

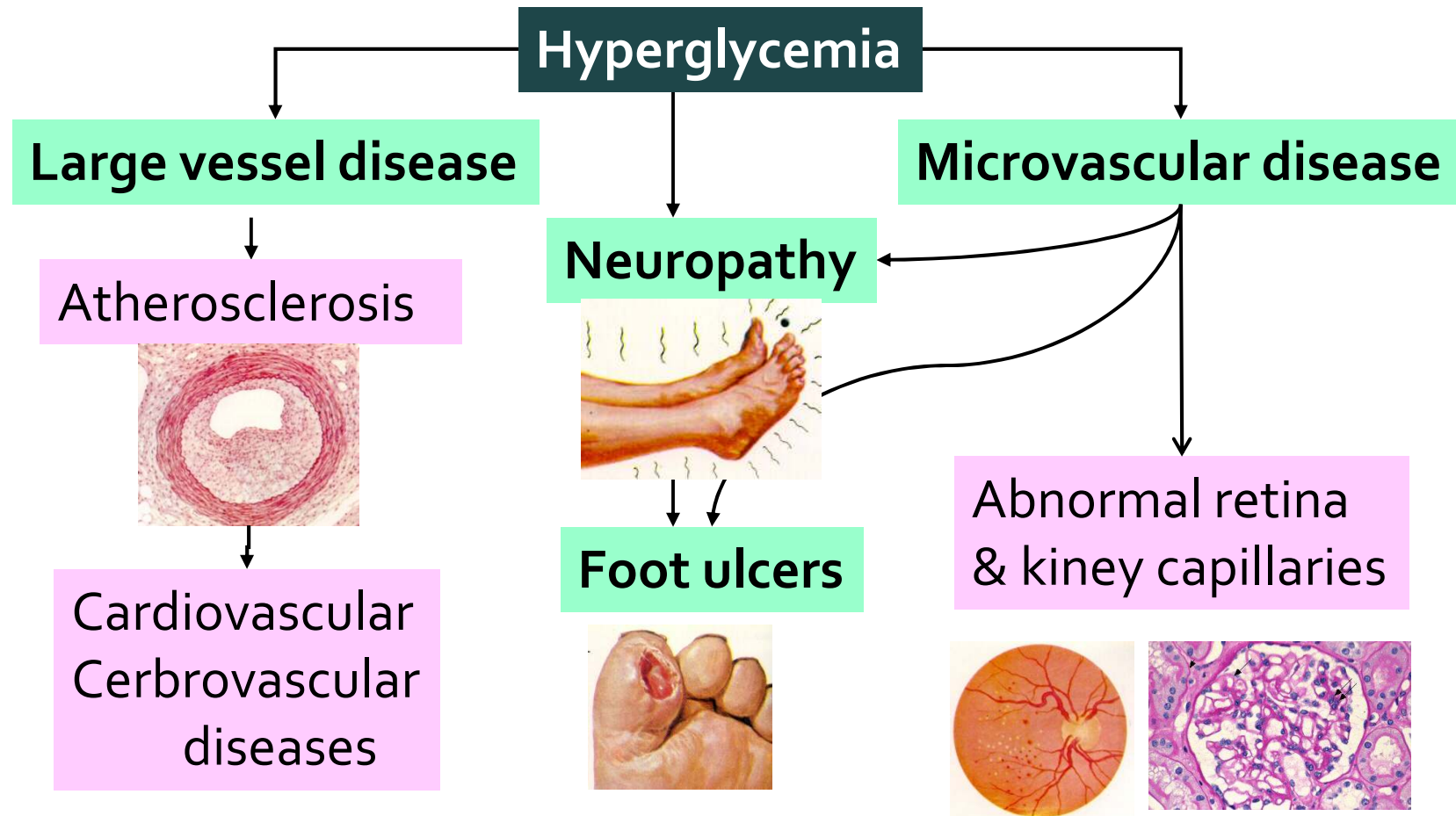
Clinical spectrum and Differential diagnosis of Diabetic neuropathy



성균관대학교 의과대학 신경과

김병준

Diabetes Mellitus: chronic complications



Definition of Diabetic neuropathy



- The presence of symptoms and/or signs of Peripheral nerve dysfunction
 - In people with diabetes
 - After the exclusion of other causes
-
- **Diabetic Neuropathies** A statement by the American Diabetes Association DIABETES CARE, 2005

