

Case Discussion in Medicine

Reversal of Diabetes Autonomic Neuropathy with Intense Treatment Monitoring — A Case Study

Shambo Samrat Samajdar¹, Shatavisa Mukherjee², Shashank Joshi³, Santanu Kumar Tripathi⁴

Diabetic autonomic neuropathy (DAN) is a significant marker of adverse cardiovascular, renal and cerebrovascular outcomes in diabetic patients. According to the American Neurological Society guidelines, screening for autonomic dysfunction should be carried out immediately after the diagnosis of type 2 diabetes (T2DM) and repeated every 5 years thereafter. Patients with poor glycemic control, cardiovascular risk factors and other micro- and macrovascular complications of diabetes are at a greater risk. The present case describes a 56 year old diabetic male presenting with complaints of tingling sensation in limbs and symptoms of gastroparesis. Proper history taking, effective screening for autonomic neuropathy and further work-up addressed the complaints within 3 months.

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Key words : Diabetes Autonomic Neuropathy (DAN), Type 2 Diabetes Mellitus, Ewing's Tests, Gastroparesis

Diabetic autonomic neuropathy (DAN) is a significant marker of adverse cardiovascular (CV), renal and cerebrovascular outcomes in diabetic patients. According to the American Neurological Society guidelines, screening for autonomic dysfunction should be carried out immediately after the diagnosis of type 2 diabetes (T2DM) and repeated 5 years thereafter. Patients with poor glycemic control, with cardiovascular (CV) risk factors and with other micro- and macrovascular complications of DM are at a greater risk. For all T2DM patients, cardiovascular autonomic neuropathy (CAN) must be ruled out even in resource constraint settings¹. The reversal of autonomic neuropathy features in T2DM with intense glucose monitoring has been reported, only sparingly². Probability of such reversal depends on several factors including the time since diagnosis of diabetes, treatment compliance, presence of cardiovascular risk factors etc. We present here a case of partial reversal of autonomic neuropathy in just 3 months of intense monitoring of glycemic control.

CASE REPORT

A 56 year old gentleman, a known patient of T2DM

Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata 700073

¹MBBS, MD, DM (Clinical Pharmacology) Post Doctoral Trainee

²M Pharm (Pharmacology) Research Scholar and Corresponding Author

³MD, DM (Endocrinology), Senior Consultant, Joshi Clinic, Lilavati Hospital and Research Centre, Maharashtra 400050

⁴MD, DM (Clinical Pharmacology), Professor and Head

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Editor's Comment :

- Consider routine screening for DAN in all T2DM patients diagnosed for 5 years.
- Go for early detection and prompt treatment of DAN.
- A composite assessment of Valsalva ratio, inspiratory/expiratory RR interval ratio and focused history is useful as a surrogate marker to detect gastroparesis.
- In presence of gastroparesis, re-adjust insulin timing to avoid post-meal hypoglycemia.
- Medication reconciliation and deprescribing, as needed, are useful.
- Just good glycemic control can delay or ameliorate gastroparesis in T2DM patients.

for 15 years, attending the Diabetes Clinic, presented with complaints of insidious-onset tingling sensation in right lower limb and decreased sensation in both lower limbs. Probing elicited the history of thermal injury (blister) in right foot, failing to sense the temperature of hot water. He was also hypertensive, on medications for 5 years. He was a cigarette smoker for 30 years. On presentation, his diabetes regimen included insulin (H Mixtard 30/70) - 24 U before breakfast and 14 U twice daily 30 minutes before each meal, besides twice daily dosing of vildagliptin 50 mg and metformin 500 mg. Further, he was also receiving single oral daily dosing for each of atorvastatin 20 mg, amlodipine 5 mg, amitriptyline 25 mg and vitamin B12 1500 mcg. His BMI was noted to be 22.8 kg/m² and CBG 56 mg/dl. The patient had a history of pre-lunch severe hypoglycemia and two episodes of hospitalization, in the last 6 months. He also gave a history of fall while walking, 5 months back, post-meal abdominal pain, bloating even with small food intake,

incomplete bladder emptying since last 10 months and recurrent loose motion (night time) for last 6 months. Patient had a disturbed sexual life for last 5 years due to erectile problem.

Investigations for glycemic status showed HbA1c 10.9%, FPG 86mg/dl, and PPPG324 mg/dl. On examination, fine touch with 10 gm mono-filament was diminished on toes, heels and dorsum of feet, but perceived normally in all meta-tarsal heads in both limbs. Vibration sense (128 Hz) was also found diminished in both great toes and medial malleoli, but was intact in both knees. Screening for Diabetes Autonomic Neuropathy (DAN) was performed that involved five simple tests as proposed by Ewing et al [3] and the findings were suggestive of loss of autonomic neurofunction, particularly the parasympathetic neurofunctional integrity (Table 1). A diagnosis of DAN with features of CAN and gastroparesis was made.

A thorough reconciliation of medications was done. Both vildagliptin and amitryptiline were omitted and amlodipine was substituted with telmisartan. Oral domperidone thrice a day was added. The patient was counselled for change in insulin regimen and dose adjustments of insulin was done with premix insulin (30/70) 22U before breakfast and 16 U twice daily just before meals. An hourly CBG check for 4 hours post meal, for 2 weeks, was advised. The follow-up visit was scheduled after 3 months. To optimize compliance, the patient was telephonically counselled every week.

On reassessment after 3 months, there was a marked improvement in the gastroparesis symptoms. No episode of hypoglycemia was experienced. The post-meal hourly CBG check in the initial 2 weeks revealed good post-meal glycemic control. The HbA1c was 7.4%. The DAN screening tests were repeated and the findings were suggestive of subtle improvement in all the parameters (Table 1).

