Diabetic Autonomic Neuropathy (DAN)

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Rochester Diabetic Neuropathy Study

• 1.3% of the population had diabetes mellitus
• Approximately two-thirds of these patients had subclinical or clinical evidence of a peripheral neuropathy
• Roughly half had a symmetric polyneuropathy
• A quarter had carpal tunnel syndrome
• *About 5% had autonomic neuropathy*
• 1% had asymmetric proximal neuropathy
Rochester Diabetic Neuropathy Study

- Absent in first 10 years
- After 15 y: 30% have evidence of symmetric neuropathy
- 5% of diabetics have autonomic neuropathy
- Prevalence depends on
  - Age
  - Duration of poor glycemic control
  - Presence of retinopathy and nephropathy
- 8% of patients with diabetes have another cause of neuropathy
DAN

• Earliest changes: Distal Sudomotor deficit and Cardiovagal Neuropathy.
• 10% have overt clinical autonomic failure
• 10% have neuropathic pain
DAN: Prevalence

- Community-based population in Oxford, England: Prevalence of DAN, defined by abnormal heart rate variability (HRV) test was 17% (Neil et al, 1989)
- Diacan multicenter study:
  - 1171 diabetic patients randomly recruited from 22 diabetes centers in Germany, Austria, and Switzerland
  - 17% of patients with type 1 diabetes and 22% of patients with type 2 diabetes had abnormal findings in autonomic CV function tests (Ziegler D et al, 1993)
DAN

• Most important factors associated with DAN: poor glycemic control, diabetes duration, age, female sex, and higher body mass index

• The 5 year mortality rate in patients with symptomatic DAN is three times higher than in diabetic patients without autonomic involvement
  • 25–50% die within 5–10 years of diagnosis
  • Leading causes of death are heart disease and nephropathy
  • DAN may contribute to nephropathy, cardiovascular disease
  • DAN is an independent risk factor for stroke
DAN: Symptoms

• Orthostatic Intolerance
• Sudomotor changes
• Heat intolerance
• Gastroparesis, constipation, diarrhea
• Erectile dysfunction
• Neurogenic bladder
DAN: OH

- Increased morbidity due to orthostatic hypotension
  - Role of greater splanchnic nerve involvement
  - Splanchnic-mesenteric bed is large (20% of total blood volume), and volume increases 300% post-prandially
  - This vascular bed is baroreflex sensitive
- Duration is a factor: 27% to 56% over 5-10 years
- Renal failure, cardiovascular disease and polypharmacy are compounding factors
Cardiovascular Autonomic Neuropathy (CAN)

• Damage to the autonomic nerve fibers that innervate the heart and blood vessels.

• Resting tachycardia, postural hypotension, exercise intolerance, enhanced intraoperative or perioperative cardiovascular lability, increased incidence of asymptomatic ischemia, and lower rate of survival after myocardial infarction.

• The Diabetes Control and Complications Trial (DCCT, 1998):
  • 1.7% had abnormal HRV at baseline for < 5 years duration of diabetes.
  • 6% had abnormal HRV with 5-9 years duration of diabetes
  • 12% had abnormal HRV with > 9 years duration of diabetes
Cardiac Innervation in DAN
Cardiac Innervation in DAN

Gastrointestinal Autonomic Neuropathy (GAN)

• Gastroparesis diabeticorum
• Gastric emptying is delayed in 30–50% of longstanding type 1 and type 2 diabetic patients (Ma et al., 2009).
• DAN can impair gastric acid secretion and gastrointestinal motility.
• Typical symptoms of diabetic gastroparesis: early satiety, nausea, vomiting, postprandial fullness, abdominal bloating, epigastric pain, and anorexia.
  • Can be silent when very mild
  • Patients with gastroparesis have emesis of undigested food consumed many hours or even days previously
  • Episodes of nausea and vomiting may last days to weeks or occur in cycles (Horowitz et al., 1991)
A 75-year-old woman was admitted to the hospital due to severe nausea and vomiting. She had a 12-year history of type 2 diabetes with erratic glucose control complicated by severe bilateral retinopathy and peripheral neuropathy.
Gastrointestinal Autonomic Neuropathy (GAN)

• Interferes with nutrient delivery to the small bowel
  • Nutritional deficiency

• Disrupts the relationship between glucose absorption and exogenous insulin.
  • May result in wide swings of glucose levels, unexpected postprandial hypoglycemia and labile diabetes.

