neuropathy may develop both in DM1 and Type 2 DM (DM2), its prevalence varies between these categories: DSP is most commonly found in DM2 (50-60.8%), whereas in DM1, Cardiovascular DAN is more frequent (60%), usually coexisting with peripheral polyneuropathy (62.5%) (Rolim et al, 2009; Van Acker et al, 2009). In both settings, the most important factor for the progression of neuropathy is glycosylated hemoglobin, followed by nephropathy, obesity, low HDL-C and hypertriacylglyceridemia (Van Acker et al, 2009).

DN is classified in two distinct categories (Edwards et al, 2008): a) Diffuse disorders, and b) Focal disorders. The former includes sensorimotor alterations –represented by DSP– and autonomic alterations, as seen in DAN. On the other hand, focal disorders include mononeuropathy, plexopathy, radiculopathy and cranial nerve neuropathy; see Table 2. Peripheral neuropathies are recognized in 60% of patients with DM (Feldman, 2008), representing one of the greatest risk factors for the development of Charcot's Osteoarthropathy, ulceration and ulterior amputation (Boulton, 2005). In DSP, sensory loss is symmetric and ascendant in a "sock-glove" pattern, proportional to the time of evolution of DM and the successfulness of metabolic control (Vinik, et al. 2003).

Table 2: Classification of Diabetic Neuropathy

Type of Neuropathy	Clasificación	Examples
Diffuse	Symmetric Polyneuropathy Diffuse sensorymotor	Small-Fiber Long-Fiber Mixed
	Autonomic Neuropathy	Abnormal pupillary function Sudomotor dysfunction Genitourinary Gastrointestinal Cardiovascular Maladaptation to hypoglycemia
Focal		Mononeuropathy Multiple mononeuropathy Plexopathy Radiculopathy Craneal neuropathy

DAN implicates loss of sympathetic and parasympathetic regulation over the basal function of organs and systems, leading to dysfunction (Edwards et al, 2008). Usually, it appears first in longer nerves such as the Vagus nerve, which encompasses 75% of all parasympathetic activity (Vinik, Freeman & Erbas, 2003), and although symptoms tend to present in patients with longer time of evolution, subclinical DAN has been recognized to appear within the first 2 years after diagnosis in patients with DM1; and within 1 year in patients with DM2 (Pfeifer et al, 1984). Within all forms of DAN, the cardiovascular presentation boasts the greatest mortality, associated

with tachycardia, orthostatic hypotension, sudden cardiac death and silent myocardial infarction, as well as potential compromise of the ability to perform moderate to high-intensity physical activity (Boulton et al, 2005). The gastrointestinal system may also be affected, manifesting as retardation of gastric emptying and alternating periods of constipation and diarrhea; whereas involvement of the genitourinary system should be suspected in patients with recurrent urinary infections and neuro-dysfunctional bladder control, which may be found in 43-78% of cases (Boulton et al, 2005). Furthermore, DAN is the leading cause of sexual dysfunction in diabetics, with a prevalence of erectile dysfunction of up to 75% among male patients (Boulton et al, 2005).

The etiology of DN is multifactorial (Sytze Van Dam et al, 2013), including micro- and macroangiopathic events (Jennings et al, 1990) and neurodegenerative changes stemming from defects in *vasa vasorum* and epi-, peri- and endoneural vessels (Jennings et al, 1990). Among the molecular mechanisms found in this pathologic phenomena are (Sytze Van Dam et al, 2013): The polyol pathway (Oates, 2002), oxidative stress (Pop-Busui, Sima & Stevens, 2006), advanced glycation (Sugimoto, Yusujima & Yagihahsi, 2008), nitro-oxidative stress (Fuji et al, 2010), endoplasmic reticulum stress (Cameron, 2013) and TNF-dependent inflammatory mechanisms (González-Clemente et al, 2005). These pathophysiologic components interact synergically, resulting in neuronal death through mechanisms associated with necrosis or apoptosis (Figure 3).

