Diabetic Autonomic Neuropathy (DAN)

April, 2013
What country has the highest percentage of people with type 2 diabetes?

A. Mexico
B. USA
C. Nauru
D. Saudi Arabia
Definitions

• Autonomic nervous system (ANS) – the portion of the nervous system that regulates individual organ function and homeostasis not under voluntary control. A number of ANS functions can, however, work alongside some degree of voluntary control.

• Diabetic neuropathy (DN) – a neuropathic disorder (somatic and/or autonomic) associated with diabetes without other causes being found

• DAN – a neuropathic disorder associated with diabetes that includes the ANS, including cardiovascular, GI, GU, and other functions
DN – General Observations

• Any nerve or combination of nerves may be damaged, although various neuropathies (somatic and autonomic) typically coexist.
• Often is asymptomatic, but still clinically significant.
• Typically the earliest of the microvascular diabetic complications to become manifest.
• There is no specific treatment for diabetic nerve damage aside from good glucose control. Treatments available do not reverse nerve damage, they can help “overcome” such damage symptomatically.
• DCCT and Steno-2 results show that prevention is the preferred “treatment.”
Decreased Cardiovascular Autonomic Neuropathy (cardiovascular reflex testing) in the DCCT Type 1 patients
Steno-2 Study
Differences in medications, diet, blood pressure, glucose control, and lipid control at the end of the study

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Intensive</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>56%</td>
<td>87%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>70%</td>
<td>97%</td>
<td>0.002</td>
</tr>
<tr>
<td>Statin</td>
<td>22%</td>
<td>85%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diet Carb</td>
<td>+4.3%</td>
<td>+9.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diet Fat</td>
<td>-6.8%</td>
<td>-10.4%</td>
<td>0.006</td>
</tr>
<tr>
<td>B/P</td>
<td>-3/-8</td>
<td>-14/-12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HgA1c</td>
<td>9%</td>
<td>7.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chol</td>
<td>-3</td>
<td>-50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>-13</td>
<td>-47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine albumin</td>
<td>+30</td>
<td>-20</td>
<td>0.002</td>
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</table>
DAN Type 2 patients in Steno 2

A. Nephropathy
- Intensive therapy
- Conventional therapy

B. Retinopathy

C. Autonomic Neuropathy

D. Peripheral Neuropathy
In 1916 (before insulin therapy), the most successful treatment for type 1 diabetes (the Allen protocol) included dietary carb restriction, and initially whiskey with black coffee every 2 hours, until the urine was free of glucose.
DAN - Types

- Cardiovascular (CAN)
- Peripheral vasculature (PVAN)
- Gastrointestinal (GIAN)
- Genitourinary (GUAN)
- Other
CAN

- Typically asymptomatic, but detectable via cardiovascular reflex testing
- Prevalence rates vary widely between studies depending on the population studied and the diagnostic tests used, but a safe estimate is a prevalence of 20-30%
- Symptoms: resting tachycardia, decreased exercise tolerance, orthostatic hypotension
- Even if asymptomatic, CAN is clinically significant, being associated with operative cardiovascular instability, silent myocardial infarction and ischemia, and increased mortality
CAN Symptoms

• Resting tachycardia due to loss of vagal tone
• Exercise intolerance due to lack of sympathetic augmentation of heart rate and cardiac output
• Postural hypotension (>20 mmHg drop in systolic BP from supine to standing) due to failure of vasoconstriction in splanchnic and peripheral vascular beds
• Loss of normal diurnal BP variation, resulting in supine night time hypertension
• Occasionally severe post-prandial hypotension
CAN – Intraoperative Instability

• Anesthesia is vasodilating, and the normal ANS response to this is vasoconstriction and tachycardia.
• Intraoperative vasopressors more often needed in those with CAN
• Possibly also increased risk of hypothermia, and decreased hypoxia-induced ventilatory drive
CAN – Silent MI and Ischemia

A

# of Study Subjects

28% with SMI

+SMI/+CAN

399

TOTAL+CAN

10% with SMI

+SMI/-CAN

1,069

TOTAL-CAN
CAN – Possible Symptoms of Cardiac Ischemia

- Chest pain
- Fatigue
- Confusion
- Edema
- Nausea
- Diaphoresis
- Cough
- Others
CAN – Increased Mortality

Figure 2

(+CAN = Cardiovascular autonomic neuropathy present; -CAN = No cardiovascular autonomic neuropathy found)
CAN – Why increased mortality?