• Delayed gastric emptying influences the absorption of orally administered drugs.
GAN

- Gastric dysrhythmias: bradygastria and tachy gastria.
- The dominant frequency of EGG is 3 cycles/min (cpm) in Normal subjects.
- GAN: The 3 cpm waves disappeared with bradygastria, and postprandial increases in the peak powers of EGG were absent in the DM group.

Evaluation:
- Endoscopy
- Manometry to detect antral hypomotility or pylorospasm
- Double-isotope scintigraphy to measure solid- and liquid-phase gastric emptying.
- stable isotope breath test.
- hyperglycemia slows gastric emptying: measure during euglycemia.
GAN: Gastric mucosal biopsy

- Gastric mucosal nerves had reduced density and abnormal morphology compared to control subjects
  - The horizontal and vertical meshwork pattern of nerve fibers that normally extends from the base of gastric glands to the basal lamina underlying the epithelial surface was deficient in diabetic subjects.

- Neurologic abnormalities on clinical examination in 12/13 diabetic subjects and nerve conduction studies abnormal in all patients.

- The epidermal nerve fiber density was deficient in skin biopsies from diabetic subjects.
Figure 2 Neuropeptide localization and distribution in confocal images of stomach mucosa in control and diabetic subjects. The left side of the image panel represents control subjects and the right side diabetic subjects.

M.M. Selim et al. Neurology 2010;75:973-981
Figure 3 Differences between diabetic and control subjects for gastric, fundus, and antrum mucosal nerve fiber density using design-based stereology (A) Fundus length density, LD, p = 0.013.
Figure 4 Confocal images of skin from the thigh of a control and diabetic subject. The left side of the panel represents a control subject’s thigh while the right side represents a diabetic subject’s thigh.
GAN: Management

• Diet modification
• Nutritional supplement
• Prokinetics
• Antibiotics
• Acarbose (alpha-glucosidase inhibitor) for post-prandial hypotension
• Epalrestat (aldose reductase inhibitor) may improve the decreased gastric motility in diabetic patients.
Gastrointestinal Autonomic Neuropathy (GAN)

• Constipation is the most common complication: nearly 25% of diabetic patients.
  • Severe constipation may be complicated by ulceration, perforation, and fecal impaction
  • Anorectal manometry to distinguish colonic hypomotility from recto-sigmoid dysfunction causing outlet obstructive symptoms.

• Diarrhea may be present in 20% of DAN patients
  • Can be sudden, explosive, and paroxysmal.
  • Contributing factors: stasis of bowel contents with bacterial overgrowth, reduced pancreatic exocrine secretions, probably due to vagal pancreatic neuropathy.
Figure 2 Patient 14: Radiologic evidence of gastrointestinal hypomotility The patient defecated at 3-week intervals.
GAN: Autoimmune Factors

• GAD antibodies, with or without anti-islet cell or anti-insulin antibodies in 6/16 diabetic gastroparesis patients (12 with type 1 diabetes).

• Ganglionic antibodies involved in some
Serum Concentrations of Ganglionic-Receptor-Binding Antibody in Patients with Acquired Dysautonomia and in Control Subjects
Recovery of Sweating Function in Patients with Subacute Autonomic Neuropathy

Suspect Autoimmune GAN when disproportionate to the severity or duration of diabetes
Genitourinary Autonomic Neuropathy

- ED
- Retrograde ejaculation
- Cystopathy
DAN: Neurovascular Dysfunction

• Impaired skin blood flow
• Decreased responsiveness to mental arithmetic, cold pressor, hand grip, and heating.
• Dry skin, loss of sweating, and the development of fissures and cracks
  • Leads to infectious ulcers and ultimately gangrene.
Hypoglycemia-associated autonomic failure

- Hypoglycemia becomes a major problem early in T1DM but later in T2DM.
  - Beta cell failure explains loss of glucagon secretion in response to hypoglycemia.
- Attenuated sympatho-adrenal response to falling plasma glucose.
  - Causes defective glucose counter-regulation
  - Contributes to hypoglycemia unawareness
- Recurrent hypoglycemia also reduces baroreflex sensitivity
  - Increased risk of labile BP, arrhythmia and sudden death
Thank you