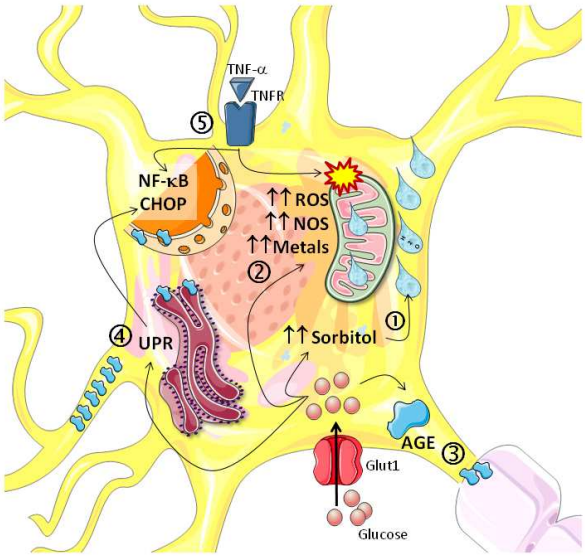


Figure 3: Mechanisms of neuronal damage.

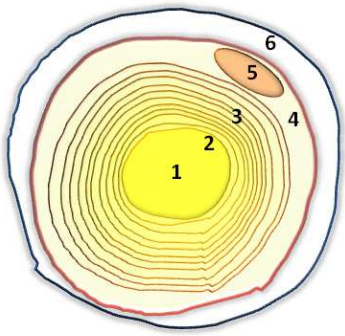
1. **Polyol pathway and neuronal edema.**
2. **Oxidative and Nitrosative stress. Associated with free metal ions and mitchondrial dysfunction.**
3. **Advanced glycation products and their effect of structural proteins**
4. **Unfolded Protein response, ending in the induction of proapoptotic protein CHOP.**
5. **TNF- proinflammatory actions, including induction of NF-kB, Krebs cycle disturbance and necroptosis.**

Although these components are widely recognized as classic features of DN pathophysiology, two novel mechanisms have received special attention in recent years: 1) Lipotoxicity associated with elevated triacylglyceride serum levels, and 2) Schwann cell dysfunction.

Regarding the former, Wiggin et al. (Wiggin et al, 2009) have reported a correlation between the loss of density of myelinated fibers and hypertriacylglyceridemia, suggesting hyperlipidemia and the consequent lipotoxicity to play a fundamental role in the progression of neuropathy, independently of the type of DM and insulin therapy (Chaturvedi et al, 2001). These findings correlate with cellular events as reported by Lupachyk et al. (2012), who found higher concentrations of triacylglycerides and non-esterified fatty acids to be linked with impaired nerve conduction and modifications in sensorial function in experimental models with Zucker *fa/fa* rats; associated with induction of nitrosative stress, particularly in Schwann cells. In our case, the patient presented with hypertriacylglyceridemia, which was successfully treated with diet and fibric acid derivative (Ciprofibrate).

Schwann cell damage may be especially important, given their active participation in the preservation of nerve action potentials, owing to their role as axon insulators through myelination, conservation of axonal caliber, and control of sodium ions within the neurotransmission mechanism (Eckersley, 2002). Indeed, this preservation of axonal architecture includes maintenance of paranodal and juxtaparanodal domains, and distribution of voltage-dependent Na^+ and K^+ channels (Salzer, Brophy & Peles, 2008). Structural defects in Schwann cells and myelin sheaths are key elements in the development of DN (Zenker, Ziegler & Chrast, 2013). These cells are excellent targets for insulin activity due to their constitutive expression of insulin receptor, IRS-1 and GLUT 1 and 3, as opposed to the expression of GLUT 1, 3, 4 and 8 in axons (Thorens & Mueckler, 2010). Diabetes-induced glycotoxicity is related to a reduction in lactate transport, which lowers ATP synthesis and in turn increases free radical production and disorders in Na^+/K^+ ATPase pump and Ca^{++}/Na^+ exchanger activity, ultimately leading to alterations in activation voltages (Pellerin & Magistretti, 2003).

