Cardiac Autonomic Neuropathy In Patients With Diabetes

FARID FAWZY, MD, PhD
Professor of Medicine, Diabetes & Endocrinology,
Zagazig University, Egypt

Case Presentation

• A 26 year old woman with brittle type 1 DM was brought dead to the ED.

• She had a 16-year history of poor glycemic control with wide B.G. fluctuations, severe hypoglycemic episodes, and hypoglycemia unawareness.

• Over time she developed persistent orthostatic hypotension with daily falls in systolic blood pressure ranging from 30–60 mmHg necessitating intermittent therapy with midodrine.

• Other complications included severe gastro-paresis, refractory diarrhea, and painful diabetic peripheral neuropathy.

• Clinical examination revealed a fixed heart rate of 115 bpm, BP 110/78 mmHg supine and 70/48 mmHg while standing, symmetrical absent pin brick and temperature sensation in stocking distribution and left Charcot joint.

• Pertinent laboratory findings were A1C 8.7%, creatinine 1.9 mg/dl, ACR 496 mg/g, and hemoglobin 10.8 g/dl.
Disclosure

• I have honoraria and sponsored conferences with Novartis, Novo-Nordisk, Eli-Lilly, Astra-Zeneca, MSD, HSO, Inspire, Takeda, Janssen, Merck Serono, and Global-Napi

• No potential conflict of interest relevant to this presentation
Agenda

• Epidemiology
• Risk Factors and Pathogenesis
• Clinical Consequences
• Screening and Diagnosis
• Therapeutic Approaches
Epidemiology of CAN

• Prevalence of CAN varies greatly from one study to another depending on the diagnostic criteria and study population.

• Prevalence varies from 1.6–2.6% in the DCCT to 90% in long standing type 1 patients waiting for a pancreas transplant.

• In a large cohort Ziegler et al. reported prevalence of 25.3% in patients with type 1 DM and 34.3% in those with type 2 DM.

• Established risk factors for CAN are glycemic control in type 1 diabetes, and a combination of hypertension, dyslipidemia, obesity and glycemic control in type 2 diabetes.

Agenda

• Epidemiology

• Risk Factors and Pathogenesis

• Clinical Consequences

• Screening and Diagnosis

• Therapeutic Approaches
Risk factors:
- Hypertension
- Dyslipidemia
- Smoking
- Age
- Ethnicity
- Genetic susceptibility
- Diabetes duration

Hyperglycemia:

Polyol ↔ AGE/RAGE ↔ ROS

↑ AGE's ↓ NGF

Cytokines ↑

PKC↑

MAPK↑

Endoneurial Microangiopathy

Neuropathy
Clinical Consequences of CAN

- Resting tachycardia & Impaired HRV
- Exercise intolerance
- Perioperative cardiovascular instability
- Orthostatic Hypotension
- Non-dipping blood pressure profile
- Silent myocardial ischemia
- Sudden cardiac death
- Autonomic cardiomyopathy

Agenda

- Epidemiology
- Risk Factors and Pathogenesis
- Clinical Consequences
- Screening and Diagnosis
- Therapeutic Approaches
• Cardio-Autonomic Response Tests (CART’s):
  - Heart rate response to respiration  
  - Heart rate response to standing  
  - Heart rate response to Valsalva  
  - Blood pressure response to standing  
  - Blood pressure response to hand grip

- Resting heart rate  
  >100 bpm is abnormal.

- Beat-to-beat HRV*  
  With the patient at rest and supine (not having had coffee or a hypoglycemic episode the night before), heart rate is monitored by ECG or autonomic instrument while the patient breathes in and out six breaths per minute, paced by a metronome or similar device. A difference in heart rate of >15 bpm is normal, <10 bpm is abnormal. The lowest normal value for the expiration-to-inspiration ratio of the R-R interval is 1.17 in people 20–24 years of age. There is a decline in the value with age†.

- Heart rate response to standing*  
  During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing. Normally, a tachycardia is followed by reflex bradycardia. The 30:15 ratio is >1.03.

- Heart rate response to the Valsalva maneuver*  
  The subject forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 s during ECG monitoring. Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with release. The ratio of longest R-R to shortest R-R should be >1.2.
• Systolic blood pressure response to standing
  Systolic blood pressure is measured in the supine subject. The patient stands, and the systolic blood pressure is measured after 2 min. Normal response is a fall of <10 mmHg, borderline is a fall of 10–29 mmHg, and abnormal is a fall of >30 mmHg with symptoms.

• Diastolic blood pressure response to isometric exercise
  The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min. The normal response for diastolic blood pressure is a rise of >16 mmHg in the other arm.

