Neuropathies A-Z Linked to Diabetes
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- Discuss diabetic neuropathies.
- Identify treatment options including pharmacological agents used to treat neuropathies associated with diabetes.
- Discuss current pharmacologic options for managing diabetes.

Diabetes
- A disease in which the body does not make enough insulin or properly use insulin resulting in hyperglycemia.
- If diabetes is left untreated or poorly controlled (A1C>7%) complications will affect all body systems.
- How long has the patient had diabetes?
  - On average 3-15 years prior to diagnosis.
- 2012 data estimates 29.1 million American have diabetes but 9.1 million people are estimated to be unaware they have diabetes.
Did You Know?

- Approximately 60-70% of people with diabetes have some form of neuropathy.
- Highest rates are among patients who have had diabetes >25yrs and overweight.
- DCCT showed a reduction in diabetic neuropathy; EDIC (13-14yrs later) revealed a high prevalence of diabetic neuropathy—every blood glucose level counts!
- Considered the most prevalent chronic complication of diabetes!

Diabetic Neuropathy

- Four main types
  - Peripheral
    - Most common/diagnosed
  - Autonomic
    - Most daunting to treat
  - Radiculoplexus (Diabetic amyotrophy)
    - Thighs, hips, buttocks, and legs more common in Type 2 diabetes
  - Focal/Mononeuropathy
    - Damage to a specific nerve suddenly in the face, torso, or leg

Pathology of Diabetic Neuropathy

Neuron: Structural and functional unit of the nervous system
Axon: central core of the nerve fiber that conducts impulses away from the nerve cell body.
Myelin: Fat substance forms a protective sheath around the nerve fibers.
Estimates are there are 95-100 billion nerve cells in the body up to 1 trillion.
Pathology of Diabetic Neuropathy

• Hyperglycemia can result in neuropathy if left untreated.
  • Prolonged exposure to hyperglycemia (inflammation) damages delicate nerve fibers.
  • Insulin not needed to move glucose into nerve cells
  • Weakens the small blood vessel walls that supply nerves with oxygen and nutrients
  • Interferes with the nerve's ability to transmit signals due to excess glucose along
  with fructose depleting the cell of intracellular metabolism.
  • Hyperglycemia along with cellular imbalance and lipid metabolism produces a state
    of oxidative stress depriving the cells of oxygen and prevents growth resulting in
    apoptosis.
  • End result is damage to neuron, axon, and myelin sheath resulting in cell death.

Factors Increasing Susceptibility
for Diabetic Neuropathy

• Poor blood glucose control
• Duration of diabetes (adolescents)
• Kidney disease
• Overweight/obesity
• Smoking
• Alcohol use
• Genetic factors/Hereditary Sensory Neuropathies
• Occupation
Symptoms of Diabetic Neuropathies
Clinical Vs. Subclinical

Typically mild at first clinically
• Numbness, tingling, or pain in the toes, feet, hands, arms, and fingers.
• Wasting of muscles of the feet or hands
• Dry skin
• Indigestion, nausea, or vomiting
• Diarrhea or constipation
• Dizziness, faintness, orthostatic hypotension
• Problems with urination
• Sexual dysfunction for both men & women
• Generalized weakness

Autonomic Neuropathy Associated with Diabetes

• Autonomic nerves permeates all organ systems
• Functions largely below the level of consciousness
• Leads to disorders that are life threatening
• Is subdivided into two subdivisions
  • Parasympathetic (Rest & Digest)
    • Vagus nerve mediates ~75% of all parasympathetic activity
  • Sympathetic (Fight or Flight)

Cardiac Autonomic Neuropathy

• Most studied of all the diabetic autonomic neuropathy
• Cardiac denervation: Heart rate variability (HRV)
  • Subclinical 1yr after diagnosis of type 2 and 2yrs after type 1
  • Resting tachycardia (r/o thyroid and/or anemia 1st)
• Exercise intolerance
• Abnormal cardiovascular response to exercise
• Silent MI
• Prolonged QT interval in persons with diabetic autonomic neuropathy
Treatment

- Resting and Stress Nuclear study for screening, especially before starting an exercise regimen
- Lipid management
  - Pravastatin (moderate intensity) hypothesized to increase adiponectin levels and improve insulin sensitivity or pitavastatin (Livalo®) vs. rosuvastatin shown to increase insulin resistance and respectively A1C levels
- Hypertriglyceridemia: icosapent ethyl (Vascepa®) & fenofibrate
- Optimize blood glucose control
- Blood pressure control/Heart Rate control: ACE/ARB & Beta Blocker
- Caution: Beta Blockers can mask the symptoms of hypoglycemia; education
- Stop Smoking
- Reduce BMI

Diabetic Foot

- Significant morbidity and mortality rates
- Characterized by an edematous, erythematous warm foot
- Eventually severe deformities contributing to foot ulcers and lower extremity amputations
- Peripheral wounds — Estimated to be the third leading cost of treating diabetes
- “Standard Therapy” leaves 70% of diabetic wounds unhealed.
  - Phase two of cellular macrophage mobilization is greatly reduced in diabetes that aids in tissue repair
- Future treatments will need to focus on restoring the normal healing cascade of the body! Break the inflammatory process.

