

Sensory Neuropathy Associated with Glucose Intolerance: A 35 Patients Study

Giseli Quintanilha, Osvaldo J.M. Nascimento, Marco Orsini and Camila Pupe
Neuroscience/Neurology Program, Federal Fluminense University, Niteroi-RJ, Brazil

Abstract: Problem statement: Peripheral neuropathy due to diabetes has been studied for several decades. Until recently, we associate the involvement of peripheral nerves with an inappropriate glycemic control in the most advanced stages of the disease. Currently, it is considered that the onset of the neural injury can occur in the initial phase of this metabolic abnormality, during the period of glucose intolerance. **Approach:** The clinical aspects of the sensory neuropathy associated to the impaired glucose tolerance were analyzed in 35 Brazilian patients. All patients met the American Diabetes Association (ADA) and the World Health Organization (WHO) criteria for glucose intolerance. **Results:** We studied 20 male and 15 female, with a mean age of 62.5, ranging from 30-83 years. A distal symmetrical lower limb involvement with positive (neuropathic pain) and/or negative (reduced temperature and pinprick sensations) symptoms and clinical signs of autonomic neuropathy were seen in most patients. The glycemic levels were not related to the severity of the symptoms or to the presence of any specific symptom. **Conclusion:** The Impaired Glucose Tolerance (IGT) neuropathy can be included in the chronic axonal polyneuropathy and usually the patients suffer from chronic pain and disability before the diagnosis. The determination of the prevalence of symptoms is essential to recognize this disease. The early diagnosis and the aggressive treatment can be crucial for the control, development and progression of the small fiber neuropathy in glucose intolerant patients.

Key words: Peripheral neuropathy, small fiber neuropathy, Impaired Glucose Tolerance (IGT), American Diabetes Association (ADA), World Health Organization (WHO), Diabetes Mellitus (DM)

INTRODUCTION

The alterations of glycemic metabolism, whether they cause transitory hyperglycemic states or reduced glucose tolerance, have been noticed as an important isolated risk factor for the development of cardiovascular diseases, retinopathy and neuropathies (Nichols *et al.*, 2008; Dick *et al.*, 2007). These morbidities are traditionally related to the severity and chronicity of the glycemic decompensation (World Health Organization, 1999). Glucose intolerance is considered a stage of the metabolic degeneration that leads to diabetes (Smith and Leroith, 2004). Current studies about glucose metabolism alterations lead us to believe that glucose intolerance can cause lesion to the peripheral nerves (Novella *et al.*, 2001). The aim of the present study is to determine in a consecutive series of patients with reduced glucose tolerance and peripheral neuropathy the prevalence of the clinical manifestations.

MATERIALS AND METHODS

Thirty-five patients were examined and their history reviewed for inclusion in the study. All patients presented sensory neuropathy and their laboratorial profiles were compatible with the diagnosis of glucose intolerance. Patients with associated diseases such as diabetes mellitus, alcoholism, HIV or HTLV-1 infections, rheumatic diseases, or with toxin, drug-induced or hereditary neuropathies were excluded from the study.

The positive sensory symptoms were classified such as burning pain or dysaesthesia and the negative symptoms were expressed as hypoesthesia. A bedside autonomic examination was performed in all patients. Special attention was given to impaired peripheral vasodilation postural hypotension (associated or not to chronotropic variations) and pupillary reflex alterations.

The laboratory investigation included fast plasma glucose and 2 h glucose during a 75 g of oral glucose tolerance test; serology for hepatitis B and C, HIV 1

Corresponding Author: Osvaldo Nascimento, Neuroscience/Neurology Program, Federal Fluminense University, Niteroi-RJ, Brazil

and 2 and HTLV 1 and 2, collagen disorders investigation, serum levels of B12 vitamin, folate, thyroid function tests and protein immunoelectrophoresis. All patients were submitted to sensory and motor neuroconduction procedures. OGTT is the measurement of plasma (or blood or serum) glucose concentrations after a standardized metabolic stress test, such as the 75 g oral glucose, according to the ADA protocol. The sensory and motor neuroconduction procedures were assessed by the distal motor latency and the amplitude of conduction velocity of median-peroneal and ulnar motor nerves. Moreover, the latency of the median-ulnar and the amplitude of the sural nerve were analyzed.

Statistical analysis related to the clinical parameters was performed by means of proportions and frequency distributions. All statistical comparisons were made using parametric tests (Student T-Test) and non-parametric tests (Mann-Whitney or Kruskal-Wallis) for the age and race parameters.

