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REVIEW ARTICLE

Autonomic Nervous System and Type 2 Diabetes Mellitus

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ABSTRACT

Diabetes mellitus has now assumed epidemic proportions in many countries of the world. With the present population of 19.4 million diabetics, and approximately 60 million by the year 2025, India would rank first in its share of the global burden of diabetes. The autonomic nervous system (ANS) is an extensive neural network whose main role is to regulate the milieu intérieur by controlling homeostasis and visceral functions. Diabetes mellitus is most commonly associated with autonomic dysfunction, in persons with diabetes; prolonged hyperglycemia leads to degradation of the microvasculature, leading to a specific form of autonomic dysfunction firmed "Diabetes Autonomic Neuropathy". The diagnosis of Autonomic Neuropathy is often difficult to establish in individuals, since clinical symptoms generally appear late in the course of the disease and may be nonspecific, Early detection of Autonomic Neuropathy would suggest the need for an aggressive approach in the management of diabetes mellitus with the help of simple autonomic function test.

Keywords: Autonomic nervous system, Autonomic neuropathy, Diabetes autonomic neuropathy, Diabetes mellitus.

1. INTRODUCTION

Sympathetic and parasympathetic innervations in the heart play a major role in the regulation of cardiac function. The existence of sensory nerve endings in the heart was first suggested in 1894 [1], although Wollard [2], in 1926, concluded that a large portion of cardiac sensory endings were of vagal origin. Indeed, Wollard [2] observed that an experimental bilateral stellectomy did not markedly modify what he considered to be the normal aspect of the sensory supply to the heart. Subsequently, Holmes [3] observed survival of the 'terminal nervous network' after vagotomy, thus hypothesizing that sympathetic afferent fibres were likely to be implicated. In 1963, Khabarova [4] observed that "afferent fibers of spinal type innervate the same regions and layers of the heart as the vagal fibers, and their afferent fibers and endings frequently lie side by side with afferent fibers and endings of the vagus nerve". This opinion has the merit of agreeing with the electrophysiological findings.

Autonomic nervous system

The Autonomic Nervous System is a division of the peripheral nervous system that controls automated body functions including Heart Rate, Blood pressure, digestion, and Metabolism. Autonomic Nervous system maintains internal homeostasis of cardiovascular, thermoregulatory, gastrointestinal, genitourinary, exocrine and pupillary functions.

It was originally thought that Autonomic Nervous system functions autonomously but actually it is under the control of different center in the brain especially the hypothalamus and medulla oblongata that receive inputs from the limbic system and other regions of the cortex. The autonomic nervous system is amazingly extensive and is involved in the function of virtually every organ system (5). Therefore, the clinical manifestations of autonomic dysfunction can be quite diverse in nature (6). Indeed; the autonomic nervous system may be involved in virtually all

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3 diseases. Any structural pathologic process affecting the brain (whether infectious, inherited, neoplastic or degenerative in nature) may result in an autonomic syndrome (7). Since each of these disorders all result from some form of disturbance in normal autonomic function, it would seem appropriate to briefly (and simply) review some aspects of its structure and operation. This brief review focuses principally on autonomic regulation of cardiovascular system in diabetes mellitus. Because myocardial infarction in diabetic patients usually is more extensive and more severe than in nondiabetic patients (8, 9, 10).

