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NO FINANCIAL DISCLOSURES
An estimated 285 million people worldwide had diabetes in 2010, according to the International Diabetes Federation. The federation predicts as many as 438 million will have diabetes by 2030.

Nearly 110 million wounds!

U.S… Yr. 2050: 48 Million DM, 9.6 Million Ulcers
Amputation secondary to NEUROPATHY and PAD
BKA associated with NEUROPATHY and PAD
Neuropathic Ulcers...

B-K Amputation?
Diabetic Foot Ulcers

- One of the most common complications of diabetes
  Annual incidence 1% to 4%\textsuperscript{1-2}
  Lifetime risk 15% to 25%\textsuperscript{3-4}
- \textasciitilde15\% of diabetic foot ulcers result in lower extremity amputation\textsuperscript{3,5}
- \textasciitilde85\% of lower limb amputations in patients with diabetes are proceeded by ulceration\textsuperscript{6-7}
- Peripheral neuropathy is a major contributing factor in diabetic foot ulcers\textsuperscript{1-7}
  - Other factors: foot deformity, callus, trauma, and peripheral vascular disease

Diabetic Peripheral Neuropathy: What is it?

- Nerve damage and dysfunction secondary to diabetes mellitus type 1 or 2
  - Consensus definition: “the presence of an abnormality of nerve conduction and a symptom or symptoms or a sign or signs of neuropathy confirm Distal Symmetrical Polyneuropathy (DSPN). If nerve conduction is normal, a validated measure of small fiber neuropathy may be used.”

Diabetic Neuropathy: The Forgotten Complication

Results of the 2005 ADA National Survey

- Only one in four survey respondents who experience symptoms of diabetic neuropathy have been diagnosed with the condition.
- The majority of respondents who experience symptoms (56%) remain unaware of the term DIABETIC NEUROPATHY.
- 62% believe that their symptoms are associated with their diabetes, but only 42% have been told by their physician that diabetes is the cause.
- Approximately one in seven people who said they talked to their doctor about their symptoms and pain reported that no cause was mentioned.

May 10, 2005 /PR Newswire via COMTEX.
Neuropathy is Commonly Underdiagnosed

For every mistake made for not knowing, 10 are made for not looking

- J.A. Lindsay

Clinical Unmet Needs in DM Neuropathy

- There are a wide range of treatments available for neuropathic pain.
- This prescribing pattern suggests that there is no one treatment that addresses all the factors.
- Despite a spectrum of drugs available with different modes of action, many patients remain inadequately treated in several aspects of the disease.

**Increasing level of importance**

- Improved efficacy
- Improved side effect profile
- Reduced time to onset of action
- Fewer drug-drug interactions
- Reduced pill burden

Datamonitor Research 2008.
Clinical Impact of DPN Total Symptoms

DPN

Painful neuropathic symptoms

Impairment Disability Handicap

Neuropathic deficits

Ataxia Weakness

Foot Ulcers... Charcot

Quality of life ↓

Falls

Fractures

Infection (skin, bone)

Surgery, Amputation 96,000/y

Mortality ↑

Cost ↑ $37B

NEUROPATHY...Charcot...Ulcer...Osteo...BKA
Some Effects of Amputation on Quality of Life

- Limitation of daily activities
- Impairment of physical activity
- Early Retirement
- Reduced Income
- Loss of Social Contacts
- Impairment of Sexual Activity
Aging, Disease and Falls

- Risk of falling typically increases when (age-related) diseases emerge
- One third of people >65y fall annually
- Each day in the US 63 people die from a fall-related injury
- An additional 1800 are hospitalized
- The commonest causes of falling are:
  - Hypertension
  - Diabetes
  - Polypharmacy
- Therefore we need to compensate for both age- and disease-related factors that can impact on balance and stability

Neuropathy in Diabetes

Centers for Disease Control and Prevention website at http://www.cdc.gov/injury/wisqars
Clinical Tests

- Reaction Time
  - Hand
  - Foot

Postural Sway

Proprioception

Vision
  - Visual Acuity
  - Contrast Sensitivity

Lower Limb Strength
  - Ankle dorsi-flexion
  - Knee flexion
  - Knee Extension

Sensation

Physiology of Falls
Risk Factors for Falls
Distal Symmetric Diabetic Neuropathies

Subtypes:

Large-fiber

- MYELINATED SENSORY-MOTOR
  - Deep-seated pain (A-δ type)
  - Wasting and weakness
  - Numbness, pins and needles, tingling & ataxia
  - Impaired vibration perception
  - Loss of position sense
  - Loss of reflexes
  - Impaired nerve conduction velocity
  - Interferes with normal life
  - Risk of falling and fractures

Small-fiber

- UNMELINATED SENSORY ONLY
  - Superficial pain (C-fiber type)
  - Electric shock, burning, allodynia
  - Autonomic dysfunction
  - Thermal imperception
  - Normal strength and reflexes
  - Electrophysiologically silent
  - Quantitative sensory testing and skin biopsies
  - Produces symptoms
  - Leads to morbidity and mortality

Large Fiber Neuropathy

Carry info regarding position and vibration
- weakness...<DTR, <Vib
- "numbness without pain"

Diagnosis: EMG, NCV
Simple Tests of Large-Fiber Function

**Time (s)**
- Tandem stand
- 1-foot stand
- Balance walk
- Foot tapping

**Distance (m)**
- 2-minute walk

**Controls (n=11)**
**Diabetic controls (n=8)**
**Diabetic neuropathy (n=14)**

* P<0.05 vs nondiabetic controls; †P<0.01 vs nondiabetic controls

SMALL FIBER NEUROPATHY

Carry info regarding pain and temperature
- stocking/glove effect
- Electrical studies are WNL