Reported prevalence of Neuropathy in diabetes



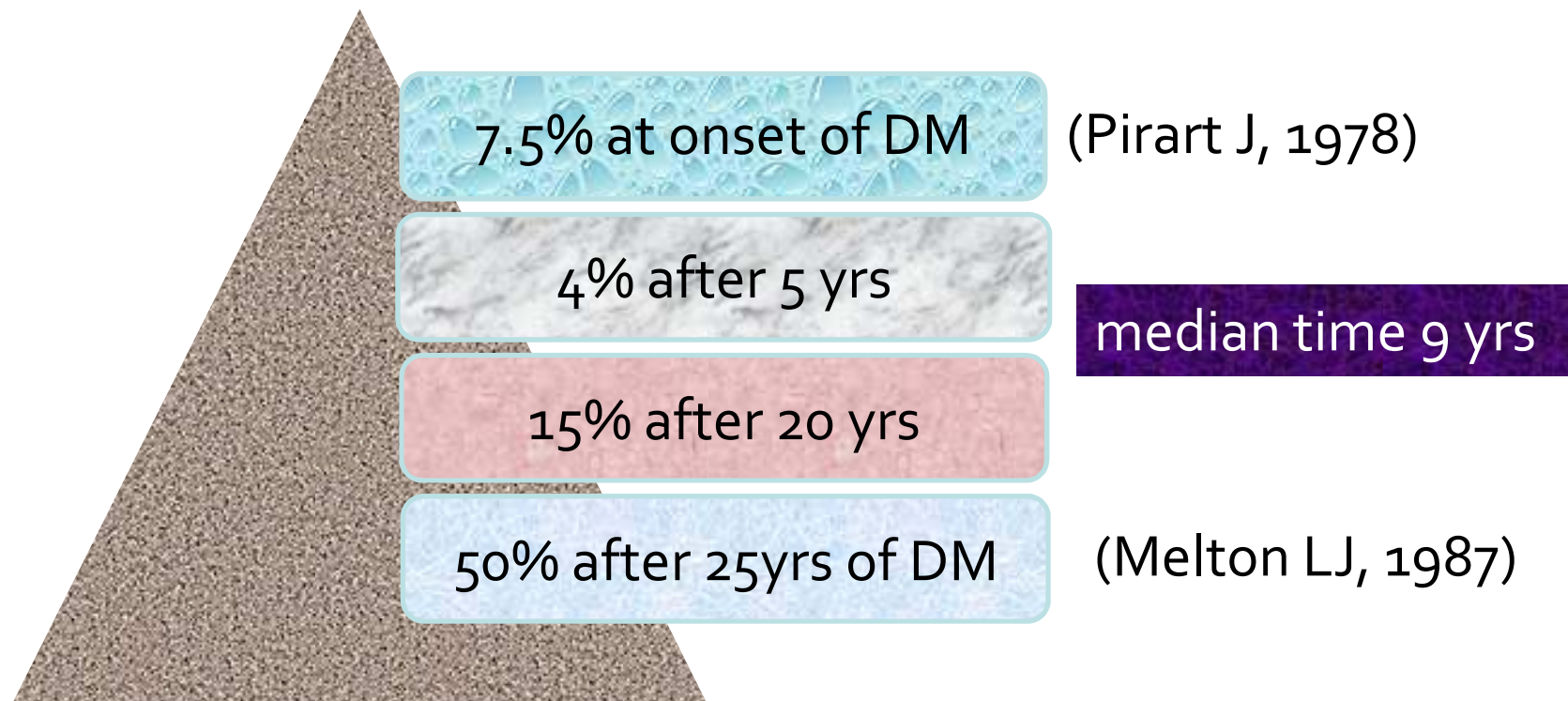
- Variability in prevalence reported by different studies :

Source	Measurement	#Pts	%Neuropathy
Chicago,1966	Objective signs, MNCS	107	10
London,1960	Valsalva	337	20
Brussels,1965	Objective signs	1175	21
Rochester,1961	EMG, Objective signs	103	42
Toronto,1961	Objective signs	100	52
Salford,1953	General findings	100	57
cleveland,1953	Subjective complaints	261	62
Denmark,1968	MNCS	14	100
London,1971	MNCS	39	100

