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Case Report

Cardiac Autonomic Neuropathy in Type 1 Diabetes Mellitus: A Case Report

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Abstract

Cardiac Autonomic Neuropathy (CAN) is a well-recognized complication of diabetes mellitus that affects both type 1 and type 2 diabetic patients. Its clinical presentation can be subtle and early detection is of utmost importance for effective management and prevention of adverse cardiovascular outcomes. We report the case of a 25-year-old male with an 8-year history of type 1 diabetes who presented with dizziness, worse on standing, together with resting and orthostatic tachycardia. Several autonomic function tests have been described in literature to confirm the presence and severity of CAN. However, in an emergency medicine setting common causes of tachycardia (some of them quite critical) must be excluded before attributing tachycardia to autonomic dysfunction secondary to diabetes. That said, CAN must always be considered in diabetic patients with relevant clinical presentation as a rule-out diagnosis. This is particularly important in view of the detrimental cardiovascular sequelae for the patients. In addition, prompt diagnosis of CAN can have a significant impact on patient's management by triggering optimization of their diabetic control and offering treatment that can alleviate their symptoms. CAN is an admittedly challenging complication of diabetes, with multi-factorial pathogenesis, and largely under-diagnosed with few cases in literature. Further research is needed to enhance our understanding of CAN and to develop early tools for effective diagnosis of diabetes complication. Thus, raising awareness among clinicians for this medical entity can prompt early consideration in our differentials and optimal treatment for the patients.

***Keywords:** Cardiac autonomic neuropathy; Diabetes mellitus; Case report; Emergency department.*

Introduction

Diabetes mellitus (DM) is one of the most prevalent endocrinology disorders worldwide and is related to significant morbidity and mortality of the population. The number of diabetic patients is increasing due to population growth and aging, together with the progressive prevalence of obesity, and sedentary lifestyle.

According to the World Health Organization (WHO) in 2014, 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years [1]. Progression of DM is associated with chronic complications including cardiomyopathy, retinopathy, nephropathy, and neuropathy. In diabetes, chronic hyperglycaemia and metabolic derangements can lead to structural and functional alterations in the autonomic nerve fibers that innervate various organ systems e.g., cardiovascular, gastrointestinal, genitourinary, sudomotor or ocular [2].

Cardiac autonomic neuropathy (CAN) is a well-recognized complication of diabetes mellitus, and results from damage to the autonomic nerve fibers that innervate the heart and blood vessels leading to abnormalities in heart rate control and vascular dynamics [3]. The autonomic nervous system, consisting of the sympathetic and parasympathetic branches, plays a crucial role in regulating heart rate, blood pressure, and cardiac contractility. Regarding the underlying pathophysiology of CAN, hyperglycaemia in diabetes results in increased oxidative stress which can cause direct neuronal damage as well as endothelial dysfunction resulting in neuronal ischaemia [4]. This oxidative stress results in the activation of numerous intracellular pathways which are ultimately related to neuronal dysfunction & death [5] as well as endothelial dysfunction leading to impaired neurovascular perfusion [6] . Moreover, diabetes affects autonomic nerves in a length-dependent fashion [7]. As a result, CAN often manifest first in the vagus nerve which is the body's longest parasympathetic autonomic nerve and the one involved in most of the parasympathetic activity. Damage to the vagus nerve causes resting tachycardia and an overall decrease in parasympathetic tone.

The prevalence of CAN in diabetes varies widely across studies, with reported rates ranging from 2% to 91% in type 1 diabetes and 25% to 75% in type 2 diabetes, depending on the population studied and diagnostic criteria used [8]. CAN is associated with a longer duration of the disease, with a prevalence in T1DM after 15 years being approximately 60% according to DCCT/EDIC study. Poor glycaemic control is a major risk factor for CAN progression [9]. Also, it has been shown that is associated with hypertension, smoking, hyperlipidaemia and obesity. The presence of diabetic retinopathy, diabetic polyneuropathy and microalbuminuria or diabetic nephropathy are clinical predictors of CAN [10].

