Clinical Neurological Society of America

January 15-18, 2022
Clearwater Beach, FL

48th ANNUAL MEETING

Diabetic Neuropathy (DNP) Classification & treatment Update

Bassam A. Bassam, MD, FAAN
Professor of Neurology
University of South Alabama

Disclosure;

- Argnex Myasthenia Gravis Advisory Board and Speaker Bureau.

Learning objectives

- Discuss various DNP presentations.
- Describe various DNP pathophysiology.
- Explain the scientific basis for treatment trials
- Review current specific and symptomatic management of DNP

Diabetic Neuropathy Definition

- "A demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy.

  It includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system"

  (Consensus Statement. *Diabetes Care.* 1988;11:592-597.)

  Over 25 Millions, and 27 % of people ≥ 65 years in USA are diabetics.

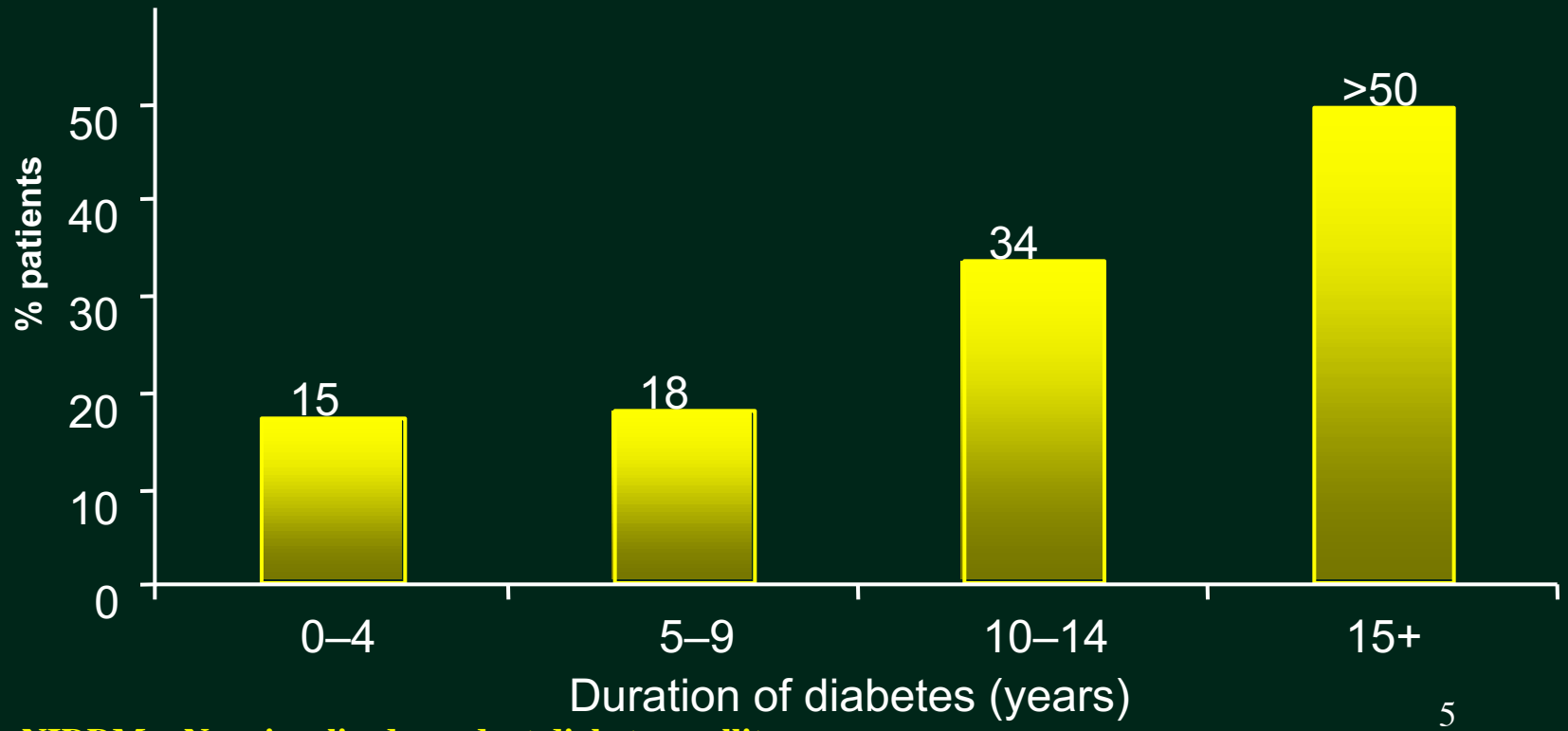
Diabetic Neuropathy (DNP) Classification

- Symmetric typically distal;
  - Distal sensorimotor polyneuropathy
  - Predominant autonomic neuropathy
  - Acute/subacute painful neuropathy (insulin neuritis, neuropathic cachexia)

- Asymmetric usually proximal;
  - Proximal diabetic neuropathy (diabetic lumbosacral plexopathy, diabetic amyotrophy, Bruns-Garland syn.)
  - Compression mononeuropathy (CTS, ulnar NP)
  - Cranial neuropathy
  - Isolated thoracic radiculopathy

Prevalence of Distal Polyneuropathy

- 6 - 15% have neuropathy at time of diagnosis
- ≥ 50% develop neuropathy within ≥ 15 years of diabetes
- 18 – 39 % of all diabetics have symptomatic neuropathy
- Glycemic control, vascular disease, HTN, smoking, age, gender, hyperlipidemia, weight, reduced activity are contributing factors.