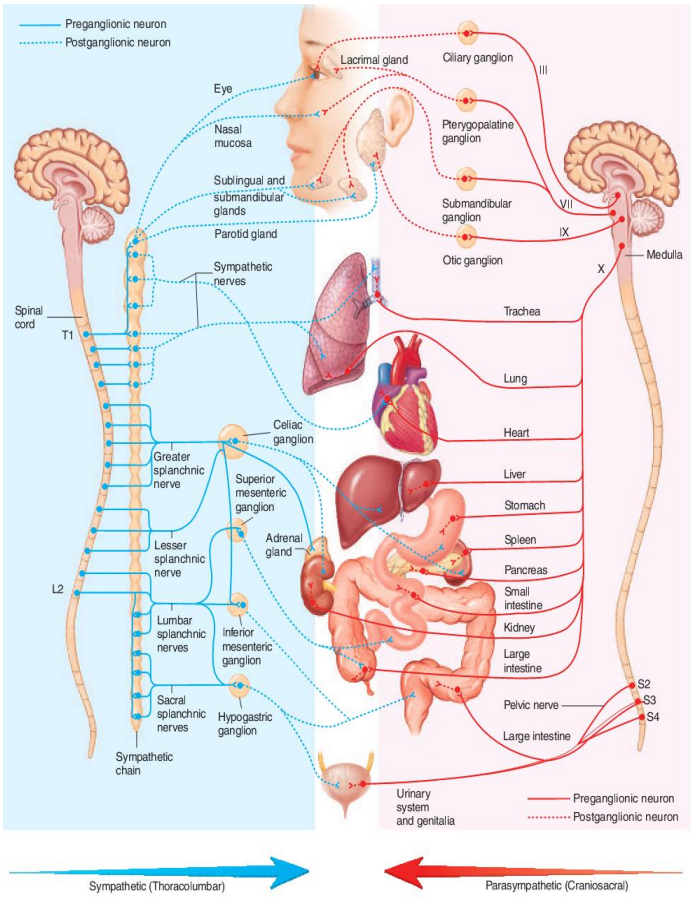

Figure-1 : Innervation of organs by autonomic nervous system

Diabetes Mellitus

Diabetes mellitus (DM), long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century [11].].

DM is a heterogenous group of disorders characterized by high blood glucose levels [12]. Type 2 diabetes is a chronic progressive disorder with increasing worldwide prevalence. India and other countries in Asia are experiencing rapidly escalating incidence of diabetes.It is the most common non communicable disease worldwide and the fourth to fifth leading cause of death in developed countries [13]. The global figure of people with diabetes is set to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025 [14]. Developing countries such as India have had the maximum increases in the last few years. The current prevalence of type 2 diabetes is 2.4% in the rural population and 11.6% in the urban population of India. It has been estimated that by the year 2025, India will have the largest number of diabetic subjects in the world [14]. It is predicted that by 2025 India will have >60 million diabetic; in other words, one in five diabetic patients in the world will be an Indian and this would be the leading cause of death in adults.

Autonomic nervous system and diabetes mellitus

The autonomic nervous system is primarily efferent, transmitting impulses from the central nervous system to peripheral organs. However, it also has an afferent component. Its two divisions — the parasympathetic and the sympathetic nervous systems — work in balanced opposition to control the heart rate, the force of cardiac contraction, the dilatation and constriction of blood vessels, the contraction and relaxation of smooth muscle in the digestive and urogenital systems, the secretions of glands, and pupillary size. Neuropathy is one of the most common complications of diabetes. About half of all people with diabetes have some degree of neuropathy, which can be polyneuropathy, mononeuropathy, and /or autonomic neuropathy. Mononeuropathy is less common than polyneuropathy and includes dysfunction of isolated cranial or peripheral nerves. Autonomic neuropathy can involve multiple systems including cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic syndrome (15). Diabetic autonomic neuropathy (DAN) is a stealthy complication of diabetes, developing slowly over the years and quietly robbing diabetic patients of their ability to sense when they are becoming hypoglycemic or having a heart attack. DAN is among the least recognized and understood complication of diabetes, despite its significant negative impact on survival and quality of life in people with diabetes [16, 17] it impairs the ability to conduct activities of daily living, and increases the risk of death. It also accounts for a large portion of the cost of care (18). The metabolic disorders of diabetes lead to diffuse and widespread damage of peripheral nerves and small vessels. Diabetes can cause dysfunction of any or every part of the autonomic nervous system, leading to a wide range of disorders. And these are serious: among the most troublesome and dangerous of the conditions linked to autonomic neuropathy are known or silent myocardial infarction (MI), cardiac arrhythmias, ulceration, gangrene, and nephropathy.