Considering now the clinical presentation of CAN, resting tachycardia secondary to vagal impairment is prevalent with resting heart rates of 90–100 bpm and occasionally heart rate increments up to 130 bpm occur. The ultimate heart rate is relative to the extent of parasympathetic to sympathetic dysfunction. A fixed heart rate that is unresponsive to moderate exercise, stress or sleep indicates almost complete cardiac denervation [11]. Reduced heart rate variation (HRV) is the earliest indicator of CAN [9]. In response to exercise, autonomic dysfunction reduces response in heart rate and BP, and blunts increase in cardiac output, thus decreasing exercise tolerance [12].

Another manifestation of CAN is orthostatic hypotension which is usually the result of damage to the efferent sympathetic vasomotor fibers. Patients with orthostatic hypotension typically present with light-headedness, dizziness, weakness, fatigue and blurred vision [13]. Orthostatic hypotension is a feature of advanced CAN and is associated with an additional increase in mortality risk [14].

Among diabetic patients those with CAN have an increased frequency of silent myocardial ischaemia compared to those without CAN. Altered pain thresholds, subthreshold ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms of painless myocardial ischemia. Moreover, CAN has been associated with left ventricular systolic and particularly diastolic dysfunction in the absence of cardiac disease [12].

Other specific but less sensitive markers of CAN that have been described are the attenuation or complete loss of the nocturnal fall of BP (recorded on ambulatory blood pressure monitoring, ABPM) [12] as well as prolongation of the QTc interval on ECG [15].

Another manifestation of CAN is postural tachycardia syndrome (POTS), which is defined as the association of symptoms of orthostatic intolerance (such as light-headedness, fatigue, headache, neuro-cognitive deficits, palpitations, nausea, and blurred vision) with an abnormal increase in heart rate early during orthostasis. The hallmark of this abnormality is the absence of a fall in BP with standing, but a tachycardia with the change in posture. The pathogenesis of POTS is obscure. Several studies have shown altered blood flow in lower extremities (either high or low flow) while in the supine position [16] as well as increased splanchnic, pelvic and leg blood volumes during orthostasis. These confirmed that POTS is related to inadequate cardiac venous return when standing, leading to tachycardia [17].

Among the diagnostic tests that have been proposed to confirm CAN, the gold standard remains the cardiac autonomic reflex tests (CARTs) described by Ewing et al. in 1970s. Sympathetic function is assessed by BP response to postural changes, the Valsalva manoeuvre, and sustained isometric muscular strain (hand grip). Parasympathetic function is assessed by HR response to deep breathing (heart rate variability, HRV), changes in postures (from lying to standing), and the Valsalva manoeuvre [8] [7] [18]. Other tests are not routinely used except in more specialized centres.

CAN is a significant cause of morbidity & mortality associated with high risk of cardiac arrhythmias and sudden death, possibly related to silent myocardial ischaemia. According to the EURODIAB study**,** autonomic dysfunction was present in one-third of type 1 diabetic patients and was strongly associated with co-existing cardiovascular disease [19].

Management of CAN consists of the symptomatic attenuation of its individual clinical manifestations. Regarding orthostatic manifestation, several conservative measures have been offered including increased fluid intake, use of lower -extremity stockings as well as avoiding if possible medication that can aggravate orthostatic hypotension. Pharmacological agents like pyridostigmine (an acetylcholinesterase inhibitor), beta-blockers and somatostatin have also been proposed. Regarding HRV and left ventricle dysfunction several studies have shown considerable improvement by offering beta-blockers (e.g., bisoprolol), angiotensin-converting enzyme inhibitors (e.g., quinapril) and angiotensin receptor blockers [12]. Of note, in the Steno memorial study by Gaede et al, controlling BP, lipids, HBA1c, together with the use of aspirin, vitamins E and C, and ACE inhibitors reduced CAN by 68% [20].

The following case underscores the role of emergency medicine physicians in the medical care of a person with CAN, as well as the importance of prompt recognition and initiation of a multidisciplinary approach in management.

Case Presentation

A 25-year-old male presented at the Emergency Department with profound dizziness, especially with standing. Dizziness in the form of unsteadiness and light-headedness has been gradually getting worse over a period of 6 weeks with a significant impact on patient's mood and quality of life.