• Silent MI
• Prolonged Q-T interval predisposing to arrhythmia
• Sleep apnea (>30% of nonobese patients with DAN have sleep apnea)
• Or, CAN may be a marker of ASHD and/or nephropathy, and not causative
CAN – Diagnosis of Asymptomatic Disease

• Usually occurs with distal peripheral polyneuropathy
• Orthostatic hypotension is a late, but severe, manifestation of CAN
• Cardiovascular reflex tests are safe but require a substantial commitment to standardize the procedure to ensure accuracy:
  – Heart rate response to deep breathing, standing, and Valsalva
  – Blood pressure response to isometric exercise and standing
Cardiovascular Reflex Tests
Listed in order of most sensitive (less severe CAN) to least sensitive (but more severe CAN)

**Beat-to-Beat Heart Rate Variation**

With the patient at rest and supine (no overnight coffee or hypoglycemic episodes), breathing 6 breaths/min, heart rate monitored by ECG, a heart rate variation (HRV) of >15 beats/min is normal and <10 beats/min is abnormal, R-R inspiration to R-R expiration >1.17. All indices of HRV are age-dependent.\textsuperscript{[+1]}

**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 normally >1.03.

Lowest normal value of E/I ratio: Age 20-24 yr: 1.17; 25-29 yr: 1.15; 30-34 yr: 1.13; 35-30 yr: 1.12; 40-44 yr: 1.10; 45-49 yr: 1.08; 50-54 yr: 1.07; 55-59 yr: 1.06; 60-64 yr: 1.04; 65-69 yr: 1.03; 70-75 yr: 1.02.
Heart Rate Response to Valsalva Maneuver

The subject forcibly exhales into the mouthpiece of a manometer to 40 mm Hg for 15 seconds 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 mm Hg, borderline is a fall of 10-29 mm Hg, and abnormal is a fall of >30 mm Hg 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 mm Hg in the other arm.

Electrocardiographic QT/QTc Intervals

The QTc (corrected QT interval on ECG) should be <440 msec.

Resting Heart Rate

Rate >100 beats/min is abnormal.
CAN – Treatment Exercise Intolerance

- An exercise program with improvement of cardiovascular fitness can also improve CAN
- Cardiac stress test before initiating an exercise program
CAN – Treatment Orthostasis

- Stop aggravating drugs
- Raise head of bed
- Get up slowly
- Dorsiflex feet/handgrip before standing
- Cross legs while standing
- Drugs: fludrocortisone (high salt diet), midodrine, fluoxetine, octreotide, EPO if anemic
- Watch for supine hypertension. ?Short-acting antihypertensive agents at bedtime (captopril)?
PVAN

- Symptoms: dry skin, itching, edema, callus, aching, tightness, cramping
- Loss of sympathetic innervation results in high peripheral blood flow through peripheral arteriovenous shunts
- May contribute to foot ulceration, Charcot arthropathy, and bone demineralization
- Specialized tests required for diagnosis: quantitative sudomotor axon reflex testing (QSART), Neuropad test, vascular response to heat
Neuropad test – Pad on for 10 minutes
Pink – normal sudomotor function
Blue – abnormal sudomotor function
PVAN - Treatment

• Stop aggravating drugs
• Foot elevation, support stockings, diuretics
• Screen for cardiovascular disease
• Midodrine
Which of these people does (or did) **not** have diabetes?

- Mary Tyler Moore
- Thomas Edison
- Ernest Hemingway
- Billie Jean King
- Vanessa Williams
- Wade Wilson
- Halle Berry
- Gary Hall Jr
- Scott Verplank

- Neil Young
- David Crosby
- Elvis Presley
- B.B. King
- Mick Fleetwood
- Jerry Garcia
- Larry King
- Elizabeth Taylor
GIAN

- Esophageal: GE reflux and/or dyspepsia – 20%
- Gastroparesis
- Enteropathy
  - Constipation – 30%
  - Diarrhea – 10%
  - Fecal incontinence – 4%
Diabetic Gastroparesis

• Typical symptoms: early satiety, nausea, vomiting, epigastric pain and bloating, BUT there may be a lack of correlation between symptoms and degree of gastroparesis.