Treatment of Diabetic Foot

- Screen at least yearly
  - Examine feet, monofilament
  - Teach patient proper foot care “Survival Skills”
    - Proper footwear
    - Trim toenails straight across
    - Inspect feet daily
    - Apply lotions after bathing but not in-between toes
    - Vicks Vapor Rub – rough nails
    - Off loading
Ear: Hearing Impairment

- Injury to vasculature or neural system of the inner ear.
- Autopsied patients with diabetes reveal sclerosis of the internal auditory artery, thicker vessel walls, demyelination of the cochlear nerve, atrophy or the spiral ganglion, and loss of the outer hair cells.
- Estimated persons with diabetes age 50-69 yrs., more than 70% have high-frequency impairment and 1/3 have low- or mid-frequency impairment.

Hearing loss

Ask your patient the following questions:
- Has anyone complained that you're not listening?
- Do you often ask people to repeat themselves?
- Do you complain that people are always mumbling?
- Do you have trouble understanding conversations with more than two people?
- Have people complained that you listen to the TV or radio too loudly?
- Do you have trouble understanding conversations in crowded rooms?
- Have you fallen in the past 3 months or caught yourself from falling?
- Assess for and recent falls or "almost" falls.
- Treatment: Refer to an ENT for further evaluation.

Focal Neuropathy

- Most often affects nerves in the head, torso, or leg.
- Inability to focus the eye.
- Double vision.
- Aching behind one eye.
- Paralysis on one side of the face.
- Pain on the outside of the shin or inside of the foot.
- Severe pain in the lower back or pelvis.
- Pain in the chest, stomach, or side.
- Mistaken for a heart disease, heart attack, or appendicitis.
- Come on quickly and improve on their own typically in 6-8 weeks.
- Treatment may include: do not cross the legs over the knees or elbows on the table.
Gastroparesis

- Nerve damage to the digestive system
- Involves the vagal, pelvic and mesenteric nerves
- Estimates are 50% or people with diabetes.
- Symptoms: persistent nausea and postprandial vomiting, bloating, and loss of appetite, and early satiety vs. asymptomatic
- Associated with the development of bezoars, bacterial overgrowth, and ulcers
- "Brittle Diabetic" = Insulin placement not taken strategically for altered digestion.

Treatment of Gastroparesis

"You look fine, you can't be sick"

- Dietitian to counsel on need for small frequent, low fat and fiber foods.
- Insulin adjustment and strategic placing with digestion
- Medications: erythromycin to speed up digestion, metoclopramide to speed up digestion and relieve nausea
- Acute: metoclopramide 10mg PO three time a day for 5 days FDA no longer than a year if benefit outweighs risks (specialist for IV use in acute hospitalization)
- Erythromycin (macrolide): Use as a potent stimulant of gastric emptying by stimulating fundic contractions. Caution: 4 weeks at a time due to side effects
- Chronic: jejunostomy and venting gastrostomy tube for nutrition and decompression. Gastric electrical stimulation may be considered for refractory symptoms.
- Under Investigation: tricyclic antidepressants, acupuncture, and placement of a transpyloric stent

Hypoglycemia Unawareness

- Hypoglycemia as defined as a blood glucose <70mg/dl without symptoms
- Typical Sympathetic Pathway: Secretion of Glucagon, Epinephrine, Catecholamine, Cortisol
- Type 1 Diabetes glucagon response can begin to be impaired after 5yrs of diagnosis and can be almost undetectable 15-30yrs after diagnosis in poorly controlled DM
- Unable to self treat due to neuroglycopenia
- Others must provide treatment
Treatment of Hypoglycemia Unawareness

- If patient is alert and able to swallow 15-15 rule (fast-acting carbohydrates)
- Administer 50ml of 50% Dextrose or Glucagon SID (Rx for home use)
- Safety Education: Always need to check BG levels before driving (<100mg/dl), wear ID, Another low BG level within 24 hours, more frequent monitoring, nocturnal awareness (2-4 am)
- BGAT training (Blood Glucose Awareness Training)
- Technology: Sensor