- different definition / tests/ lack of standard criteria



- Prevalence: Overall 30%

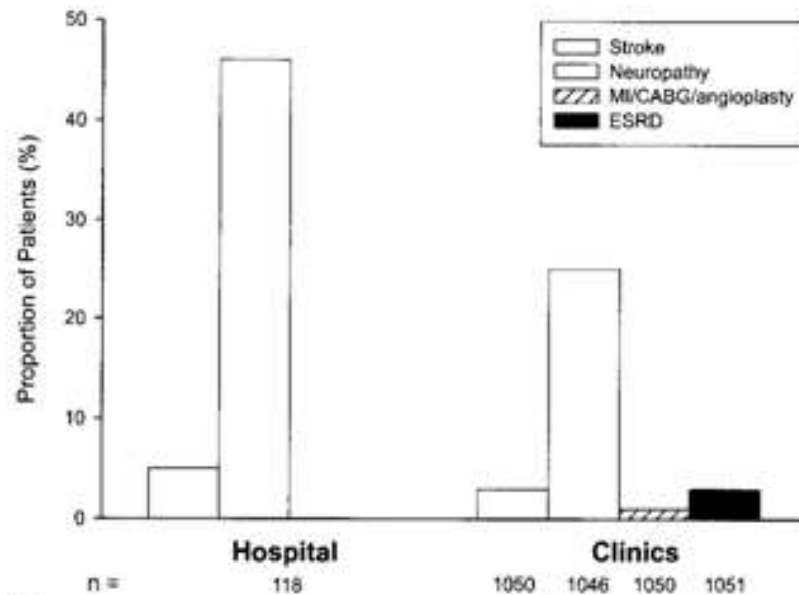




Diabcare Asia 2001 - Korea

: Country Report on Outcome Data and Analysis

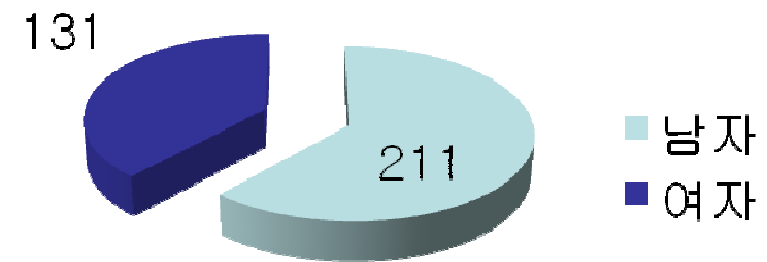
Rhee et al., The Korean Journal of Internal Medicine: 20:48-54, 2005



C

Neuropathy was common in both patient groups, with 46% of patients reporting neuropathy in the hospital group and 25% of patients reporting neuropathy in the clinics group.