Autonomic neuropathy is also associated with an increased risk of sudden death. One of the most overlooked complications of diabetes is CAN [19]. CAN results from damage to the autonomic nerve fibres that

innervate the heart and blood vessels and it causes abnormalities in heart rate control and vascular dynamics [20]. Reduced heart rate variation is the earliest indicator of CAN [21] the link between diabetes mellitus and CVD (cardiovascular disease) is well established and recognized. Recently, in the National Cholesterol Education Program (NCEP), diabetes has been considered a factor for cardiovascular risk development [22]. Thus it is recommended that greater precautionary measures, similar to those for established CVD, should be taken in patients with diabetes. These changes are based on findings showing that CVD occurs at a significantly higher rate in individuals with diabetes than in the general population [23–25] In particular, the Nurse's Healthy Study has provided evidence of increased risk of CVD events before diagnosis of diabetes, with risk levels increasing further after diabetes diagnosis [23] compared with non diabetic individuals, patients with diabetes carry a greatly increased risk not only of sustaining cardiovascular events, but also of poor outcomes associated with CVD. Several studies have provided evidence for an increased mortality risk among diabetic individuals with CAN compared with individuals without CAN [26,28] A study by O'Brien et al. [27] reported 5 year mortality rates of 27% in patients having asymptomatic autonomic neuropathy compared with an 8% mortality rate in diabetic subjects with normal autonomic function tests.

Rathmann et al.[28] reported the results of a study designed to assess the risk of mortality due to CAN among patients with CAN but without a clinical manifestation of severe complications (proteinuria, proliferative retinopathy, coronary heart disease or stroke) 8 years after their first clinical examination. Impairments in the autonomic nervous system may also con-tribute to the pathogenesis of diabetic nephropathy and cardiovascular disease. Autonomic neuropathy is also an independent risk factor for stroke (29)

Mortality rate

Of patients with symptomatic autonomic dysfunction, 25% to 50% die within 5 to 10 years of diagnosis. (30,31) The 5 year mortality rate in patients with diabetic autonomic neuropathy is three times higher than in diabetic patients without autonomic involvement(32).Leading causes of death in diabetic patients with either symptomatic or asymptomatic autonomic neuropathy are heart disease and nephropathy.

Clinical features of autonomic neuropathy

Diabetes can cause dysfunction of any or all parts of the automomic nervous system, leading to a wide range of disorders.

- Decreased diameter of dark adapted pupil
- Argyll-Robertson type pupil
- Hypoglycemia unawareness
- Hypoglycemia unresponsiveness
- Cardiovascular Tachycardia, exercise intolerance
- Cardiac denervation
- Orthostatic hypotension
- Heat intolerance
- Neurovascular Areas of symmetrical anhydrosis
- Gustatory sweating
- Hyperhidrosis
- Alterations in skin blood flow
- Constipation
- Gastroparesis diabeticorum
- Diarrhea and fecal incontinence
- Esophageal dysfunction
- Genitourinary
- Erectile dysfunction
- Retrograde ejaculation
- Cystopathy
- Neurogenic bladder
- Defective vaginal lubrication

Autonomic function tests

Autonomic function tests are reliable, reproducible, simple, quick to carryout and all non invasive. In the early 1970s, Ewing et al. proposed five simple noninvasive cardiovascular reflex tests that have been applied successfully in many studies (work reported in 1985 [33]). Simple noninvasive cardiovascular reflex tests have now become the gold standard by which an autonomic neuropathy is diagnosed objectively and by which other tests are judged.

Heart rate tests	Normal	Borderline	Abnormal
Heart rate response to deep breathing (maximum minus minimum heart rate)	≥ 15 BPM	11-14 BPM	≤ 10 BPM
Heart rate response to standing up (30:15 ratio)	≥ 1.04	1.01-1.03	≤ 1.00
Heart rate response to valsalva manoeuvre (valsalva ratio)	≥ 1.21	--	≤ 1.20

Table: 1. cardiovascular autonomic function tests with values (parasympathetic test)

Blood pressure tests	Normal	Borderline	Abnormal
BP response to standing up (fall in SBP)	≤ 10 mmHg	11-29 mmHg	≥ 30 mmHg
BP response to sustained handgrip (increase in DBP)	≥ 16 mmHg	11-15 mmHg	≤ 10 mmHg

BP: Blood pressure, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

Table: 2. cardiovascular autonomic function tests with values (sympathetic test)

It needs to have acceptable and defined reproducibility and there should be a clear distinction between normal and abnormal tests.

The aims of laboratory assessment of autonomic function includes

1. To detect the presence of autonomic failure
2. To quantify the severity and the type of deficit
3. To determine the distribution of autonomic failure
4. To determine the site of the autonomic lesion
5. To detect the presence of altered sympathetic effect.