NIDDM = Non–insulin-dependent diabetes mellitus

Distal Sensory or Sensorimotor and Autonomic Polyneuropathy

- Most common type of all neuropathies
- Distal sensory disturbances in “length-dependent” pattern (Stocking & glove pattern)
  - usually seen when DM present for several years
  - NCS abnormalities in 10% at time of DM diagnosis
- Due to metabolic derangement and microvascular abnormalities of endoneural capillaries leading to “dying-back” distal axonopathy.

Distal Sensory or Sensorimotor and Autonomic Polyneuropathy

- Greater loss of small nerve fibers, relative sparing of proprioception & DTRs are usually preserved
- Typically distal symmetric sensory features predominate (positive and/or negative symptoms)
- Slowly progress and extends up (stocking/glove pattern)
- Neuropathic pain present ≥ 1/3 of cases
- Weakness is usually absent or noted later (toes/feet)
- Co-existing upper limbs CTS and/or ulnar NP are relatively common
- Autonomic symptoms are variably encountered

Small Fiber Dysfunction Consequences;

- Progressive numbness and neuropathic pain impact
- Painless thermal, mechanical, and chemical injuries often are principal contributor to foot ulcers (most common medical cause of limb amputations)
- Painless diabetic arthropathy (Charcot's joint)
- Subgroups of patients has mostly small fibers (type I) versus large fibers sensory loss consequences (elderly with type II long standing DM).

Diabetic Autonomic Neuropathy

- Usually coexists with, and autonomic symptoms are more prominent with increased duration of DM, poor glycemic control, and severity of DNP
- Pure autonomic neuropathy may occur in DM type I
- Impotence (most common), sweating abnormality, constipation/diarrhea, gastroparesis, bloating, postural hypotension, resting tachycardia
- Cardiac arrhythmias contributes to increased cardiac morbidity and mortality
- Diabetics with MI are twice as likely to die as matched control **(Hilsted et al. Cl. Aut. Disorders 1997)**
- Severe DANP has been correlated with AEs on survival.

Diabetic Dysautonomia

Peter Soh, MD, MPH, Bassam Bassam, MD
UNIVERSITY OF SOUTH ALABAMA DEPARTMENT OF NEUROLOGY

UNIVERSITY OF SOUTH ALABAMA

Introduction

Diabetes can have a pathological effect on the autonomic nervous system affecting blood pressure, heart rate, and the gastrointestinal system. Assessing clinical symptoms of dysautonomia in the adult diabetic is important for secondary prevention and tertiary prevention of orthostatic hypotension-related ground-falls and reduced quality of life. Orthostatic hypotension (OH) can be a sign of cardiovascular dysautonomia and be due to either a lack of compensatory heart rate to hypotension when standing or decreased vasoconstriction leading to insufficient perfusion to the brain. As a result, patients may feel light-headed or lose consciousness.

Diabetes is also linked to delayed gastric emptying and gastroparesis more commonly in patients who have diabetes for at least 10 years (Camilleri, 2007). Diabetic neuropathy has been related to impaired relaxation of the proximal stomach leading to a decrease in volume change in patients with diabetes mellitus type 1 (DM1) autonomic neuropathy creating symptoms of early satiety and bloating (Samsom). Factors that could underlie gastrointestinal (GI) associated symptoms include apoptosis of enteric neurons, oxidative stress in the cell death process, loss of inhibitory neurons, changes in GI neuron number, changes in GI neuron size, and an increase in excitatory neurons (Chandrasekharan, 2007).

A 10-year follow-up study in the Journal of Diabetes and Its Complications showed that more than 30 percent of DM1 and DM2 patients had presence of OH (Gaspar, 2015). This same data showed that 21 percent of DM1 with OH had a history of myocardial infarction, and 20 percent of patients with DM2 with OH had a history of stroke. Further, patients with DM and OH had a higher mortality rate and higher prevalence of micro-vascular comorbidities such as nephropathy (74%), retinopathy (89%), and peripheral neuropathy (95%), than DM patients without OH. Treatment with midodrine or droxidopa have shown moderate effect above placebo but therapeutic options overall are limited. Other therapies include volume expansion, compression garments, and postural adjustment (Figueroa, 2010). Our goal was to obtain clinical data on autonomic symptoms in patients with chronic diabetes to better understand the clinical course of this disabling disease process.

Methods

We accomplished our study goal by collecting data from patients with chronic diabetes and dysautonomic symptoms using an 11-part questionnaire. Data from the questionnaire was used to calculate prevalence, average onset, and duration of symptoms, as well as associated exacerbating factors and comorbidities. This cross-sectional study was performed during a four-year period from patients in the neurology clinic and inpatient setting. All questionnaires were administered by interviewer for quality control.

Results

20 patients were surveyed in this study. No patients reported a previous diagnosis of diabetic dysautonomia.