• ECG QT/QTc intervals
  The QTc should be <440 ms.
**Other diagnostic tools**

- Scintigraphic evaluation of sympathetic innervation of the heart with Positron Emission Tomography (PET) scans.
- Microneurography which records electrical activity from the peroneal, tibial or radial sympathetic nerves.
- Corneal confocal microscopy (CCM).

**SCREENING FOR CAN**

**Whom?**
- Patients with type 2 diabetes at the time of diagnosis.
- Patients with type 1 diabetes after 5 years of diagnosis.
- Earlier screening in type 1 with suggestive symptoms of CAN.
- Pre-operative assessment for all patients with diabetes.
- Patients with diabetes planning an intense exercise program.

**How?**
- Standard Clinical Testing (CART’s)
- Electrophysiological and imaging studies
- Corneal Confocal Microscopy (CCM)
- Risk assessment scores (Age, BMI, HTN, & resting heart rate)

**When?**
- Screening should be repeated annually if negative.
Agenda

• Epidemiology
• Risk factors and pathogenesis
• Clinical consequences
• Screening and diagnosis
• Therapeutic Approaches

General Measures

• Timely diagnosis for effective management.
• Lifestyle changes including graded supervised exercise program.
• Optimizing glycemic control in patients with type 1 DM. (Framingham Heart Study, DCCT & EDIC)
• Correction of CV risk factors specially in patients with type 2 DM.
**Pathogenesis-based pharmacotherapy**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Compound</th>
<th>Aim of treatment</th>
<th>Status of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve sorbitol ↓</td>
<td>Fidaxomycin</td>
<td>Effective in RCTs, trials ongoing</td>
<td></td>
</tr>
<tr>
<td>Myo-inositol ↓</td>
<td>Myo-inositol</td>
<td>Equivalan</td>
<td></td>
</tr>
<tr>
<td>Nerve hypoxia ↓</td>
<td>α-Lipoic acid</td>
<td>Oxygen free radicals ↓</td>
<td></td>
</tr>
<tr>
<td>Protein kinase C ↑</td>
<td>Protein kinase C-β inhibitor (esubastatine)</td>
<td>NBF ↑</td>
<td>RCTs ongoing</td>
</tr>
<tr>
<td>C-peptide ↓</td>
<td>C-peptide</td>
<td>NBF ↑</td>
<td>Studies ongoing</td>
</tr>
<tr>
<td>Neurothrombin ↓</td>
<td>Nerve growth factor (NGF)</td>
<td>Increase in NGF, growth ↑</td>
<td>Studies ongoing</td>
</tr>
<tr>
<td>LCFA metabolism ↓</td>
<td>Acetyl-carnitine</td>
<td>LCFA accumulation ↓</td>
<td></td>
</tr>
<tr>
<td>GLA synthesis ↓</td>
<td>γ-Linolenic acid (GLA)</td>
<td>Increase in GLA and LCFA</td>
<td></td>
</tr>
<tr>
<td>NEG ↑</td>
<td>Amioguanidine</td>
<td>AGE accumulation ↓</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment of orthostatic hypotension**

- **Nonpharmacologic interventions:**
  - Increased water consumption
  - Lower extremity stockings
  - Avoid sudden postural changes to standing up
  - Avoid vasodilators, diuretics, α-blockers, phenothiazine (Largactil) and TCA.
  - Eating frequent, small meals.
  - Avoid maneuvers that increase intra-abdominal and intra-thoracic pressure.

- **Pharmacological therapy:**
  - Midodrine: selective α1-adrenergic agonist and the only FDA-approved drug.
  - Fludrocortisone: a synthetic mineralocorticoid
  - Octreotide: inhibits gut vasoactive peptides leading to splanchnic vasoconstriction.
  - Erythropoetin: increases intravascular volume and blood viscosity
  - Pyridostigmine: a cholinesterase inhibitor.
  - Nonselective beta blockers: antagonizing the hyperactive sympathetic drive.
Summary & Conclusion

• Although common and serious, CAN is frequently overlooked.
• Clinical consequences of CAN include resting tachycardia, intraoperative C.V. instability, absent nocturnal dipping, orthostatic hypotension, silent ischemia and arrhythmias.
• Patients may have subclinical CAN for years and screening with CART’s and CCM is strongly recommended.
• Treatment principles include control of glycemic control & CV risk
• Pathogenesis-based medications like aldose reductase inhibitors, ACE inhibitors, c-peptide and ALA are promising.
• Orthostatic hypotension, indicates advanced CAN and