RESULTS

Twenty female patients (57.1%) and 15 male patients (42.9%) were included, out of which 29 were white (82.9%), five were black (14.2%) and one was Asiatic (2.9%). Most of patients (31-89.0%) presented positive symptoms (pain and/or paraesthesia), while 7 patients (20.0%) presented negative symptoms.

The signs and symptoms were symmetrical in 77.1% of the patients and asymmetrical in 22.9% of the patients (Fig. 3). Thirty-two patients (91.4%) had complaints related to neuropathic pain (burning and or shock sensation). Only three patients did not referred pain (8.6%). Clinically defined autonomic involvement was verified in eleven patients (31.4%) what was not observed in the remaining twenty-four patients (68.6%). The most common clinical presentation was a small fiber neuropathy encountered in 27 patients (77.1%). The other eight patients (22.9%) presented symptoms suggesting associated involvement of large fibers.

The lowest fasting glycemia was 77 mg dL⁻¹ and the highest 125 mg dL⁻¹, being the glycemic level average 104.2 mg dL⁻¹ with a standard deviation of 9.68. The majority of the patients presented fasting glycemia between 100 and 110 mg dL⁻¹. The lowest glycemia at OGTT was 148 mg dL⁻¹ and the highest 197 mg dL⁻¹ being 171.8 mg dL⁻¹ the average, with a standard deviation of 13.1. Most of the patients had an OGTT glycemia between 170 and 180 mg dL⁻¹ (Fig. 1).

The electrodiagnostic results were abnormal in 19 patients (54.3%), most of which with an axonal

polyneuropathy pattern. Sixteen patients had normal neuroconduction (45.7%). The axonal and symmetrical polyneuropathy was the pattern more prevalent (68.0%) followed to multiple mononeuropathy patterns. Only two patients (11.0%) presented with alterations suggestive of bilateral carpal tunnel syndrome.

The patients with positive signs presented higher fast glycemic levels (105.4 mg dL⁻¹) than the patients with negative symptoms (97.8 mg dL⁻¹), although there was no statistical significance (Fig. 2). The symmetrical clinical presentation was more prevalent in comparison with asymmetrical presentation in patients with abnormal fast glycemia as well as in those with glucose intolerance. These findings were more expressive in the last group with a statistical significance (p = 0,046; Fig. 3). There was a mild tendency for the higher fast glycemia levels as well as in OGTT in patients with autonomic involvement, although there was no statistical significance.

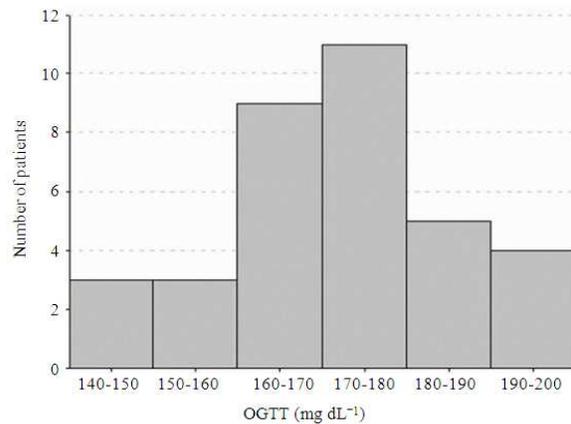


Fig. 1: Frequency distribution of patients regarding the level of OGTT glycemia

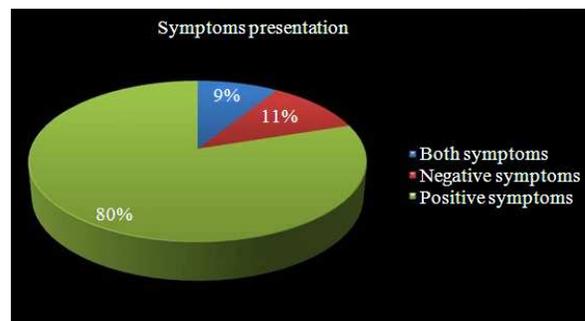


Fig. 2: Percentage of symptoms presentation in neuropathic patients

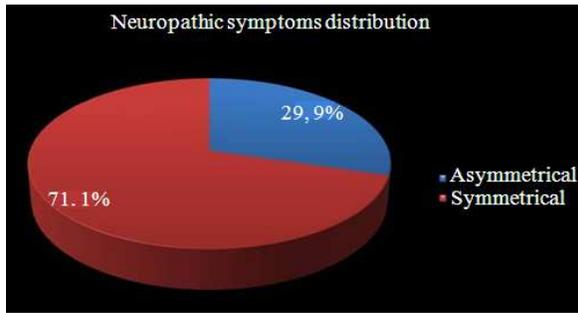


Fig. 3: Percentage of asymmetrical and symmetrical distribution of symptoms in neuropathic patients