Diagnosis: Clinical info
Skin biopsy
Differential Dx of Small Fiber Neuropathy

MS
Raynauds
FMS
RSD/CRPS
Restless Leg
Neuroma
CAUSES OF SMALL FIBER NEUROPATHY

Autoimmune
Sarcoid
Sjogren’s Syndrome
Inflammatory Bowel Disease
Lyme Dis
EtOH abuse
Drugs, Toxins
Amyloidosis
Lupus
Vasculitis

Small Fiber Neuropathy

- Pain is C-fiber type, burning, superficial, allodynia
- Early hyperesthesia and hyperalgesia, impaired neurovascular function
- Late hypoesthesia and hypoalgesia
- Impaired warm thermal and pain thresholds, decreased IENF
- Decreased sweating
- Normal strength, reflexes and EMG!!!
DIABETIC NEUROPATHY

The Use of 1 and 10g Monofilament Test
Diabetic Neuropathy: A Small Fiber Disease

Normal Skin Biopsy

Normal innervation with small nerve fibers seen in the epidermis (arrows). Skin biopsy specimens with protein gene product 9.5 immunostaining.

Small Fiber Neuropathy Biopsy

A specimen from a patient with small fiber neuropathy shows denervation with no small nerve fibers seen in the epidermis.

Tavee J, Zhou L Cleveland Clinic Journal of Medicine 2009;76:297-305
Work-up for Peripheral Neuropathy:

- A1c (Glycohemoglobin)
- CBC
- Chemistry Profile
- TSH
- B12, Folic Acid Level
- Serum Protein Electrophoresis (SPEP)
- Sedimentation Rate, ANA, RPR, RA
- Heavy Metal Screen (Lead, Arsenic, Mercury)
- *EMG/NCV
- *Biopsy/CSF
- *Genetic screening
Pain Can Directly Lead to Sleep and Psychological Symptom Problems

Paradigm of pain

Sleep interference can directly result from chronic pain and exacerbate pain

Psychological symptoms are strongly associated with NeP, anxiety and depression

Management strategies of NeP patients is to improve overall patient functionality and treat all comorbidities to improve QOL


Depression, Anxiety, Sleep – More Commonly Present with Neuropathy than Not

A prospective study of 122 symptomatic DPN patients compared those who had >6 months of metformin to those without metformin

• Metformin-associated cobalamin deficiency may contribute to the clinical burden of DPN ($P<0.001$).

The severity of DPN positively correlates to increases in the cumulative metformin dose ($P<0.001$)

The Neuropathy Impairment Scale has been designed in an effort to maximize the measurement of potential changes in all motor, sensory and reflex activity in the lower limbs. Total score ranges from normal = 0 to maximum of 16.

$n = 122$

Diabetic Neuropathy Treatment Options

Glucose Management

Pain Management

Interventional Tx
- Regional N Blocks
- Sympathetic Blocks
- Spinal Cord Stimulators
- Infusion Therapy

SURGERY
- Tarsal Tunnel Deconpression
- Neurolysis

TCAs, Pregabalin
Gabapentin / Duloxetine
Opioids
Medical Foods (Metanx)
Vitamins (B12, Folic acid...)
Topical Compounds

Adapted from Tavakoli M and Malik R. Expert Opin Pharmacother. 2008;9(17):2969-2978.
Medical Food – Regulated by FDA

Nutritional support specifically modified for the management of the distinct nutrient needs that result from the disease or condition, as determined by medical evaluation.

- Metanx® is dispensed by prescription under supervision of a HCP
- Metanx® addresses the underlying condition such as endothelial dysfunction / DPN
- Metanx® is scientifically recognized in peer-reviewed literature

Patient received baseline skin punch biopsy and given L-methylfolate, Me-Cbl, P-5-P (Metanx®) twice daily and followed for six months. Left image represents baseline skin punch biopsy at left calf. Right image represents six month follow up skin punch biopsy. Patient average increase of 3.75 nerve fibers per mm. Skin Punch Biopsy Analysis and Images Performed by Theraphath, LLC.

Metanx® is a medical food dispensed by prescription for the clinical dietary management of endothelial dysfunction in patients with diabetic peripheral neuropathy. Use under medical supervision.

Results from a 20 week, open label trial of Metanx® in 24 patients with a partial response to pregabalin.

After nutritional management with Metanx®:
- The average absolute pain reduction after 20 weeks in the study group was 3.0 compared to .25 in the control group ($P<0.001$).
- After 20 weeks, the study group experienced greater pain relief compared to the active control group, 87.5% vs. 25.0% reduction in NPS respectively ($P=0.005$).

Diabetic neuropathies are a heterogeneous group of disorders that occur in about 50% of patients with diabetes. Approximately 40% are painful.

DPN is the most common form of neuropathy and is a mixed sensorimotor neuropathy involving small and large fibers, with each fiber having a different etiology and producing its own constellation of features.

The pathogenesis is being unraveled and therapy directed at oxidative/nitrosative stress and autonomic imbalance have lead to major breakthroughs in management with the ability to reduce cardiovascular events, regenerate nerves, stop falls and reduce foot ulceration. There are promising agents in the wings including gene therapy that address the core pathogenic mechanisms and are potential targets for therapy in the future.

Diabetic Neuropathy

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