Diabetic cardiovascular autonomic neuropathy

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Cardiovascular autonomic neuropathy (CAN) is one of the most overlooked of all serious complications of diabetes mellitus (DM), which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. The patient's history and physical examination are not effective for early detection of autonomic nerve dysfunction, and thus is important for identify early stages of CAN with an easily available tool, which are non-invasive cardiovascular reflex test. CAN is frequently associated with distal symmetric polyneuropathy (DSP), but are few available electrophysiological data about the relationship between CAN and DSP.

The general part consists of three chapters addressing issues regarding epidemiology, pathophysiology of diabetic neuropathy, and on clinical manifestations, clinical implications, diagnosis and staging of CAN and DSP.

The first study designed to evaluate the presence of CAN on 149 patients with type 2 DM. This study was composed of four substudies.

The first substudy evaluated the prevalence, symptomatology and association between CAN and vascular risk factors, microvascular and macrovascular complications. **Results:** The prevalence of CAN was 38,9%. In the early stages patients were asymptomatic, and in advanced stages the most common symptoms were gastrointestinal and cardiovascular. In the group with NAC duration of diabetes was higher, glycemic control was poor, patients had higher body mass index (BMI), higher blood pressure (BP) and were more oftn smokers. Univariate logistic regression analysis showed that NAC was in dependent manner associated with longer diabets duration, younger age at onset, presence of retinopathy, DSP and smoking. Multivariate logistic regression analysis showed that the risk of NAC was significantly higher with longer diabetes duration, younger age at the onset of diabetes, poor glycemic control, high cholesterol level, smoking, with increasing BMI and the presence of DSP. **Discussion** of the results revealed similarities and discrepancies betwee similar studies. Our results were consisitent with those obtained in the most previous studies, showing that the poor glycemic control, diabetes duration and coexistence with traditional cardiovascular risk factors (hypertension, smoking, obesity, hypercholesterolemia) are accompanied by appearance of CAN. Existence of CAN was correlated with existence of other microvascular and macrovasclar complications. **Conclusions** reaffirm the link between glycemic control, duration of diabetes, systolic BP, lipid profile, obesity and its distribution, as well as between the existence of CAN and other micro-and macrovascular complications.

In the second substudy evaluated in the same group of patients the link between severity of CAN and severity of other microvascular (DSP, retinopathy) and macrovascular complications (carotid and peripheral atherosclerosis). **The results** showed the existence of statistically significant correlations between the severity of damage of the cardiac autonomic system and the severity of DSP confirmed by electrophysiological study, respectively between the severity of CAN and severity of diabetic retinopathy. The same statistically significant correlations were obtained between severity of CAN and the severity of atherosclerosis on the carotid artery (measured by intima-media thickness) and in the peripheral vascular vessels (measured by ankle-brachial index). **Discussion** have reviewed data from the literature on similar studies, which are relatively few in number. Our reported results are consistent with those previously reported, and the explanations of these correlations between the existence of CAN and other microvascular and macrovascular complications can be explained by poor glycemic control and the duration of diabetes, which are "universal" risk factors for the development and progression of all diabetic complications. **Conclusions** highlighted the need to conduct a complete screening of all diabetic complications, especially in patiens who are detected with CAN, and diagnosis of one diabetic complication requires mandatory screening for detection and other micro- and macrovascular diabetic complications.