The patient reported that he had been feeling lightheaded after standing up, and that he needed to stop and sit down because of this happening every few minutes. He also complained of frequent palpitations worse on standing or walking. On questioning he didn't report any hearing loss, neither nausea nor vomiting. No syncope or pre-syncope reported and he denied any changes in his bowel habits. He didn't complain about any abdominal pain or urinary tract symptoms. No fevers or recent infections and illnesses and no unwell contacts reported. Patient denied recent trauma or surgeries. He only reported 8-10kg weight loss over the past 3-6 months and reduced appetite. He denied smoking, alcohol consumption or use of recreational drugs. He lives with friends, and he works from home as software engineer. His past medical history included type 1 diabetes mellitus, diagnosed when patient was 17-year-old and Grave's disease, with the former being tightly controlled the last 2 years. Patient was using his long and short acting insulin as previously instructed by his diabetes team.

During his initial presentation, the patient was mildly tachycardic on rest with a variation between 90 to 100 beats per minute (bpm) and his heart rate regularly jumped on standing to 120-130 bpm during which he was symptomatic, yet there was no blood pressure drop. The patient reported that he felt extremely unsteady during these episodes but not like the room was spinning. Symptoms were getting worse on standing but not while sitting or lying. His neurological exam along with the rest of his clinical examination per system was unremarkable. No postural drop in his blood pressure noted on testing for orthostatism. The patient expressed his concerns about weight loss as he reported that he lost approximately 8-10 kg in the last 3-6 months and that his appetite has been poor. On examination his BMI (19.2 kg/m^2) was within normal range with no evidence of sarcopenia.

On further investigations, his blood glucose levels along with ketones were normal. ECG demonstrated borderline sinus tachycardia and his chest x-ray was normal. The rest of his blood results including full blood count, urea & electrolytes, bone profile, iron studies, liver function tests and thyroid function tests were unremarkable. His eGFR was 104 ml/min/1.73m^2 and a random cortisol blood level was 316 nmol/L. His CRP result was <1.0 mg/dL and D-dimers came back negative, ruling out pulmonary embolism with respect to his low pretest probability. However, his latest HbA1c came back 64 mmol/mol, reflecting a rather poor glycaemic control.

At the emergency department, he had boluses of balanced crystalloid fluids with partial response of his tachycardia initially, which settled to 75-80 bpm, but he still experienced postural symptomatic tachycardia while he was standing and his resting heart rate was high most of the time as depicted in Table 1. A joint decision with the medical team was made to admit this patient for further investigations and treatment plan. Throughout his admission his observations had been stable, and all his blood results came back normal.

He had been apyrexial, passing urine and able to eat & drink. An MRI of his head was performed, to exclude cerebellar/brainstem cause, which was also unremarkable.

Table 1. Heart rate variability during rest.

Cardiac Parameters (lying position)	A&E	Admissions Ward Day 1	Admissions Ward Day 2
HR (bpm)	99	100	94
BP (mmHg)	142/76	133/74	128/91

The impression of the treating team was that patient's presentation was consistent with cardiac autonomic neuropathy related to type 1 diabetes manifested as postural tachycardia syndrome (POTS), resulting in his postural tachycardia and the symptoms of dizziness and unsteadiness, as well as high resting heart rates. On discharge, further testing as an outpatient was suggested including echocardiogram to exclude structural cardiac abnormalities, Holter monitoring for arrhythmias detection and TILT table testing for reflex syncope investigation. Finally, a diabetes follow-up appointment was arranged for the patient and instructions about blood glucose monitoring and insulin therapy were given.

Discussion

CAN is a well-recognized complication of diabetes mellitus, affecting both type 1 and type 2 diabetic patients. In this case report we present a compelling clinical presentation of CAN in a type 1 diabetic patient, highlighting the manifestations, the diagnostic challenges, and the implications for patient care. The case underlines the importance of early detection and proactive management in preventing adverse cardiovascular outcomes in diabetic patients.