In this context, it is convenient to describe the types of nerve fibers and their interactions with support cells, such as Schwann cells and neuroglia. Peripheral nerves may be sensitive, motor or autonomous, and are structurally constituted by an axon, the axolemma, a myelin sheath, a neurolemma or sheath of Schwann, and the endoneurium (Manzano, Giuliano & Nóbrega, 2008). These fibers are further subclassified in three groups according to their width, myelination and function (Figure 4) (Manzano, Giuliano & Nóbrega, 2008).



Type	A-α	A-β	A-γ	A-δ	B	C
Diameter	12-22 µm	5-12 µm	2-8 µm	1-5 µm	<3 µm	0.1-1.3 µm
Velocity	70-120 m/s	30-70 m/s	15-30 m/s	5-30 m/s	3-15 m/s	0.6-2 m/s

Figure 4: Types of peripheral nerve fibers.

1. Axon, the thin long projection of the neuron which conducts action potentials away from its cell body. 2. Axolemma, the cell membrane surrounding the axon, which mantains its transmembrane potential by virtue of its ion channels. 3. Myelin sheath, the enwrapping outgrowth of Schwann cells which envelops and insulates axons. 4. Neurolemma, the outermost cytoplasmic ring of Schwann cells. 5. Nucleus of Schwann cell. 6. Endoneurium, loose layer of connective tissue which encloses nerve fibers.

The classic symptoms of DSP are hyperalgesia and allodynia, characterized by abnormal reactions to non-noxious cutaneous contact, which trigger electric hyperactivity in pain neural pathways (Basic-Kes et al, 2009). The underlying modifications in neuron physiology include changes in ion flux patterns, synaptic connectivity and neurotransmitter receptor profiles (Zenker, Ziegler & Chrast, 2013; Thorens & Mueckler, 2010; O´Connor et al, 2004), overall known as neuronal plasticity (O´Connor et al, 2004). The neuropathic pain experienced by DM patients stems from slower conduction speed and the onset of spontaneous depolarization in polymodal axons of Type C fibers, and it is mediated chiefly by Substance P (O´Connor et al, 2004), a tachynin-like neuropeptide responsible for nociception. Indeed, the main fibers involved in this process are group C type I fibers which contain Substance P and tyrosine kinase A, and are responsive to capsaicin and acidosis (Hökfelt, Pernow & Wahren, 2001), being highly sensitive to local pH changes (Imme & McClesky, 2001); in contrast to group C type II fibers which are dependent on ATP/P2X and protons (Hökfelt, Pernow & Wahren, 2001).

Although the post-receptor pathway for Substance P activity remains poorly described, it has been demonstrated that after binding to its NK1 receptor, it induces the release of reactive oxygen species from the mitochondrial compartment, which in turn act as second messengers, modulating spontaneous activity of TPRV1 vanilloid receptors, inducing pain (Linley et al, 2012). This pathway exploited in the mechanism of action of capsaicin, a highly irritative phenolic amide found in chili peppers (Solanaceae family, *Capsicum* genus) (Govindaraian, 1986), leading to depletion of Substance P, reserves in nociceptive neurons through interference of its synthesis (Burks, Buck & Miller, 1985), downregulation of its receptors (Marvizón et al, 2003), and finally, repression of the expression of NK1 and TRPV receptors (Kunde, Crawford & Geraghty, 2013). In light of these properties, capsaicin was used in our patient as a coadjuvant treatment along with duloxetine, garnering satisfactory control of hyperalgesia and allodynia.