In the third substudy we evaluated effects of patient age, duration of diabetes, the existence NAC, diabetic retinopathy and macroangiopathy on electrophysiological parameters that assess function of motor and sensory fibers. **The results** showed that the amplitude of the motor action potential (MAP) and of sensitive action potential (SAP) in all examined nerves correlate negatively with the duration of diabetes and glycemic control. The strongest correlation was between diabetes duration and amplitude of MAP on peroneal nerve, respectively amplitude of SAP on the sural nerve. It was noted that in the group of patients with CAN, amplitude of MAP and of SAP as well as motor and sensory conduction velocity was significantly reduced. Age of patients, the existence of retinopathy, carotid and peripheral atherosclerosis did not influence the electrophysiological parameters of motor and sensory nerves. The discussions reiterated that poor glycemic control and duration of diabetes are major risk factors for impaired motor and sensory fiber functionality. Axonal degeneration is the primary mechanism of impairment of motor and sensory nerves in diabetes and their damage is dependent on the length of each nerve. In addition, impaired motor and sensory fibers is concomitant and with autonomic fibers, that demonstrate that there is no difference in vulnerability between fibers thick, fine motor and sensory myelinated and thinly myelinated autonomic fibers. **The conclusions** have pointed out that damage is concomitant in the autonomic, motor and sensory fibers in DM and the role of risk factors involved in the emergence of two complications of diabetes.

In the fourth substudy we assessed the link between electrophysiological parameters of motor and sensory fiber function and the parameters of autonomic parasympathetic function in patients with type 2 DM, in order to detect which of the three tests of heart rate variability (HRV) could be used additional to subsequent nerve conduction study for early detection of CAN. **The results** showed that HRV during deep breathing (HRV DB) and HRV during Valsalva were strongly correlated with amplitude of MAP. Amplitude of SAP in all evaluated sensory nerves correlate with HRV DB. Other electrophysiological parameters (distal latency and conduction velocity) were not correlated with HRV test results. **Discussions** of this substudy were linked to explain the correlations detected between HRV and electrophysiological tests for motor and sensory function assessment, noting that this study is unique study today, no similar studies reported in the literature. HRV DB compared to HRV Valsalva correlated most strongly with both amplitude of MAP and of the SAP, parameters reflecting motor and sensory fibers function in diabetes. The findings of this substudy stressed that HRV DB is a useful test, more predictable to detect parasympathetic dysfunction and can be used as a screening test for CAN detection in diabetic patients.

The second study was designed to evaluate the presence of CAN on 30 patients with type 1 DM. Results: The prevalence of CAN was 70%. Autonomic symptoms were the most common gastrointestinal combination followed by combination of gastrointestinal and cardiovascular symptoms. The correlation between the presence of symptoms and severity of cardiovascular damage was observed only in advanced stages of CAN. In the group of patients with CAN we noted that the duration of diabetes was higher and glycemic control (measured by HbA1c levels) was more deficient. There were statistically significant differences on those with CAN regarding the existence DSP, retinopathy, reduced glomerular filtrate rate and increased IMT. No differences were observed between the two groups with regard to the existence of traditional cardiovascular risk factors. Univariate and multivariate analysis showed that the risk of CAN increases with age of patients, with poor glycemic control, duration of diabetes and with the existance of DSP. **The discussions** presented our results compared with those previously reported studies conducted on patients with type 1 DM and explained the primary role of chronic hyperglycaemia and diabetes duration in CAN development. It has also been explained the association observed between the presence of CAN and DSP, retinopathy and carotid atherosclerosis. The findings of this study pointed out that traditional cardiovascular risk factors are not implicated in the CAN development in type 1 DM and glycemic control as close to normal is only effective measure in preventing the development of this complication.

The third study was designed as a comparative study of risk factors for CAN in type 1 and in type 2 DM, and also to evaluate the link between CAN and micro-, macrovascular complications in the 2 groups. **Results**: In both groups of patients the risk of having CAN increased with patients age, duration of DM and with poor glycemic control. Cardiovascular risk factors have influenced the emergence of CAN only in patients with type 2DM, without exerting any influence on patients with type 1 DM. Regarding complications, in both groups showed a strong association between CAN, DSP, retinopathy and carotid atherosclerosis. The findings of this study pointed out the similarities and differences observed between CAN in type 1 and type 2 DM, respectively. Underlined the central role of hyperglycemia as potentially modifiable factor in the emergence of CAN in both types of DM.