ROUTINE AUTONOMIC FUNCTION TEST

a. autonomic reflex screen.

1. Quantitative sudomotor axon reflex test distribution.
2. Orthostatic blood pressure and heart rate response to tilt.
3. Heart rate response to deep breathing.
4. Valsalva ratio.
5. Beat to beat blood pressure to the Valsalva manoeuvre, tilt and deep breathing.

b. reflex sympathetic dystrophy screen.

1. Thermographic skin temperature distribution.
2. Comparative resting sweat output study.
3. Comparative quantitative sudomotor axon reflex test study.

In the report and recommendations of the San Antanio consensus conference on diabetic neuropathy in 1988 it was agreed that five simple non invasive tests were most useful to study cardiovascular reflex activity (34). Three tests, the heart rate response to Valsalva manoeuvre, deep breathing, standing up, are based on beat to beat measurement on heart rate changes, while the other two tests, the responses to blood pressure response to standing and sustained handgrip, depend on conventional indirect blood pressure measurements with cuff and stethoscope. Additional stresses like tilting, coughing, squatting, and apnoeic face immersion have been proposed from time to time, but advantages of these tests have never been demonstrated(35,36).

Power spectral analysis of heart rate and blood pressure variability has become a tool to explore neural regulatory mechanisms (37, 38).

But the following established autonomic function tests have been well standardized and accepted

1] Resting heart rate

> 100 beats/minute is abnormal

2] Heart rate variation during deep breathing

- The subject in lying down position was asked to breath quietly and deeply at a rate of six breaths per minute [five seconds inspiration and five seconds expiration for every breath].
- Heart rate response to deep breathing is a sensitive laboratory measure to assess vagal heart- rate control (35)
- A difference in heart rate of less than 10 beats/minute is abnormal.

Expiration: inspiration R-R ratio > 1.17 is abnormal

3] Heart rate response to standing [30:15 ratio]

This test was performed with the subject lying down quietly on the bed for about five minutes and then was asked to stand up unaided quickly, The R-R interval is measured at beats 15 and 30 after the patient stands, A 30:15 ratio of less than 1.00 is abnormal. R-R intervals appears to be more physiological, since it more directly reflects cardiac autonomic outflow (39, 40)

4] Heart rate response to Valsalva manvoeuvre. [Valsalva ratio]

The patient forcibly exhales into the mouthpiece of a manometer,exerting a pressure of 40 mm Hg for 15 seconds.

The result will be calculated from the following formula:-

$$\frac{\text{Longest R.R interval after the strain (phase IV)}}{\text{Shortest R.R interval during the strain (phase II)}}$$

A ratio of longest to shortest R-R interval of less than 1.2 is abnormal

5] Blood pressure response to standing.

[Postural change in blood pressure]

Systolic blood pressure is measured when the patient is lying down and 2 minutes after the patient stands. A fall of more than 30 mm Hg is abnormal

6] Blood pressure response to sustained hand grip exercise

The patient squeezes a handgrip dynamometer to establish his or her maximum the patient then squeezes the grip at 30% maximum for 5 minutes. A rise of less than 16 mm Hg in the contralateral arm is abnormal

7] Electrocardiography

A QTc of more than 440 ms is abnormal Depressed very low frequency peak or low frequency peak indicate sympathetic dysfunction Depressed high frequency peak

indicates parasympathetic dysfunction Lowered low frequency/high-frequency ratio indicates sympathetic imbalance.

8] Neurovascular flow

Noninvasive laser Doppler measures of peripheral sympathetic responses to nociception

CONCLUSION

Most diabetes complications can be prevented if the glycemic status of patients with diabetes can be maintained within a nearly normal range however, diabetes complications can develop despite intensive glycemic control, poor glycemic control also plays a central role in the development and progression of autonomic dysfunction. If one could identify the contributing factors, early detection of cardiac autonomic neuropathy and prompt intervention would be clinically meaningful for the prevention of adverse cardiovascular outcomes in patients with type 2 diabetes. Early detection of Autonomic Neuropathy would suggest the need for an aggressive approach in the management of diabetes mellitus to reduce mortality and morbidity in these patients.

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