On a different matter, the risk of developing DAN has been reported to be higher in the presence of peripheral neuropathy (OR 2.53), increased HbA1c (OR 1.69), elevated serum triacylglycerides (OR 1.58), high waist circumference (OR 1.36), microalbuminuria (OR 1.24), and pubertal-onset DM (OR 1.08) (Voulgari et al, 2011). Moreover, it is thought to be more frequent in DM1 patients due to their longer life expectancy since the advent of recombinant insulin analogues with distinct and diverse activity profiles, accompanied by early diagnosis and adequate nutritional management (American Diabetes Association, 2014; Massin et al, 1999). Although the benefits offered by these analogues have allowed for their successful implementation, achieving metabolic control (HbA1c <7%) is often a more difficult endeavor in these patients, particularly in younger subjects due to age-related factors such as a lack of acceptance and adherence to therapeutic plans, deficient parental integration to these protocols, and puberty-associated factors (Rosenbloom et al, 2008).

In the situation of pediatric patients reaching adulthood, the transition from parental care towards self-care and management is an especially relevant element as it depends on the psychological maturity of the adolescent (Rosenbloom et al, 2008; Peters & Laffel, 2011). In these individuals, depression associated to factors such as strict nutritional and

medication regimes, peer pressure and sexual development may deeply affect treatment compliance (Rosenbloom et al, 2008; Peters & Laffel, 2011). In the case we report, the patient was found to have voluntarily neglected insulin administration on several occasions, culminating in the development of ketoacidosis and hospitalization. Indeed, these psychological aspects are pivotal in order to accomplish metabolic goals and decelerate the onset of chronic complications of hyperglycemia (Rosenbloom et al, 2008).

In pediatric ages, neuroautonomic manifestations are diverse and should be surveyed in every consultation (Table 3). Gastrointestinal symptoms are rarely observed in this demography, although a slight correlation has been reported between gastric emptying time and hyperglycemia (r=0.54, p=0.08) (Vazeou et al, 2004), being more frequent in females, particularly in obese subjects with a history of recurrent epigastric pain (Sfarti et al, 2010). On the other hand, early signs of cardiac DAN include diastolic dysfunction in patients with DM1 and microangiopathy (Vazeou et al, 2008), attenuation of the baroreceptor reflex and pulse pressure in correlation with the duration of the disease (Abd El Dayem, Battah & Soliman, 2011).

Table 3: Clinical signs associated with Diabetic Autonomic Neuropathy.

Organ	Sign
Pupils	Impaired pupillary adaptation to lowered light
Sudomotor	Dry skin Anhydrosis Intolerance to warm temperature Digestion-related perspiration
Cardiovascular	Tachycardia at rest Exercise intolerance Orthostatic hypotension Silent myochardial ischemia
Gastrointestinal	Esophagic dysmotility Gastroparesis Constipation Diarrhea Fecal incontinence
Genitourinary	Neurogenic Bladder Erectile dysfunction Retrograde ejaculation Female sexual dysfunction

Although the progression of the disease may be slowed, it is not considered to be preventable in all patients due to the multifactorial nature of the process; however, glycemic control remains the most important goal in this aspect (American Diabetes Association, 2014,Park, Park & Baek, 2004). While all medication used in the management of neuropathy is implemented on the basis of altering pathophysiologic mechanisms of the disease, no protocols have been established regarding drug combinations in this context (Boucek, 2006). One of the most interesting aspects of this case was the remission of pain-related symptoms after starting on duloxetine and capsaicin, remaining still after suspension of both drugs, suggesting reversibility of neuronal damage even in cases as severe as ours.

In order to assess this progression, DSP should be evaluated annually utilizing methods such as (American Diabetes Association, 2014): a) Exploration of pain sensation to pinching (mechanic pain threshold) and touch sensation to cotton swabs, both transmitted through Type C and A-δ fibers; b) Vibration perception threshold of Type A-β fibers, assessed with 128 Hz tuning forks; c) Semmes-Weinstein monofilament test for the evaluation of deep protective sensation by Pacinian corpuscules; and d) Calcaneal/Patellar reflex exploration, assessing proprioceptive sensation by Golgi tendon organs. The combination of these techniques offers over 87% sensitivity for detecting DSP (American Diabetes Association, 2014). The utilization of tuning forks renders higher sensitivity and positive predictive value when compared to neurothesiometers (Kästenbauer et al, 2004). Furthermore, vibratory methods offer 53% sensitivity and 99% specificity, while superficial pain assessment through the pinching method offers 59% sensitivity and 97% specificity (Perkins et al, 2001).