Table 1

Average onset of diabetes (n=18)	19.5 years ago [2-35 years]
Prevalence of pupillary autonomic neuropathy (n=20)	70% (14/20)
Average onset of visual disturbances with light accommodation (n=11)	3 years ago
Frequency of visual disturbances with light accommodation (n=13)	Daily - 85% (11/13) Weekly - 15% (2/13)
Duration of visual disturbances with light accommodation (n=14)	Seconds - 50% (7/14) Minutes - 43% (6/14) Hours - 7% (1/14)

Table 2

Prevalence of orthostatic symptoms (n=20)	95% (19/20)
Average onset of orthostatic symptoms (n=15)	5.3 years ago [1-24 years]
Frequency of orthostatic symptoms (n=18)	Daily - 61% (11/18) Weekly - 39% (7/18)
Prevalence of erectile dysfunction (n=18)	83% (15/18)
Average onset of erectile dysfunction (n=15)	6.7 years ago
Frequency of erectile dysfunction (n=14)	Always - 64% (9/14) Often - 14% (2/14) Occasionally - 21% (3/14)

Table 3

Prevalence of post-prandial autonomic symptoms (n=20)	80% (16/20)
Average onset of post-prandial autonomic symptoms (n=13)	4.4 years ago
Frequency of post-prandial autonomic symptoms (n=14)	Daily - 64% (9/14) Weekly - 21% (3/14) Monthly - 14% (2/14)
Duration of post-prandial autonomic symptoms (n=14)	Minutes - 64% (9/14) Hours - 36% (5/14)
Prevalence of gastroparesis (n=18)	67% (12/18)
Average onset of gastroparesis (n=12)	3 years ago
Frequency of gastroparesis (n=12)	Daily - 33% (4/12) Weekly - 50% (6/12) Monthly - 17% (2/12)
Duration of gastroparesis (n=11)	Minutes - 27% (3/11) Hours - 55% (6/11) Days - 18% (2/11)

19 of 20 patients had diagnosis of diabetes. 17 patients reported having DM type 2 and two patients reported reported having DM type 1. Average history of diabetes was 19.5 years. 70% of patients had difficulty adjusting vision to bright or dark rooms with average onset three years prior to questionnaire. See table 1. 95% of patients had orthostatic symptoms when rising from seated or supine position. Hot weather (n=8) was the most common aggravating factor for orthostatic symptoms followed by exercise (7), bowel movement (7), hot bath (6), and alcohol consumption (4). Average onset of orthostatic symptoms was 5.3 years prior to questionnaire. 83% of patients had erectile dysfunction with average onset of 6.7 years prior to questionnaire. See table 2. 80% of patients had post-prandial autonomic symptoms such as sweating, flushing, early satiety, tachycardia, abdominal pain, nausea, or vomiting. Patients with post-prandial symptoms had average onset of 4.4 years prior to questionnaire, and 64% of these patients had a daily frequency of post-prandial symptoms. 67% of study patients reported gastroparesis with average onset of 3 years prior to questionnaire. More than half of these patients had duration of symptoms for hours and 18% of these patients had duration of gastroparesis for days. See table 3. The most common reported comorbidity was peripheral neuropathy (N=7), followed by retinopathy (5), myocardial infarction (4), nephropathy (2), and cataract (1).

Conclusions

Diabetic dysautonomia is a neuropathy that can greatly impact the quality of life of patients. A comprehensive clinical history helps with diagnosis as patients may have multiple symptoms not localizable, or symptoms underreported due to perception that multiple symptoms are not related to the same pathogenesis. Our descriptive data on diabetic dysautonomic symptoms provides a better understanding of the clinical course of this underdiagnosed morbidity. A larger study sample size in the future will be helpful for further understanding of this underreported disease process.

Bibliography

1. Camilleri M. Diabetic Gastroparesis. New England Journal of Medicine. 2007;356(8):820-829.
2. Samsom M, Roelofs JM, Akkermans LM, van Berge Henegouwen GP, Smout AJ. Proximal gastric motor activity in response to a liquid meal in type I diabetes mellitus with autonomic neuropathy. Dig Dis Sci. 1998;43(3):491-496.
3. Chandrasekharan B, Srinivasan S. Diabetes and the enteric nervous system. Neurogastroenterol Motil. 2007;19(12):951-960.
4. Gaspar L, Kvasilek P, Komornikova A, et al. Orthostatic hypotension in diabetic patients-10-year follow-up study. J Diabetes Complicat. 2016;30(1):67-71.
5. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: As easy as A, B, C. Cleve Clin J Med. 2010;77(5):298-306.

Acute Painful Hyperglycemic Neuropathy (Diabetic neuropathic cachexia)

- Uncommon variant of DNP, with acute/subacute onset
- Usually males with DM type II, unintentional rapid weight loss with poor and worsening glycemic control
- Presents with intense diffuse, unremitting pain is in the legs and feet, with less severe proximal and diffuse pain
- Mild sensory loss and NCS abnormalities
- Weight gain, then slow recovery over months
- Nutritional supplement & glycemic control monitoring

Insulin Neuritis

- First reported by Caravati 1933
- Uncommon and highly unpleasant entity
- Appears after the initiation of aggressive insulin therapy or oral agents
- Intense feet and legs burning pain, often requires narcotics
- Objective findings on examination and NCS are mild
- The pain generally resolve in few months, but the underlying polyneuropathy remains
- Nutritional supplement & blood glucose monitoring
- Sural nerve biopsy showed loss of small fibers

(Berl et al. Acta Neuropath 1986;72 “one patient”)

Diabetic Polyradiculoneuropathy

- Combination of symmetric and asymmetric entity
- Initially symmetrical polyneuropathy, then a confluent multiple acute/subacute bilateral sacral, lumbar, thoracic or less commonly cervical radiculopathy
- The progression may be steady or stepwise
- Most often seen in severe diabetics age >50 years
- Weakness affecting proximal & distal lower limbs
- Prominent pain, sensory disturbances and weakness, often debilitating
- Vascular, metabolic & ± inflammatory pathogenesis
- Recovery is slow and often incomplete

Proximal Diabetic Neuropathy

(Diabetic Lumbosacral Plexopathy, Diabetic Amyotrophy, Diabetic Radiculoplexus neuropathy, Bruns–Garland Syn)

- Seen in ≥1% of DM II, males > females, over age 50 years
- Usually involve the LS plexus, less commonly thoracic or cervical roots/plexus or nerves
- Acute onset severe unilateral thigh pain, followed by weakness and atrophy of the involved muscles
- Minimal sensory loss & depressed knee reflex
- Weight loss & associated sensory DNP in the majority
- Monophasic and spontaneous slow recovery in most
- Variants include; asymmetric bilateral lower limb, less common upper limbs (9 of 65 cases) thoracic and foot drop.
- Inflammatory vasculopathy or ischemic basis
- Caloric supplements, IVIG, methylprednisolone?