• Gastroparesis can, therefore, present primarily as difficulty with postprandial glucose control

• Typically (but not always) occurs in patients with other well established microvascular complications

• Diagnosis requires either UGI or EGD to rule out obstruction
Gastroparesis

- Symptomatic gastroparesis has been estimated to occur in 5-12% of patients with diabetes.
- But it may be as frequent as 30-50% of long standing patients with diabetes, some without symptoms.
- Equally frequent in type 1 and type 2.
- Natural history is that of stability without an increase in mortality.
How to measure gastric emptying

• Scintigraphy – egg whites labeled with Technetium-sulfur colloid, with jam and toast as a sandwich and water. Scan stomach hourly for 4 hours.
• Isotope breath tests
• 3-D ultrasound
• MRI
• Capsule telemetry
Scintigraphic study in gastric stasis (left panel) and gastric dumping (right panel) at 2 and 4 hours; the blue hatched lines at 2 and 4 hours refer to normal gastric retention. Compared to normals, the tracer is removed more slowly at 2 and 4 hours with gastric stasis, and more rapidly at 2 hours with gastric dumping.

Gastroparesis - Treatment

• Hyperglycemia (>180 mg/dl) acutely decreases gastric emptying, therefore glucose control is important
• Diet: homogenized food, more liquid, less fat and fiber, small frequent meals, avoid alcohol
• Avoid exacerbating drugs: calcium channel blockers, tricyclics, clonidine, GLP1 agonists, pramlintide, opiates
Gastroparesis - Treatment

- Metoclopramide
- Erythromycin (motilin agonist)
- Antiemetics (prochlorperazine)
- Domperidone and Cisapride available only under an FDA compassionate use limited access program when all else has failed
Gastroparesis - Treatment

• In severe cases, nutritional support with a jejunal feeding tube may be needed

• Experimental:
  – Endoscopic injection of botox into the pylorus
  – Gastric electrical stimulation
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mild (10–15%)</th>
<th>Moderate (16–35%)</th>
<th>Severe (&gt;35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption of homogenized food</td>
<td>When symptomatic</td>
<td>When symptomatic</td>
<td>Routinely, and use of liquid nutrient supplements</td>
</tr>
<tr>
<td>Nutritional supplementation</td>
<td>Rarely needed</td>
<td>Caloric liquids by mouth or, rarely, by PEJ tube</td>
<td>PEJ tube may be required</td>
</tr>
<tr>
<td>Pharmacologic treatment</td>
<td>Metoclopramide (Reglan), 10 mg as required, and dimenhydrinate (Dramamine), 50 mg as required</td>
<td>Metoclopramide, 10 mg thrice daily before meals by mouth, or domperidone (Motilium), 10–20 mg thrice daily before meals, with or without erythromycin (e.g., E-mycin), 40–250 mg thrice daily before meals, and dimenhydrinate, 50 mg as required, or prochlorperazine (Compazine), 25 mg as required</td>
<td>Metoclopramide, 10 mg thrice daily before meals by mouth, or domperidone, 10–20 mg thrice daily before meals, with or without tegaserod (Zelnorm), 2–6 mg twice daily, or erythromycin, 40–250 mg thrice daily before meals, and dimenhydrinate, 50 mg as required, prochlorperazine, 25 mg as required, or intravenous 5-HT₃-receptor antagonist (e.g., ondansetron [Zofran])</td>
</tr>
<tr>
<td>Nonpharmacologic treatment</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Gastrostomy-tube decompression and PEJ feeding, parenteral nutrition, or compassionate use of gastric electrical stimulation</td>
</tr>
</tbody>
</table>
Glucose control in the gastroparetic patient

- Change the timing of meal time insulin to post-prandial
- Switch from quick acting analogue to human regular
- With CSII – square wave
- In type 2’s – avoid sulfonylureas, meglitinides, GLP1 agonists, and pramlintide
GIAN - Enteropathy

- Constipation: stool softeners
- Diarrhea:
  - Rule out other causes: especially metformin, sugar substitutes (sorbitol), celiac, exocrine pancreatic insufficiency
  - Multiple possible causes: abnormal motility resulting in small bowel bacterial overgrowth, accelerated intestinal transit, increased bowel secretion
GIAN – Diarrhea Treatment

• Treat other identified cause(s)
• Bacterial overgrowth – antibiotics
• Accelerated transit/increased secretion:
  – Loperamide
  – Codeine
  – Clonidine
  – Octreotide
GIAN – Fecal Incontinence Treatment

- Loperamide
- Biofeedback training
- Rarely surgery
The most recent data indicates that in the US the annual medical cost for the treatment of diabetes is $176 BILLION.