Nevertheless, the Semmes-Weinstein monofilament test appears to offer the smallest margin of error, as well as require minimal training (Lee et al, 2003). This technique encompasses evaluation of 10 distinct sites in feet, with sensitivity varying between 57-93%, specificity 75-100%, positive predictive value 84-100% and negative predictive value 36-94% for the diagnosis of DSP (Freng, Schlösser & Sumpio, 2009). Moreover, different kinds of filaments yield distinct predictive results depending on the sites they are used in; for example, application of the 4.3/2-g monofilament renders remarkable diagnostic values in the hallux and the 5th metatarsal, with 60% sensitivity and 73.8% specificity (Kamei et al, 2005) with positive results being linked to alterations in vibratory perception and syncope, reflecting small-fiber damage (Perkins et al, 2001). These data have led to the proposal of limiting the sites of evaluation in order to guarantee more homogeneous results (Boucek, 2006). Particularly, the use of the 10g monofilament in 3 areas offers several advantages, including a higher risk in ulceration depth (Tan, 2010) and a lack of perception of this filament is regarded as an independent risk factor for ulceration, due to the loss of protective sensitivity (Tan, 2010).

Finally, nerve conduction assessment techniques and electromyography (Brij et al, 1996) may be implemented in the diagnosis of DSP, regarded as the most objective tests to this end (Hsu et al, 2012; Said 2007), returning documentation on the type of neuronal injury and its localization (Boulton 2005; Said 2007). In symptomatic DN, findings include longer conduction speeds due to demyelination, and lower action potentials, owing to axonal loss (Boulton 2005; Tan, 2010; Said 2007). The application of needle electromyography is reserved for assessment of abnormal spontaneous potentials and exploration of motor unit configuration, as required in cases of generalized neuropathy, atrophy of proximal muscle groups, and radiculopathy (Boulton 2005; Said 2007).

Additionally, nerve conduction studies are valuable tools in the evaluation of nerve preservation, yet they may not be applicable in all cases, such as in polyneuropathy affecting small fibers, since these do not participate in sensorial action potentials (Said 2007). In DN, axonal loss with reduction or absence of action potentials may be observed, predominating in lower limbs, although according to the stage of progression, it may involve the hands; however, many DM patients may present nerve conduction abnormalities without any clinical signs. Weisman et al. (2013) reported the predictive profile of the conduction speed of individual nerves and combinations in the diagnosis of DSP, where the conduction speed in the peroneal and the sural nerve identified cases with sensitivities of 80% and 83% respectively, and 89% and 72% specificity, correspondingly. Furthermore, the sum of the F wave of tibial latency plus peroneal conduction speed, and the sum of 3 conduction speeds of the lower limb (sural peroneal and tibial) predicted a 4-year incidence with 79-81% sensitivity and 63-77% specificity.

There are other methods for pain and quality of life assessment, such as DN4 (*Douleur Neuropathique 4 Questions*) for pain, which boasts 95% sensitivity and 96.6% specificity (Unal-Cevik, Sarioglu-Ay & Evcik, 2010); the LANSS Pain Scale (*Leeds Assessment of Neuropathic Symptoms and Signs*) with 70.2% sensitivity and 96.6% specificity (Unal-Cevik, Sarioglu-Ay & Evcik, 2010; Bennet, 2001); and the McGill Pain Questionnaire (Burckhardt & Jones, 2003). Although these methods allow for a quick screening and personal assessment of pain in correlation to clinical findings, confirmation through tuning fork assessment, monofilament test or anatomic-specific pulse and reflex exploration should always be sought.