(Dyck JB et al. J Peripher Nerv Syst 2005;10)

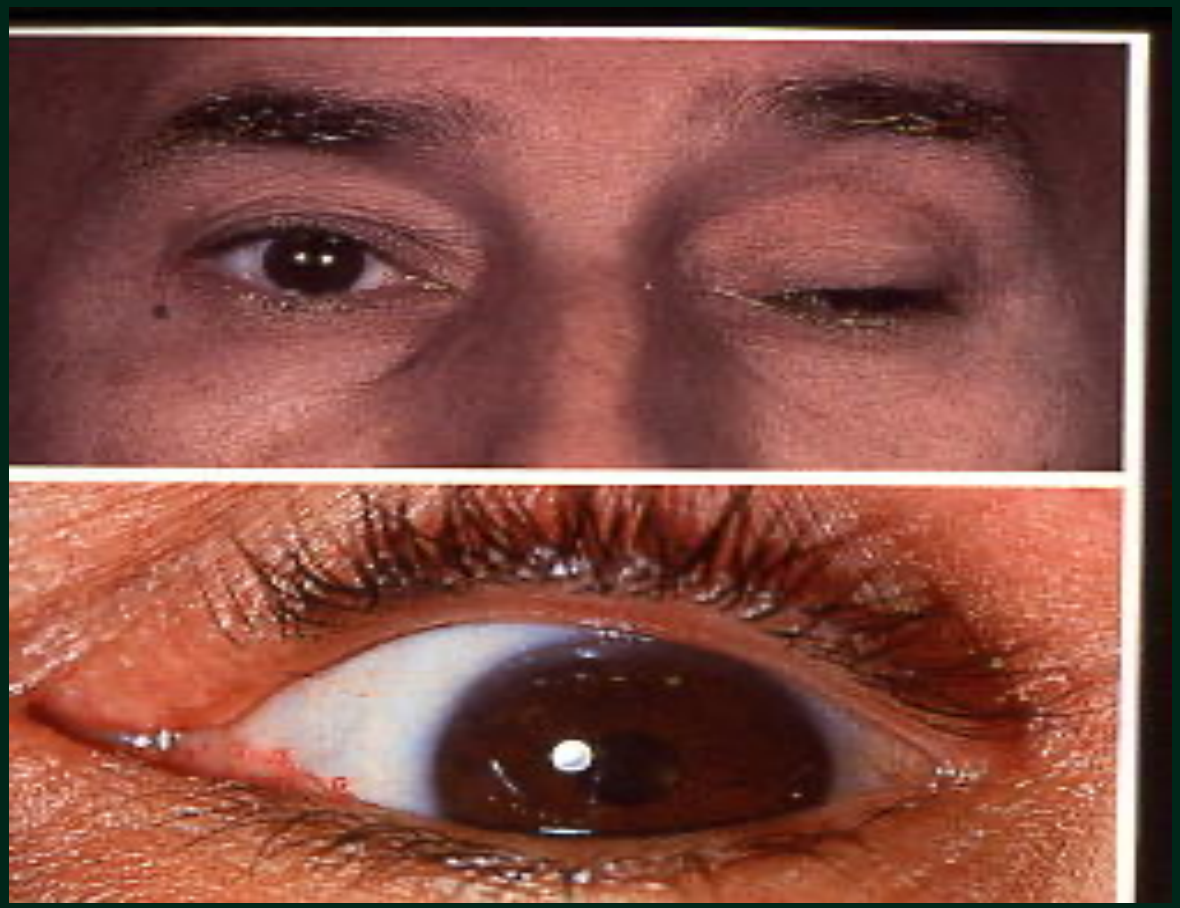
Compression Neuropathies (CNP) and Limb Mononeuropathies

- Diabetics are more susceptible to CNP, particularly with associated peripheral neuropathy
- Increased nerve tissue vulnerability and obesity
- CTS in 30% of NCS, 10 –15% are symptomatic, and ≥ 8% of all CTS patients are diabetics
- Symptomatic ulnar NP at the elbow in ≥ 2% of diabetics, asymptomatic mild slowing across elbow is common
- Symptomatic diabetic CNP should be managed like other CNPs
- Acute onset mononeuropathy NOT at common nerve compression sites & mononeuropathy multiplex are not among DM complications
- Slow recovery, determined by the site and axonal loss