<table>
<thead>
<tr>
<th>What is the largest driver of this bill?</th>
<th>What % of this bill is for diabetes education?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Prescription drugs</td>
<td>A. 30%</td>
</tr>
<tr>
<td>B. Hospital care</td>
<td>B. 15%</td>
</tr>
<tr>
<td>C. Diabetes supplies</td>
<td>C. 5%</td>
</tr>
<tr>
<td>D. Diabetes education</td>
<td>D. &lt;1%</td>
</tr>
<tr>
<td>E. Physician office visits</td>
<td></td>
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</table>
GUAN

- Bladder dysfunction - DCCT: 20% of men & 38% of women
- Erectile dysfunction – prevalence rate 35-75% of men
- Dyspareunia (decreased vaginal lubrication) – prevalence rate 27% of women
Bladder Dysfunction

• Decreased ability to detect a full bladder
• Incomplete emptying
• Recurrent UTI’s
• Overflow incontinence
Bladder Dysfunction

- **Diagnosis:** rule out BPH in men and structural gynecologic disorders in women, urodynamic testing
- **Treatment:** urination schedule with Crede maneuver
- Bethanechol
- Intermittent catheterization, surgery
Erectile Dysfunction

• In addition to DAN, other etiologies frequently coexist:
  – Vascular
  – Iatrogenic (medications, especially antidepressants)
  – Hormonal (low “T”) – decreases libido more than erectile function
  – Psychogenic – “fear of failure”
Erectile Dysfunction – Treatment
Cardiovascular risk reduction

Lifestyle interventions

- Esposito et al,\textsuperscript{16} 2004: 3.00 (1.09 to 4.91)
- Esposito et al,\textsuperscript{15} 2006: 3.40 (1.23 to 5.57)
- Wing et al\textsuperscript{17}: 0.90 (−0.93 to 2.73)
- Lamina et al\textsuperscript{18}: 2.79 (−0.23 to 5.81)
- Pooled effect: 2.40 (1.19 to 3.61)

Pharmacotherapy for CV risk factors

- Dadkhah et al\textsuperscript{19}: 3.10 (1.86 to 4.34)
- Herrmann et al\textsuperscript{20}: −0.50 (−13.97 to 12.97)
- Pooled effect: 3.07 (1.84 to 4.30)
Erectile Dysfunction - Treatment

• Response rate to phosphodiesterase-5 inhibitors (Viagra, Levitra, Cialis) of 60%

• Others:
  – Vacuum assist device
  – Intraurethral alprostadil (MUSE)
  – Intrapenile injection of alprostadil (Caverject)
  – Penile prosthesis
DAN – Other Manifestations

- Pupillary abnormalities result in failure of dilation in the dark, resulting in poor night vision
- Sweating abnormalities – distal anhidrosis, proximal hyperhidrosis, gustatory sweating
DAN - Summary

1. DAN, like somatic neuropathy, can be asymptomatic, but still clinically significant.
2. CAN often requires cardiovascular reflex testing for diagnosis. Orthostatic hypotension is a late manifestation of CAN.
3. CAN is associated with silent MI and increased mortality, but the cause for the increase in mortality is likely multifactorial.
4. GIAN commonly causes gastroparesis which can make glucose control difficult.
5. Diabetic enteropathy fortunately is less common, but can be debilitating.

6. GUAN in men is most commonly manifest by erectile dysfunction, which has a reasonably good response rate to phosphodiesterase-5 inhibitors.

7. Pupillary and sweating abnormalities also result from DAN.

8. DAN is best treated by prevention via glucose control (type 1) and multifactorial risk factor intervention (type 2).
9. Symptomatic treatments for already established DAN’s are available, with variable degrees of success.
The first portable glucose meter (Ames Reflectance Meter) was developed in 1969, but the first home glucose meter was not marketed until 1981. The first person to actually use a portable glucose meter at home (in 1969) was named Richard Bernstein. At the time he was:

A. An engineer

B. A physician

C. A chemist

D. A study participant