DISCUSSION

DAN is a frequent chronic complication of DM with potentially life-threatening outcomes. Despite its significant negative impact in quality of life in the affected, it has been one of the least recognised and comprehended complications of diabetes. DAN may affect many organ systems throughout the body, eg, Gastrointestinal (GI),

Genitourinary (GU), and Cardiovascular (CV). Major clinical manifestations of DAN thus include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, and hypoglycemic autonomic failure⁴. GI disturbances are common and may include enteropathy, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with irregular glucose control and in presence of post meal hypoglycemia. In this present case, patient was initially taking insulin 30 minutes before breakfast, but owing to gastroparesis there was delayed food absorption which led to recurrent post breakfast hypoglycaemia. Considering pharmacokinetics of human insulin (onset of action ~ 30 minutes) and existing gastroparesis, this patient was advised to take insulin just before the meals which reduced the incidents of hypoglycaemic events. This report highlights the importance of reconciliation of existing treatments and individualizing treatment as necessary in a given patient. Dose of insulin should be titrated as per pre and post meal CBG values, but one needs to monitor CBG for longer duration, may be up to 4 hours, as in this case. A single 2-hour post meal CBG value may prove misleading, particularly in presence of gastroparesis.

Ideally, DAN related gastroparesis should be identified by gastric emptying scintigraphy of a radiolabeled solid meal, that evaluates motor function

Table 1 — Findings of DAN Screening

Test	Description	Baseline	After 3 Months	Normal
Expiration/inspiration (E/I) ratio	The patient was asked to take deep breaths for 10 minutes with frequency about 6 breaths/min.	1.05	1.3	≥1.2
Valsalva maneuver	The patient was asked to blow into the special manometer to maintain the pressure at about 40 mmHg for 15s.	1.1	1.16	>1.2
Postural heart rate response : maximum-minimum (30:15 ratio)	Heart rate was measured in the horizontal position and again two minutes later after standing upright.	1	1.09	>1.03
Postural blood pressure response	Blood pressure (mm of Hg) : lying down 1 min after standing upright 3 min after standing 5 min after standing	130/66 130/80 122/82 126/82	140/76 130/80 132/82 136/82	
Isometric handgrip test (dynamometer)	Blood pressure (mm of Hg) : before handgrip 5 min post handgrip Difference between DBP (mm of Hg)	130/66 167/72 6	140/76 167/86 10	

of stomach and quantifies the emptying of the meal. However, such tests are broadly unavailable in resource constrained settings. Cardiac autonomic neuropathy (CAN) assessment can be an indirect marker of probing gastroparesis. In the present case, based on elicited history and clinical examination, a provisional diagnosis of diabetic gastroparesis was made. Our DAN screening findings emphasizing changes in Valsalva and deep breathing ECG suggested parasympathetic dysfunction, which serves as an indirect surrogate marker for detection of DAN associated gastroparesis.

The American Diabetes Association recommends the use of the Ewing's tests in the diagnosis of DAN. Ewing's tests are simple and doable in resource-constrained settings also. Thus DAN screening using Ewing's tests can be integrated in routine monitoring of T2DM patients. Both expiration-inspiration ratio and Valsalva maneuver measure the ability of the vagal nerve to slow the heart rate during procedures which increase heart rate. The Valsalva maneuver represents both sympathetic and parasympathetic components. The isometric handgrip test and postural blood pressure show changes in sympathetic function and involve principles of baroreflex-mediated blood pressure fluctuations⁵.

Diabetic gastroparesis needs dietary modification, glycemic control, de-prescribing, if needed of drugs which may have detrimental effects on gut motility, and specific pharmacotherapy. In this patient we de-prescribed vildagliptin, amitriptyline and amlodipine. Generally incretin based therapy and alpha glucosidase inhibitors are withdrawn if patients are suffering from diabetic gastroparesis. There exists a controversy with use of metformin due to its gastrointestinal side effects. However, insulin resistance is known to contribute to diabetic gastroparesis and metformin ameliorates it. Many physicians thus prefer to continue it with close monitoring. In the present case, metformin was continued. Amitriptyline and amlodipine, due to their anticholinergic potential, tend to further worsen gastroparesis. The anticholinergic burden of different concomitant medications in T2DM patients should be assessed using appropriate tools, and those with high burden score should better be omitted after a risk-benefit analysis. Prokinetic drugs like metoclopramide, domperidone or acotiamide are sometimes required. In the present case, domperidone was used.

Hyperglycemia itself delays gastric emptying, even in the absence of neuropathy or myopathy. Generally, it is mediated by reduced phasic antral contractility and the induction of pyloric pressure waves.^[6] Hyperglycemia antagonizes ameliorating effects of prokinetic agents. Glucose levels should be maintained below 180 mg/dL, which would help to avoid inhibiting gastric myoelectric control and motility. Continuous Glucose Monitoring (CGM) can seamlessly assess glycemic control and can guide insulin injection timing in presence of gastroparesis. However, use of CGM was not feasible in our facility. In order to minimize occurrences of dysglycemic episodes, what is needed is employing individualized intervention. In this case, prompt glycemic control helped in reversing gastroparesis and CAN related abnormalities. Both the sympathetic and parasympathetic derangement were corrected within 3 months. The reversal of autonomic neuropathy features in T2DM with intense glucose monitoring has been reported, only sparingly². However, our experience with this patient is not in conformity with other reported studies⁷ where prolonged period of improved control failed to reverse established autonomic dysfunction of diabetes. Nonetheless, with lessons from the index patient, we resolved to routinely screen all T2DM patients diagnosed for more than 5 years, for DAN, and to institute closer treatment monitoring and control with a hope of avoiding and/or reversing of such complications. An early detection of autonomic dysfunction in T2DM patients can encourage the physician to improve metabolic control, thus ensuring better treatment outcomes.

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