2002-9 ~ 2009-12

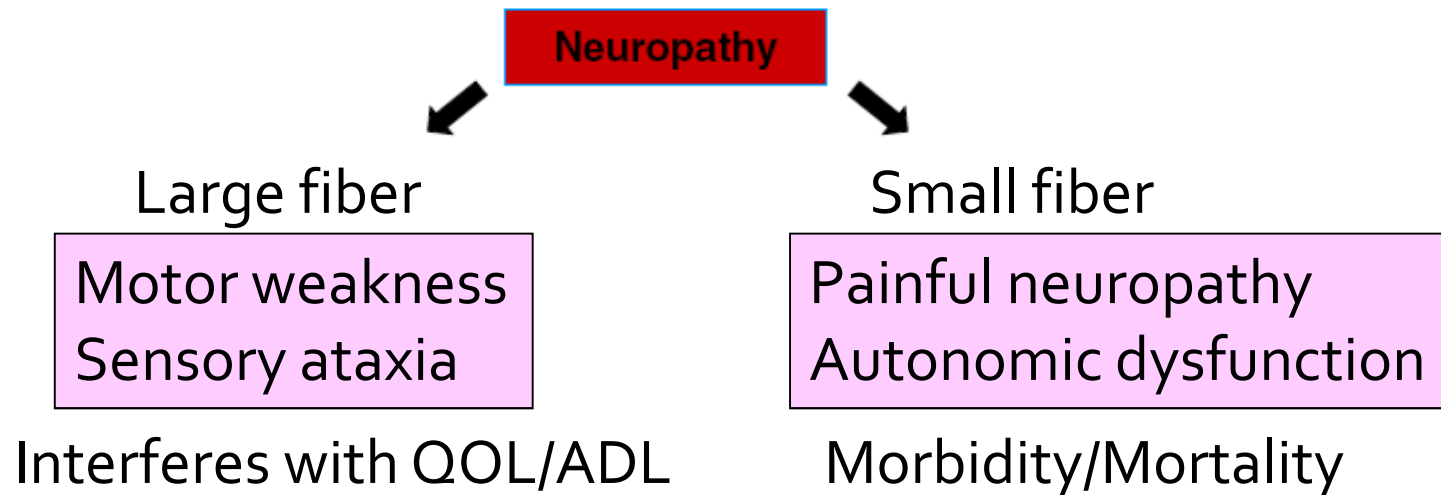
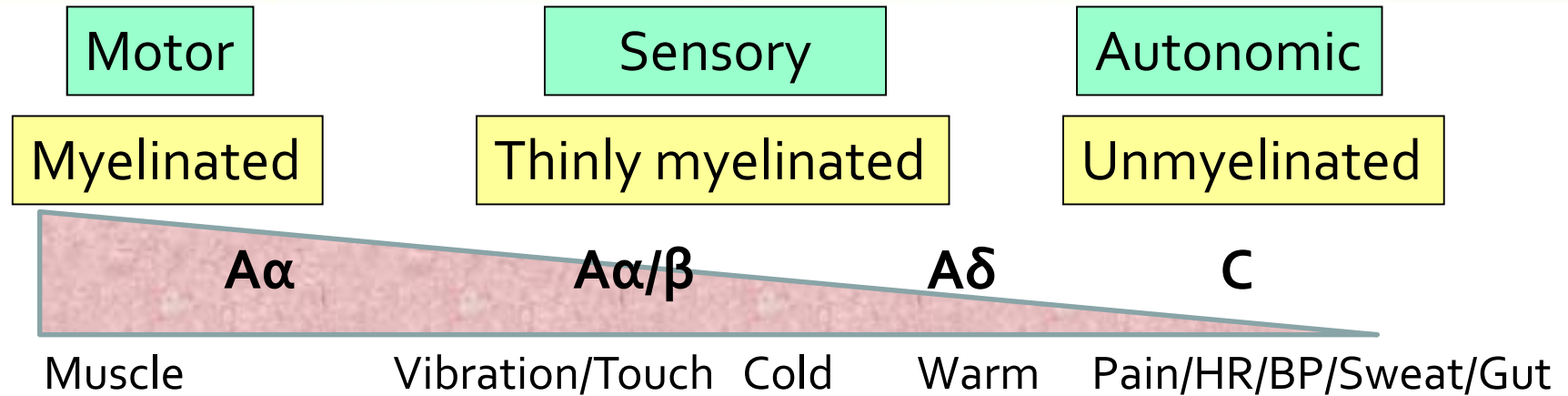


Mean age 60.3

Etiologies of idiopathic polyneuropathy

Diagnosis	# Patients	%
Hereditary	120	29.8
Cryptogenic sensory polyneuropathy	93	23.1
Diabetes mellitus	62	15.4
Inflamm. demyelinating polyneuropathy	53	13.1
Multifocal motor neuropathy	21	5.2
Vitamin B12 deficiency	9	2.2
Cryptogenic SMPN	7	1.7
Drug-induced	6	1.5
Sensory neuronopathy	4	1.0
Other	27	6.7