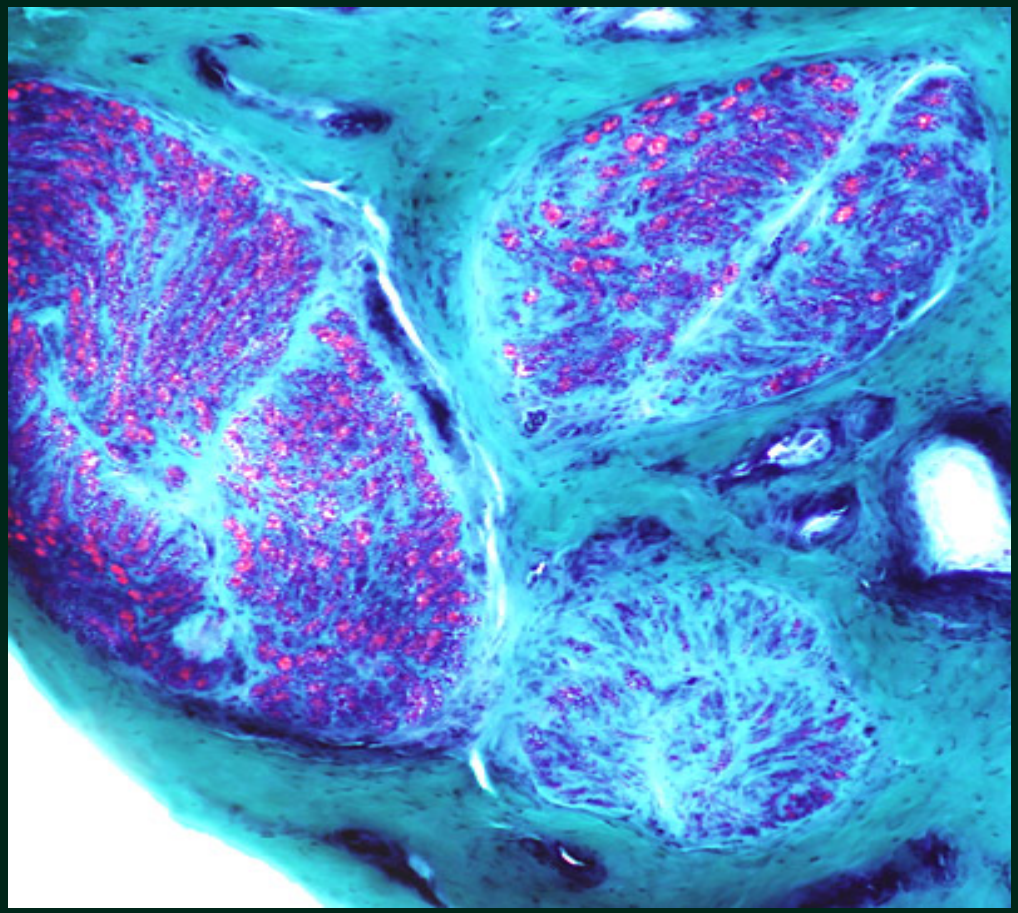
Diabetic Cranial Neuropathies

- Seen in 1% of diabetics vs. 0.1% in matched control (Watanabe et al.)
- Usually, patients > 50 years old with multiple comorbidity
- III CN most frequently affected, followed by IV and VI CNs, and less commonly VII CN
- III CN palsy; acute onset ocular pain, headache, diplopia and ptosis. Pupillary function sparing is characteristic
- Recovery is often complete in weeks to few months (mean 2.5 m) in 72% of patients
- Histopathologic findings supportive of nerve ischemia (centrofascicular fiber loss)

Diabetic Ophtalmoplegia: III nerve palsy



Perkin, G D et-al. In: Atlas of Clinical Neurology. 1986: p.12.18



Differential fascicular involvement of nerve

Facial Nerve Palsy in Diabetics

- Facial neuropathy is more common in older diabetics than nondiabetics (2 - 6% of pts.)
- Usually has similar course to Bell's palsy
- Pain is often present, unilateral facial weakness, and less often loss of taste and hyperacusis
- Differential diagnosis; idiopathic, Lyme disease, Varicella-zoster and trauma
- Recovery depends on extent of axonal loss (CMAP amplitude, and lesion severity)

Isolated Thoracic Radiculopathy
(Truncal radiculopathy, Diabetic thoracoabdominal NP)

- Distinctive disorder, usually seen in DM type I or II, M > F older pts., poor DM control, and weight loss
- Segmental chest or abdomen pain, allodynia, and sensory loss, that may not follow segmental pattern
- ± Focal muscle weakness (abdominal bulge)
- Diagnosis is clinical and needle EMG testing
- The pain intensity and location mimics medical, surgical or orthopedic conditions
- Probable similar pathogenesis to PDN
- Pain usually subsides in 4 – 12 months
- Cutaneous sensory loss may persist lifelong.

Assessment of Diabetic Neuropathy

- Patients with DM should be evaluated yearly for evidence of DPN even if they do not report neuropathy symptoms.
- Patients without known DM and symptoms of neuropathy should be screened for DM.

- **Noninvasive**
  - Lab studies
  - NCV/EMG
  - Autonomic function tests
  - Quantitative sensory testing
- **Invasive**
  - Punch cutaneous skin biopsy
  - Sural nerve biopsy

Laboratory Studies;

Other causes of NP must be considered or excluded

- Typically; BC, TSH, T4, serum B12, serum Folate, SPE & SPIE. HIV and heavy metals screen only if indicated
- **Large fibers sensory features;**
  screening for Sjögren's, Vit. B6, Vit. E, paraneoplastic
- **Autonomic symptoms;**
  screening for amyloidosis, porphyria, GBS, hereditary, paraneoplastic
- **Demyelinating features;**
  screening for hepatitis, IMN, CSF analysis
- **Mononeuropathy/ multiple mononeuropathy;**
  screening for vasculitis, CTD, infiltrative neoplastic, or sarcoidosis