On the other hand, DAN assessment is recommended starting 5 years after diagnosis of DM1 (American Diabetes Association, 2014), surveying the following manifestations: Tachycardia at rest, exercise intolerance, orthostatic hypotension constipation, gastroparesis, erectile dysfunction, intolerance to hypoglycemia and sweating dysfunction (American Diabetes Association, 2014). The RINES-VALCARDI test (Chacín, Jatem & Rojas, 2009) is a diagnostic tool developed in Venezuela by Dr. Luis Chacín in 1981, wherein heart rate is registered with a conventional 12-lead electrocardiograph in 6 1-minute cycles: at rest, during deep inspiration, during expiration, while performing the Valsalva maneuver, and while softly massaging the left and right carotid sinuses (Figure 2). Results ≤15 points are compatible with cardiac DAN. Indeed, in comparison to non-diabetic subjects, diabetic individuals with RINES-VALCARDI scores ≤15 points presented greater frequency of postural hypotension (40%), loss of morning urinary urgency (53,3%), periodic nocturnal diarrhea (40%) and erectile dysfunction (44,4%) (Figuera et al, 1997). A new, less cumbersome version of the test has been recently proposed by the same research group (Chacín et al, 2009), which involves the utilization of a pulse oximeter for heart rate monitoring during each of the 6 cycles, registering this parameter at 0", 15", 30", 45" and 60". For each cycle, the difference between the highest and lowest values is calculated, and finally all 6 differences are added to obtain a final score. With this form of test, scores <27 points appear to detect cardiac DAN with 60.86% sensitivity, 86.61% specificity, 92.45% positive predictive value and 45.6% negative predictive value.

Regarding pharmacologic therapy of DN, a wide array of drugs with diverse mechanisms of action may be utilized, including (Attala et al, 2010): Inhibition of monoamine reuptake, calcium channel blockers N-Methyl-D-Aspartate receptor antagonists, Substance P-depleting agents, opioid agonists, GABA modulators, and NSAIDs. Indication of the drugs is issued in a progressive, stratified fashion including combinations, since monotherapy appears to offer relief to less than 50% of cases (Weisman et al, 2013). First-line medication includes (Vinik & Casellini, 2013): □2-□ agonists (pregabalin or gabapentin), serotonin-norepinephrine reuptake inhibitors (SNRI) (duloxetine) and tricyclic antidepressants (TCA). If pain management is inadequate or these are contraindicated, second-line treatment involves the following combinations (64): TCA with SNRI, TCA with □2-□ agonists or SNRI with □2-□ agonists. Finally, if control remains insufficient, an opioid is added into the combination. The corresponding efficacy rates and numbers needed to treat (NNT) are (Vinik, 2010): a) TCA OR 22.2 and NNT 1.5-3.5; b) Duloxetine OR 2.6 and NNT 5.7-5.8; c) Traditional Anticonvulsants OR 5.3 and NNT 2-9-4.3; and e) Opioids OR 4.3 and NNT 2.6-3.9.

According to the American Neurology Academy (Bril et al, 2011) and the Toronto Consensus Panel on Diabetic Neuropathy Management (Tesfaye et al, 2011), Level A of recommendation is Pregabalin (300-600 mg/day), whereas all other medication is considered Level B: Gabapentin 900-3600 mg/day, Duloxetine 60-120 mg/day, Amitriptyline 25-100 mg/day, Sodium Valproate 500-1200 mg/day, Tramadol 210 mg/day, and 0.075% Capsaicin cream. TCA are contraindicated in patients with glaucoma, orthostatic hypotension, overweight and cardiovascular disease. Duloxetine is contraindicated in subjects with hepatic disease, and □2-□ agonists

contraindicated in subjects with edema and weight gain (Bril et al, 2011).