Lower Intestinal Tract Dysfunction

- Results from damage to the efferent autonomic nerves
  - Diabetic diarrhea, constipation, and/or fecal incontinence r/t anal sphincter incompetence
- Leads to abnormal motility, secretion, and/or absorption
  - "Diabetic" diarrhea and/or constipation (estimates 20-60% of people with DM)
  - Profuse, watery, and occurs at night. Then alternates with constipation.
  - Bacterial overgrowth found in 34% of patients
  - Access for use of Probiotics
- Treatment: Antibiotic therapy. Tetracycline fallen out of favor of rebalancing enteric flora. Antibiotic therapy should be empiric and broad to cover both aerobic and anaerobic microorganisms. Goal is targeted for:
  - Amoxicillin-clavulanate ~75% effective in patients with diabetes

Neurogenic Bladder

- Motor function of the bladder is impaired: up to 50% or greater of people with diabetes
- Diminished bladder sensation/need to void
- Difficulty emptying bladder
- Dribbling
- Overflow incontinence
- Frequent urinary tract infections
- Bladder residual >150ml
Diagnosis/Treatment of Neurogenic Bladder

- Cystogram
- Post void residual
- Elevated BUN/CRE
- Decreased GFR
- Schedule urination every 2-4 hours (waking hours)
- Manually palpate bladder
- Self catheterization

Tx UTI but aim for prevention
- Avoid medication that could increase urinary retention
  - Anticholinergic agents, tricylic antidepressants, & Calcium channel blockers

Orthostatic Hypotension

- Systolic blood pressure falls >20 mm/Hg upon standing
- 1st Control blood glucose levels: Referral to a specialist
  - Orthostatic Hypotension: Compression stockings, abdominal binder, and precautions upon rising/physical counter maneuvers
  - Maintaining hydration, small frequent meals,
  - Raising the head of the bed
  - Review medication contributing to orthostatic hypotension
    - Antidepressants, diuretics, amitriptyline, antihypertensive agents, alpha-blockers, sildenafil and other phosphodiesterase-5 inhibitors
  - Fludrocortisone and sodium chloride
    - Unresponsive to mineralocorticoids and non-pharmacological interventions
      - midodrine 2.5mg TID or droxidopa 100mg TID

Peripheral Neuropathy

- Most common diagnosed diabetic neuropathy
- Loss of Sensation to extremities: Paresthesia: burning/tingling bilaterally, progresses to burning and stinging with stabbing pain at times.
- Nerves to the feet are the longest in the body
- Progression of the disease results in an increase risk of injury and falls.
- Evidence supports prediabetes state development of peripheral neuropathy
Treatment of Diabetic Nerve Pain

- Nerve pain:
  - Alternative therapies: physical therapy, acupuncture, magnetic therapy, and biofeedback
  - Assess for excessive use of acetaminophen and ibuprofen
  - Anti-epileptic medications: gabapentin, pregabalin (Lyrica®), or carbamazepine can be prescribed for nerve pain. Side effects: drowsiness, dizziness, and swelling
  - Antidepressants such as tricyclics: desipramine and imipramine provide relief of mild to moderate pain. Side effects: dry mouth, sweating, weight gain, dizziness, and constipation.
  - Antidepressants such as SNRI (serotonin and norepinephrine reuptake inhibitors): duloxetine can relieve pain with fewer side effects. Possible side effects: nausea, sleepiness, dizziness, decreased appetite and constipation

Pupillomoter

- Abnormal pupillary response to darkness
- Slower than usual dilation
- Stress caution during night driving
- Always turn lights on when entering a dark room
- Use nightlights in darkened hallways and restrooms
- Schedule yearly eye exam (Healthy People 2020)

Radiculoplexus Neuropathy: Diabetic Amyotrophy

- Sometimes referred to proximal neuropathy
- More common in T2DM
- Causes muscle weakness – assess for any recent falls (almost)
- Affects muscles in the thighs, legs, buttocks, and hips (a.k.a. sciatica)
- Typically unilateral, sudden severe pain, and possible abdominal swelling
- Usually resolves in time but can reoccur.
Sexual Dysfunction

- Results from autonomic neuropathy
- Men = erectile dysfunction - decrease quality of life
  - 3 fold probability in men with diabetes
  - Men with diabetes are less responsive to drug therapies
- Women = decreases sexual desire, arousal, orgasm, vaginal dryness, and pain
  - Dysfunction is estimated at 4.7% in women vs. 3.9% in men. The highest rates in post menopausal women

Treatment of Sexual Dysfunction

- Men: sildenafil (Viagra, Revatio), tadalafil (Accirca, Cialis), and vardenafil (Levitra)
  - Start at lowest dose 2nd and is determined by renal, BPH, heart (use of nitrates), and liver history
- Women: vaginal lubricants, treat any underlying depression, clitoral therapy device, and Mediterranean diet
  - Hormonal therapy controversial especially in women who are post menopausal
  - Smoking cessation