The Electrodiagnostic evaluation

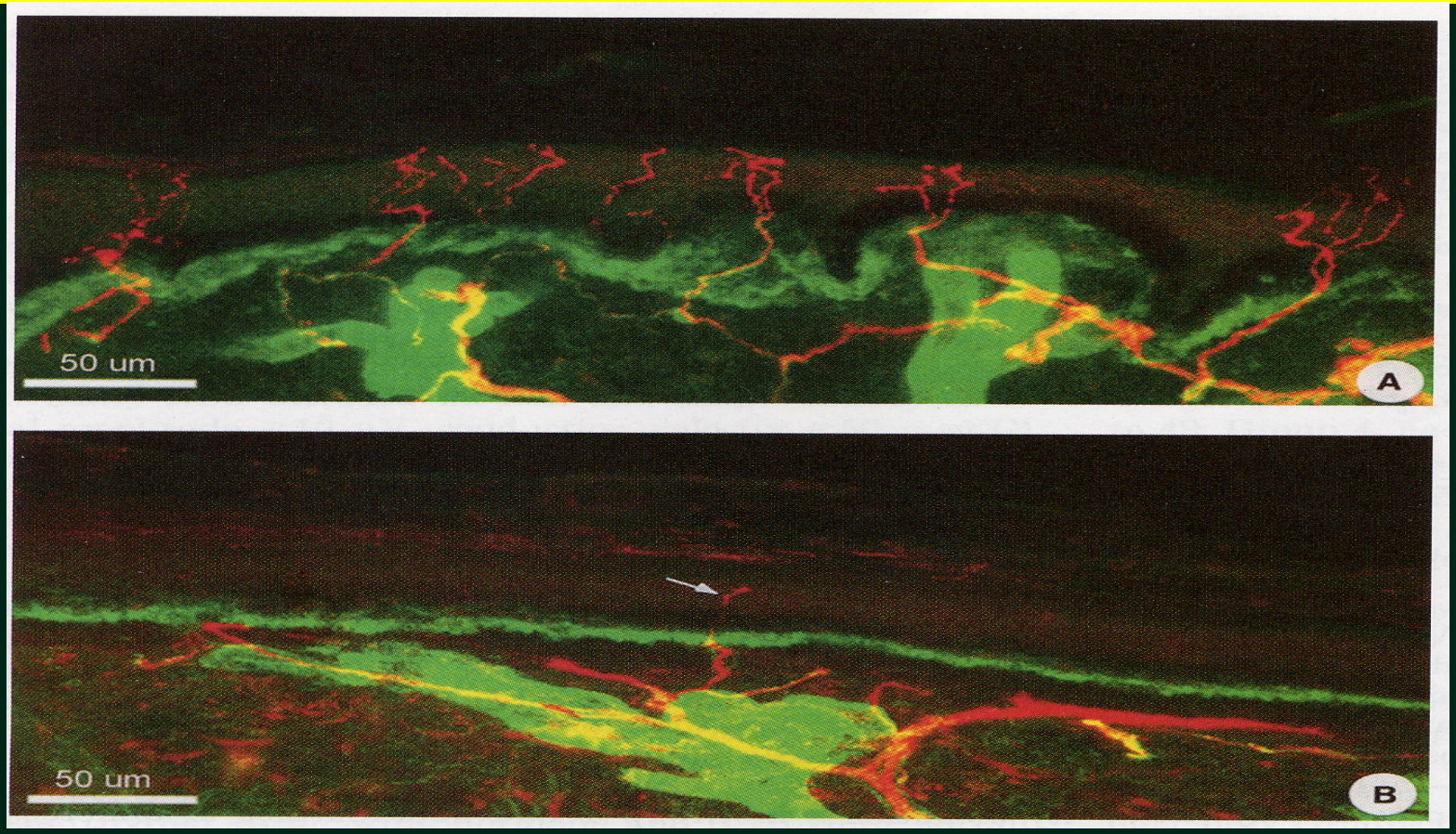
- Confirm the presence of neuropathy
- Determine neuropathy type and severity
- Diagnose co-exciting focal NP & exclude other NMDs
- Mean CV values in DNP are 5 – 10 m/s slower than controls, and to a lesser degree in asymptomatic pts
- Slow CV in demyelinating range is unlikely, and can be due to metabolic factors
- SNAP amplitude reduction is the most sensitive abnormality and seen in early disease
- Reasonable correlation with duration of diabetes and severity of neuropathy.

Other Neurodiagnostic Tools

- **Autonomic function testing:**
  - R-R interval variation, Valsalva ratio, tilt table, SSR
  - QSART and other sweat testing
  - abnormal in 13% diabetics without NP, 50% with DNP, and 100% with symptomatic ANP
  - **Not widely available**
- **Quantitative sensory testing (QST):**
  - assess small & large sensory fibers function
  - heat, cooling and vibratory detection threshold
  - **Poor reproducibility**
- **Intraepidermal nerve fiber density (IENF):**

  A skin biopsy using fluorescent technique labeling for protein gene product, and collagen IV, analyzing the number, branching and density of the intraepidermal nerve fibers density.