The patients with abnormal neuroconduction have a highest glycemic index, in high level OGTT, although there is no statistical significance. Among these patients with abnormal neuroconduction, the electrophysiological patterns described were not correlated to the fasting glycemia levels. However, there was a significant statistical difference ($p < 0.05$), in post-OGTT glycemia according to the neuroconduction findings classification group ($p = 0.020$). The patients with multiplex mononeuropathy seem to present lower indexes, with statistical significance, despite the small sample (4 cases), $p = 0.006$.

DISCUSSION

In this study the presence of painful symptoms cannot be related to the glycemic fast levels and neither to the obtained OGTT levels. However, there was a noticeable tendency to glycemic higher levels in the small group of patients in which pain was not referred. The glycemic levels were also higher in the few patients who complained of negative symptoms.

The prevalent symptom in our sample was pain, reported by 91.4% of the individuals. Other authors observed the same prevalence evaluating patients with chronic sensory painful neuropathy (Green *et al.*, 2010; Sumner *et al.*, 2003). Novella *et al.* (2001), analyzed a group of seventy-six sequential patients that presented Impaired Glucose Tolerance (IGT) or diabetes, defined by OGTT and idiopathic sensory neuropathy looking for positive symptoms and observed that 65.0% of the patients with painful neuropathy had alterations in their glycemic metabolism and out of these 55.5% presented IGT. In our group of patients there was also unequivocal prevalence of positive symptoms.

In our patients the neuropathy was associated with reduced glucose tolerance and with a symmetric sensory clinical pattern, mainly involving small fibers. Positive symptoms as neuropathic pain and autonomic

symptoms were predominant. Green *et al.* (2010) suggested a contribution from the IGT to the development of small fiber neuropathy. These authors studied a sample of 72 patients with an idiopathic sensory neuropathy. Out of these patients there were 50.0% with OGTT compatible with IGT and 18.0% compatible with Diabetes Mellitus (DM). Neuropathic pain was significantly more common in the subgroup with IGT when compared to individuals with normal OGTT ($p < 0.025$). That study, however, did not exclude the individuals that had a familiar history of neuropathy, while our study does not considered patients with a family history.

The glycemic fasting levels in 8 patients varied from values considered normal, to even in values within the interval classified as fasting hyperglycemia. These findings points to the importance of the two dosages, fasting glucose and OGTT in order to diagnose the alterations of the glycemic metabolism.

In our sample, the glycemic levels could not be associated to the severity of the neuropathy or with the presence of certain specific signals/symptoms. The reviewed studies did not referred to the glycemic levels in pre-diabetic patients and the clinical presentation. However, many studies associated the severity of the diabetic neuropathy symptoms to glycemic control (Llewelyn *et al.*, 2005; Vinik and Mehrabiyan, 2004). In addition, most of patients clinically presented a small fiber neuropathy emphasized with the normal neuroconduction/EMG studies. Although some trials shows abnormalities in sensory latency and amplitude in median-ulnar and sural nerves (Sahin *et al.*, 2009).

The inclusion of the OGTT in the screening of sensory neuropathies, even in cases with fasting glycemic levels less than 100 mg dL^{-1} , can reduce the number of neuropathies previously considered idiopathic and allows early treatment of the metabolic state before the appearance of irreversible lesion of the peripheral nerves. Despite that, the diagnosis of glycemic disorder in a stage that is possible to prevent progression to DM can result in less morbidity, since evidences points to a clear association between precocious stages of insulin resistance and the beginning of the pathogenic process that does not only involve the peripheral nerve, but also other target organs.

Most neuropathies associated to IGT can be classified in the group of small fiber neuropathies being pain the prevalent symptom. Reversion to a euglycemic state is observed in patients with IGT, therefore it is necessary to observe the degree of reversibility of the neuropathy after the improvement of the metabolic state.

CONCLUSION

An investigation of metabolic alterations related to glucose can clarify several sensory peripheral neuropathy cases misdiagnosed as having idiopathic neuropathy. The early diagnosis and the aggressive treatment can be crucial for the control, development and progression of the small fiber neuropathy in glucose intolerant patients. If this approach is not followed the patient's condition can evolve to diabetic sensory neuropathy. Further studies with a large sample of patients would be essential for establishing a relationship between polyneuropathy and IGT and setting the involvement of small and large nerve fibers.

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