Temperature Regulation (Sudomotor)

- Autonomic neuropathy affects the nerves that controls sweating.
- Profuse sweating at night or while eating (Gustatory hyperhidrosis)
- Caution with exercise and avoid extreme temperatures: to avoid overheating.
- Anhidrosis - a complete lack of perspiration and can be life threatening
- Dry skin is another clinical symptom
Global Management of Neuropathy

- Blood Glucose Control A1C <7%
- Control of Blood Pressure
- Lipid Management
- Smoking cessation
- Exercise
- Meal Planning
- Limit alcohol use

Glycoslated Hemoglobin (A1C)

\[ A1C\% = \frac{\text{Retrospective Blood Glucose Levels}}{\text{Fasting and before meals}} \]

\[ \begin{align*}
12 & \rightarrow 298 (240-347) \\
11 & \rightarrow 295 (217-341) \\
10 & \rightarrow 249 (193-282) \\
9 & \rightarrow 212 (200-249) \\
8 & \rightarrow 183 (147-217) \\
\text{Goal} & \rightarrow 154 (123-185)
\end{align*} \]

- Diagnosis at 6.5%
- 6 \rightarrow 126 (100-154)
- 5 \rightarrow 97 (60-130)

Blood Glucose levels for Control

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood Glucose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting and before meals</td>
<td>70-130mg/dl</td>
</tr>
<tr>
<td>2 hours post Meal</td>
<td>≤ 180mg/dl</td>
</tr>
<tr>
<td>After 1st bite of food</td>
<td>≤ 140mg/dl</td>
</tr>
<tr>
<td>Bedtime</td>
<td>90-155mg/dl</td>
</tr>
</tbody>
</table>

- "Diet" Controlled/no medications: Check BG levels once to twice a day but at staggered times.
- Oral Antihyperglycemic Agents: Check BG levels once to twice a day at staggered times.
- Basal Insulin and oral antihyperglycemic agents: Fasting and one other time at staggered times.
- Basal/Bolus (diabtess): Check blood glucose levels at least 4 times a day 8K, L, D, W.
Assessment & Plan

Oral Agents as a “Substitution” for the Pancreas

- Biguanides (metformin) for “basal” coverage
  - Lactic Acidosis: monitor kidney function, procedures requiring contrast and IV dye
- Sulfonylureas/Meglitinides: glimepiride (Amaryl®), glipizide (Glucotrol®), regaglinide (Prandin), nateglinide (Starlix)
- True sulfa allergy
- Insulin Stimulators for “bolus” coverage
  - DPP-4 Inhibitors: sitagliptin (Januvia®), saxagliptin (Onglyza®), alogliptin (Nesina®), linagliptin (Tradjenta®)
  - GLP-1 analogs: exenatide (Byetta), extended release exenatide (Bydureon®) or liraglutide (Victoza®), albiglutide (Tanzeum®)

Every Blood Glucose Counts “Post Prandial Levels”

- Only for type 2 diabetes/wt.loss.
- Contraindicated in patient with medullary or Thyroid carcinoma.

Side effects: Thyroid C-cell tumor (animal study), Pancreatitis, atrial fibrillation, URI, N/V, injection, site reaction.
The Miracle

Although insulin doesn't cure diabetes, it's one of the biggest discoveries in medicine. When it came, it was like a miracle. People with severe diabetes and only days left to live were saved. And as long as they kept getting their insulin, they could live an almost normal life.

Types of Insulin: Actions and Administration

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Action</th>
<th>Administration and Dosage</th>
<th>Carbohydrate Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td>1-2h</td>
<td>3-4h</td>
<td>4-6h</td>
<td>Fast-acting</td>
<td>Subcutaneous injection</td>
<td>Small or no change</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-8h</td>
<td>12-24h</td>
<td>24-36h</td>
<td>Intermediate-acting</td>
<td>Subcutaneous injection</td>
<td>20-30% change</td>
</tr>
<tr>
<td>Long-acting</td>
<td>8-12h</td>
<td>24-36h</td>
<td>36-48h</td>
<td>Slow-acting</td>
<td>Subcutaneous injection</td>
<td>30-50% change</td>
</tr>
<tr>
<td>Ultra-long-acting</td>
<td>24-36h</td>
<td>48-72h</td>
<td>&gt;72h</td>
<td>Ultra-slow-acting</td>
<td>Subcutaneous injection</td>
<td>50-70% change</td>
</tr>
</tbody>
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References


References Cont.