Intraepidermal nerve fiber density



Periquet, et-al. Painful Sensory Neuropathy. Neurology 1999; 53: 1641-1647

Pathogenesis of Diabetic Neuropathy

- **Metabolic Derangements;**

  Persistent hyperglycemia is a primary factor

  - abnormal glycosylation of neural and other proteins
  - excess flux of fructose and sorbitol and reduced nerve inositol
  - oxidative stress with apoptosis and mitochondrial dysfunction
  - deficiency of nerve growth factor that support neurons
  - Autoimmune-mediated neurotoxicity

- **Microvascular and circulatory abnormalities;**
  - thickening & hyalinization of small vessel walls
  - increased endoneurial vascular resistance and decreased nerve blood flow → endoneurial hypoxia

Treatment Rational Based on Metabolic Hypothesis

Polyol pathway activation	→	Aldose reductase inhibitors
Reduction of myoinositol	→	Myoinositol substitution
Reduced nerve growth factor	→	Human recombinant nerve growth factor
Alterations in essential fatty acid metabolism	→	gamma-linolenic acid (evening primrose oil)
Acetyl-L-carnitine depletion	→	Substitution of acetyl-L-carnitine
Free-radical-mediated oxidative stress	→	Antioxidants (alpha-lipoic acid)

Aldose Reductase Inhibitors (ARIs) & Recombinant Nerve Growth Factor (rNGF)

- **ARIs were used in a number of trials since 1980**
  - Equivocal or negative results, possibly due to poor trial design and short treatment duration (Ranirestat and Fidarestat showed modest improvement)
  - Trials confounded by AE's, poor design and too small
- **rNGF** a neurotrophic factor, that promotes survival, differentiation, and maintenance of small nerve fibers, shown to be reduced in skin biopsy in pts with DNP
  - Large phase III multicenter trial was not able to confirm beneficial effect

ARIs; in Greene, et al. *Neurology.* 1999. // **rNGF; in** Apfel, et al. *Neurology*. 1998;51:695-702.

Other Trials of DNP management

Trials showed no convincing effectiveness;

- Gamma-linoleic acid (precursor of fatty acids)
- Alpha-lipoic acid (antioxidant**)**
  (ziegler D et al. Diabetic Care 2011)
- ACE inhibitors (isosorbide vasodilator)
- Myoinositol substitution
- Aminoguanidine (inhibitor of glycation)
- Protein Kinase C inhibition (increase cytokines and inhibit Na+/K+ ATPase
- Gene therapy by intramuscular VEGF
- Methylcobalamine (increase synthesis of Lecithin)

Glycemic Control in DNP

Maintaining strict blood glucose control has been demonstrated in large clinical trials to stabilize, improve and reduce the occurrence of diabetic neuropathy and other diabetic complications.

Effect of Intensive Diabetes Treatment on Diabetic Neuropathy

- **DCCT Research Group** followed 1441 pts with IDDM randomized to conventional (1 or 2 injections) versus intensive insulin (3 or more injections or pump) treatment
  - Intensive insulin therapy reduced the occurrence, or slowed the progression of the DNP at 5 years by 64%, clinically and by NCS.
  - Similar effects are yet to be documented in NIDDM
- The UKPDS Group followed a large number of DM type II pts. for an average of 10 years, with glycemic control at HgbA1c 7%, versus 7.9% standard treatment showed 25% reduction of NP and microvascular complications
- Most patients required about 0.6 -0.7 Unit /kg/ Day.

DCCT Research Group, NEMJ 1993 & Ann Int Med 1995
UK prospective Diabetic Study Group, Lancet 1998.
American Diabetes Assc. 2019. Wexler DJ. Waltham, MA: Up To Date 2020.

Effects of Pancreatic Transplantation on Diabetic Neuropathy

- Pancreatic transplant in 115 pts. with IDDM versus control with IDDM treated with insulin, both has baseline DNP and were followed for up to 10 years
- Both clinical and nerve conduction indices improved in the transplant group, and steadily worsened in the control group
- However pancreatic transplant is effective only early in the disease, and the effect was not sustained in long term follow-up

Navarro et al. Ann Neurol 1997;42:727-736

Treatment Issues in DNP Variants

- Proximal DNP improved with IV methylprednisolone. However; effective therapy has not been established
- Surgical release in symptomatic CTS. Conservative management of mild/moderate ulnar NP, and surgical decompression in severe cases
- Multiple surgical decompression in multiple focal DNP is not beneficial, and should only be applied as clinically indicated.

Stewart et al., JNeurol Sci 1996
Dyck JB et al., JPeripher Nerv Syst 2005
Chaudhry V, et al. Neurology 2006

Diabetes mellitus + CIDP

- Symmetric, progressive distal & proximal NP, similar to CIDP alone and meeting the criteria for CIDP
- Differences from CIDP
  - older age (average 67 years)
  - more gait imbalance
  - EDXs show more axonal loss & sural SNAP more often absent
- Less responsive to treatment (corticosteroids 56%, PE 20% and IVIG 44%)
- Less magnitude of functional recovery

(Chan YC et al. Cochrane Database Systematic Review 2017)

Neuropathic Pain in DNP

- Nearly 1/3 of diabetic neuropathy patients have spontaneous or evoked pain, which may compromises quality of daily living
- Start a given medication at a low dose and gradually titrate to efficacy
- If a patient experiences partial pain relief with 1 drug, a combination of 2 or more of different class drugs can often yield better results

Management of pain in DNP

Widely used drugs with demonstrated efficacy in clinical trials;