The clinical presentation of CAN, varies widely, rendering it a rather challenging diagnosis, especially in a busy emergency department. Our patient, a 25-year-old male with an 8-year history of type 1 diabetes presented with lightheadedness worse on standing, tachycardia both resting and orthostatic, exercise intolerance and considerable weight loss for the past couple of months. Such symptoms are often nonspecific and may overlap with other conditions. However, a high index of suspicion is crucial in recognizing CAN in diabetic patients [15]. Diagnostic evaluation of CAN relies on both clinical findings and objective testing. In this case from an Emergency Medicine perspective, serious complication of diabetes such as diabetic ketoacidosis has been excluded since patient's ketones were low (<0.1 mmol/L) and venous blood gas results were unremarkable. Hypoglycaemia was also excluded as patient's glucose levels were also normal. Among other differentials, anaemia was ruled out by his normal FBC (Hb 154 g/L, MCV 92 fL) and thyrotoxicosis was excluded by his normal TFTs (TSH 0.86 mU/L, FT4 16.6 pmol/L and FT3 5.3 pmol/L). Furthermore, an infection was unlikely since the patient had consistently been apyrexial with no localizing infectious symptoms and unremarkable urinalysis, chest x-ray and inflammatory markers. In addition, pulmonary embolism was ruled out in view of his low pre-test probability and his negative D-dimers results. In view of the presence of two autoimmune endocrinopathies (type 1 diabetes and Grave's disease), Addison's disease had justifiably been included in the differentials. However, the incompatibility of the rest of the patient's clinical presentation (absence of hypotension, hyponatraemia with hyperkalaemia, profound fatigue or hypovolaemia) differed the prevalent diagnostic work up away from Addison's. In this context, even with an equivocal cortisol level (a value of 316 nmol/L but still not profoundly low i.e., <100 nmol/L) an ACTH stimulation test has not been requested.

Having ruled out more common and in some cases life-threatening causes of tachycardia we were led to the diagnosis of CAN considering our patient's past medical history of diabetes and particularly findings such as the presence of tachycardia on standing with the absence of drop in BP, a finding consistent with POTS which is a common manifestation of CAN as well as the previous poor diabetic control (indicated by his high HbA1C of 64 mmol/L) which is a pivotal risk factor for the development of CAN. All in all, considering the patient's clinical presentation, the exclusion of many relevant conditions and the underlying history of previous poor diabetes control as well as the resting increased heart, CAN was a highly relevant diagnosis [15].

Autonomic function tests (CARTs), including heart rate and blood pressure fluctuation with different maneuvers, are considered the gold standard to confirm the presence and severity of autonomic dysfunction [12] [15] [18]. While these tests are essential for diagnosing CAN, they are not readily available in settings like the emergency department and their interpretation requires expertise. Therefore, Emergency Medicine physicians must be familiar with the clinical manifestations and should consider referrals to specialized autonomic function clinics when appropriate.

The management of CAN is primarily based on glycaemic control and cardiovascular risk reduction [12] [15]. Tight blood glucose control as demonstrated in the Diabetes Control and Complications Trial (DCCT), has been shown to reduce notably the risk of CAN [21]. In addition to glycemic control, interventions such as blood pressure management, lifestyle modifications and medications targeting autonomic symptoms and cardiovascular risk factors are crucial in the management of this condition [12] [8] [15].

In this case, our patient was a young individual, athletic, with a normal BMI, who was unable to attend and tolerate physical exercise for the last couple of months and unable to follow his daily routine, something that stresses even more the importance of identifying characteristics of CAN, in otherwise healthy, yet diabetic, young individuals.

CAN carries significant morbidity and mortality, with increased risks of arrhythmias, silent myocardial ischemia, and sudden cardiac death [12]. In this case, early suspicion of CAN led to appropriate involvement of specialists such as dietitians, diabetologists and cardiologists with an outpatient-based follow up arranged for the patient with ambulatory HR and BP monitor, echocardiogram and TILT-table testing as well as liberal diet including up-titration of salt and fluid intake, moderate exercise, and close monitoring for the need of pharmacological management of his tachycardia. A close follow-up is warranted to assess the progression of CAN and adjust management accordingly.

Conclusion

In conclusion, the case of potential CAN in this type 1 diabetic patient acts as poignant reminder of the importance of early detection and proactive management of this rather underdiagnosed condition. Another important factor highlighted by this case is that the complexity of CAN necessitates a multidisciplinary approach for appropriate management involving dietitians, endocrinologists, cardiologists, and primary care physicians. An early and important sign of CAN that Emergency physicians can recognize and initiate treatment pathways early is resting tachycardia. Future research should explore the mechanisms of CAN and the most effective strategies for prevention and management.

Conflict of Interest

The authors declare no conflicts of interest.

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