Achievement of metabolic goals accompanied by possible reversibility of neural damage was observed in these cases, where patient reeducation, psychological therapy, adequate weight gain, adherence to insulin therapy, improvement of lipid profile and inclusion of physical activity in daily routine served as key components for restitution of the functional anatomy of nerve tissue. Evidence of neuropathic damage reversibility exists in contexts such as cachectic DN (Tesfaye et al, 2011), characterized by intense neuropathic pain and wasting syndrome associated with the initiation of insulin therapy and the sudden lowering of HbA1c (Weintrob et al, 1997). This clinical picture is accompanied by finings of nervous potential ablation and slower conduction speeds in both motor and sensitive nerves (Weintrob et al, 1997; Kihara et al, 1994). Although its pathophysiology is yet to be elucidated, Grewal et al. (2006) have described the first report of objective confirmation of damage reversibility through nerve conduction studies during pain crises within the cachectic phase, suggesting this reversion to be dependent on replenishment of neuronal normoxia.

It is well-known that the application of intensive insulin therapy allows for the restoration of intraaxonal sodium ion transit patterns, in turn improving action potential capacity (Sima & Brismar, 1985). Furthermore, the reversion of hyperglycemia-triggered damage in DN may also be associated with the restoration of myoinositol metabolism defects and sodium permeability gradients (Brismar, Sima & Greene, 1987). Although several mechanisms are involved in axonal damage (Sytze Van Dam et al, 2013), these specific components share the polyol pathway as an etiopathogenic element. Williamson et al. (Williamson et al, 1993) have proposed hyperglycemia to generate the same effects as ischemia through the sorbitol pathway – termed hyperglycemic pseudohypoxia– such as an elevation of the NADH/NAD^+ ratio, which induces electric, mechanic and vascular dysfunction with a consequent rise in lactate production. Moreover, it has been reported that the main mediator of oxidative neuronal damage is Aldose Reductase (AR), a key enzyme in the polyol pathway (Chung et al, 2003).

The increase of NADH due to AR and its consequent redox imbalance augment diacylglycerol synthesis and Protein Kinase C activity, leading to lowered Na^+/K^+ ATPase pump activity, myoinositol depletion, induction of prostaglandin synthesis, and production of reactive oxygen species and nitric oxide (Brismar, Sima & Greene, 1987). Moreover, this state of pseudohypoxia may trigger the expression of HIF-1 through nitric oxide acting on the genetic regulation of this protein (Marfella et al, 2002), enabling its participation in aberrant angiogenesis, a classic feature found in diabetic patients (Kota et al, 2012). Because AR is predominantly expressed in Schwann cells (Tomlinson & Gardiner, 2008), this aspect of neuropathic damage does not begin in neurons themselves, but rather in their myelination and support cellular system.

Considering this succession of cellular and clinical events, a possible interventional window may be outlined, wherein the main source of damage leading to conduction impairment first appears in Schwann cells (Zenker, Ziegler & Chrast, 2013); with this state of refractoriness and/or sodium gradient alteration being sufficient to modify axonal conduction patterns and “stunned” neurons, before the onset of overt clinical manifestation (Arnold et al, 2013). This phenomenon may also be observed in autonomic nerves, as reported by Kiyono et al. (2005) who found that a progressive potentiation of the polyol pathway induces sympathetic fiber dysfunction, associated with down-regulation of norepinephrine transporters, a loss of cardiac neuroautonomic control. The early detection of the neuropathic phenomenon and adequate, quick and precise control of hyperglycemia may allow for reversion of the events previously described, by rescuing neurons from stunning and impeding the development of the irreversible histopathologic changes seen in DN.

In conclusion, because DN is one of the most concerning complications – owing not only to its complex pathophysiology, but also to its booming incidence in the last decade (Mohsin et al, 2005) – early detection, strict glycemic control and management of amplifying factors are extremely valuable tools in order to delay progression and potentially favor reversibility of this disease.

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Disclosure

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