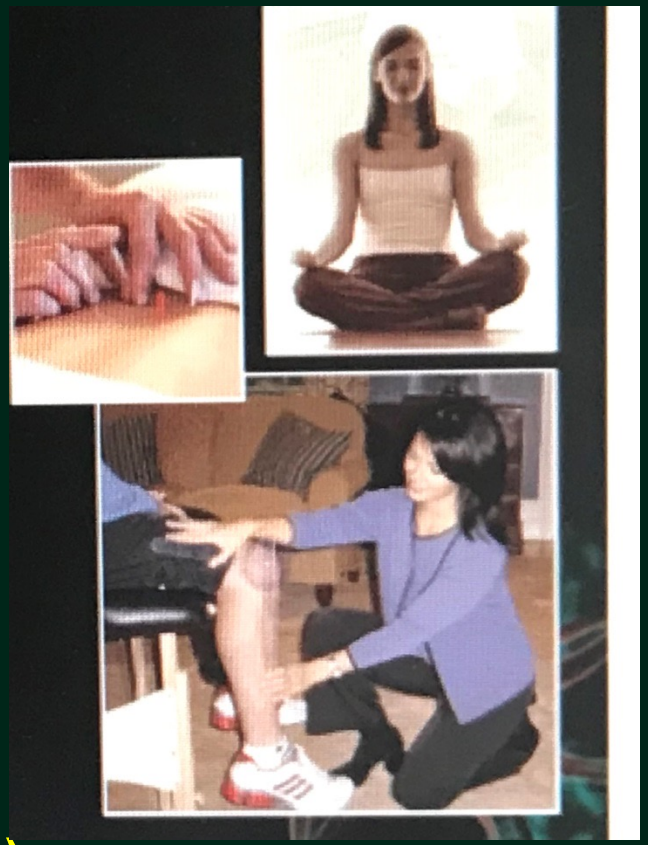
- **Tricyclic antidepressants**
  - **Pain relief is independent of antidepressant properties**
  - **Major limitation is the side effects, especially in elederly**
  - **Dose 50-150 mg/day & reaches maximum efficacy in 3 Weeks**
- **Pregabalin and Gabapentin;**
  - **adverse events are dizziness, somnolence and edema**
- **SNRIs (Duloxetine, Venlafaxine);**
  - **simple dosing and have favorable side effects (nausea, somnolence and dizziness are the most common)**
- **Tramadol**
  showed significant reduction in pain intensity at week 6

Harati, et al. *Neurology.* 1998;50:1842-1846

- **Refractory pain; Mexiletine, IV lidocaine,** phenothiazi**ne, TENS**

Nonpharmacological Treatment of Neuropathic Pain

- Cognitive behavioral strategies
  - Meditation
  - Biofeedback
  - Relaxation therapy
- Physical rehabilitation
- Acupuncture
- Transcutaneous electrical nerve stimulation.
- High frequency spinal cord stimulation device



(Petersen EA et al. JAMA Neurol 2021)

Neuropathic pain management at a Glance

- Pregabalin and Gabapentin are effective and should be used (level A)
- Duloxetine, Venlafaxine and Amitriptyline are effective as a monotherapy or add-on therapy
- Tramadol, Capsaicin, Oxycodone are probably effective and should be considered in refractory cases
- Other treatments have less robust evidence or negative evidence
- Effective treatments have side effects that should be monitored
- Only few studies have sufficient information on treatment effects on function and QOL.

Management of Autonomic Neuropathy (ANP)

Wide spectrum of symptoms may occur (CVS, GIT, UG, pupillary, sudomotor, endocrine ..)

Cardiovascular dysfunctions;

- Increased incidence of silent MI, ventricular arrhythmias, CHF, and higher MI mortality
- Beta-blockers inhibit arrhythmias in this setting
- Precautions for increased cardiovascular lability during anesthesia
- Identify exercise tolerance status before strenuous exercise program (stress test)

Management of Autonomic Neuropathy

Postural hypotension;

- Severe manifestation of cardiovascular ANP
- Head-up tilting of the bed
- High elastic support stockings
- Increased salt intake, fludrocortisone or Midodrine

Erectile dysfunction;

- Most common complain in ANP
- Both organic and psychogenic causes
- Rule out testosterone deficiency
- Moderately effective treatment sildenafil, tadalafil, vacuum devices, or penile injection agents (prostaglandin)

Management of Autonomic Neuropathy

Gastrointestinal diabetic ANP

- Affect 1/3 of pts, extends along the entire GI tract
- Common symptoms; anorexia, nausea, postprandial vomiting, bloating, abdominal pain, intermittent diarrhea and constipation
- Frequent small meals and low-fat diet
- Gastroparesis (Metoclopramide, bethanechol, Mozapride)
- Antidiarrheal (Clonidine, Loperamide), and high-fiber diet for constipation

Management of Autonomic Neuropathy

Urinary bladder dysfunction;

- Related to decreased sensation & reduced contractility
- Voiding difficulty, increased inter-voiding interval, slow stream, incomplete emptying and incontinence
- Frequent scheduled voiding and cholinergic agents (bethanechol), self catheterization in severe cases

Sudomotor dysfunction;

- Anhidrosis, trunk and face compensatory hyperhidrosis, gustatory sweating
- Precautions to avoid heat exhaustion and education

Prognosis and Treatment Outcome

- Distal symmetric DNP is slowly progressive.
  Close diabetic control delay the progression
- Proximal DNP initially progress, followed by slow varying improvement
- No specific treatment for III CN neuropathy, but the majority recover over few to several weeks
- The recovery of VII CN depends on the degree of axonal loss, estimated by CMAP amplitude
- Symptomatic CTS improve after surgical release.
  Surgical release of the ulnar nerve at the elbow is less successful

Take-home message

- DNP is the most common complication and major source of morbidity and mortality in DM
- Despite advances in understanding the pathophysiology treatment of DNP remains limited
- Exclude nondiabetic etiology
- Recognize the importance of glucose control in the prevention and slowing of DNP progression
- Recognize the role of electrophysiologic testing in evaluation of diabetic neuropathy
- Be familiar with symptomatic, and pain management in diabetic neuropathy

References list;

- Neuromuscular manifestations of acquired metabolic, endocrine and nutritional disorders. Neuromuscular Disorders Treatment and Management 2nd Edition , chap 21; 528-533, Bassam, BA, Bertorini, TE.

THANK YOU

www.neuroamerica.org

Clinical
Neurological
Society of America