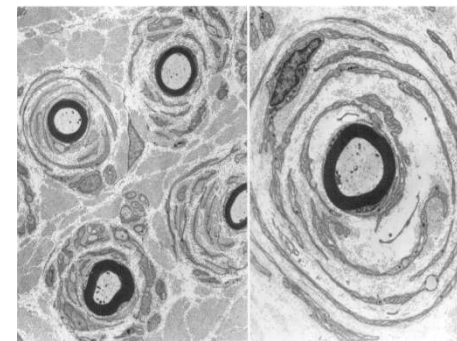
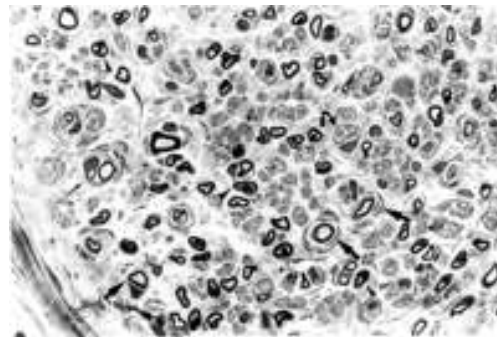
Functions of peripheral nerves



Clinical diagnosis of neuropathy



- Five key clinical questions
 - Inheritance → Hereditary vs. Acquired
 - Temporal evolution → Acute vs. Chronic
 - Distribution → Symmetric vs. Asymmetric
 - System involvement → Motor vs. Sensory
 - Pain nature → Small vs. Large fibers
- Pathology → Axonal vs Demyelinating



Case 1: F/ 51



- 양발바닥 저림
- 약 20여년 전부터 당뇨로 치료중임.
- 2년전부터 양쪽 발바닥이 저리다고 함.
- 화끈거리는 것 같기도 하다고 함.
- 감각이 떨어지거나, 위약감이 있지는 않다고 함.
 - 발등의 대칭성 온도감각 저하
 - 정상 근력
 - 건반사 소실

Case 1 ; analysis



- Inheritance
 - Temporal evolution
 - Distribution
 - System involvement
 - Pain nature
 - Pathology
 - Less motor symptom
 - Absent DTRs
- Acquired
 - Chronic
 - Distal symmetric
 - Sensory
 - Small fibers
 - Axonal vs Demyelinating?
 - Small fibers
 - Peripheral neuropathy

Acquired Chronic symmetric distal axonal polyneuropathy

Classification



- **Class I Subclinical Neuropathy**
 - Abnormal electrodiagnostic tests (EDX)
 - Abnormal quantitative sensory testing (QST)
 - Other Abnormal autonomic function tests (AFT)
- **Class II Clinical Neuropathy**
 - Diffuse neuropathy
 - Distal symmetric sensorimotor polyneuropathy
 - Autonomic neuropathy
 - Focal neuropathy
 - Mononeuropathy
 - Mononeuropathy multiplex
 - Plexopathy / Polyradiculopathy
 - Cranial mononeuropathy

Report and Recommendations of the San Antonio Conference on Diabetic Neuropathy. Diabetes 1988; 37:1000

1. Distal symmetric Diabetic polyneuropathy



- Most common form of diabetic neuropathy
- Distal symmetric length-dependent sensorimotor polyneuropathy
 - distal lower limbs
 - length-dependent sensory symptoms
 - predominant small-fiber involvement
- Neuropathy -> trauma -> ulceration -> faulty wound healing, infection, necrosis, gangrene

Case 2 M/50



- DM(+)
- 2000-4 shooting pain
- 2001 NCS; early polyneuropathy
- 2004 start insulin
- 2006-2 severe pain at night

- N/E; areflexia
- FBS/PP2 183/336, HbA1c 9.3%

- Treatment; Gabapentin + Amitriptyline
- Course; Improved 2 months later

2. Acute painful diabetic neuropathies



- Pain
 - Burning & hypersensitivity: Feet
 - May be severe, Often worse at night
- Signs: Often only mild changes
- Associations
 - Poorly controlled diabetes
 - Recent onset of insulin therapy
 - Rapid weight loss
- Improvement: After control of diabetes & weight gain

Case 3 46/M



- Diabetic
- Subacute onset right L/E pain
- N/E
 - Right L/E atrophy
 - Loss of K/J, A/J
- EMG: LS plexopathy
- Spine MRI: Not diagnostic
- Treatment
 - Antineuralgic drugs
 - Epidural block
 - Phentanyl patch
 - Trazodone
- Course; improved 1yrs later



3. Lumbosacral plexopathy



- Nosology: Similar syndromes
 - Proximal diabetic neuropathy
 - Diabetic amyotrophy
 - Multifocal diabetic neuropathy
 - Cf) Non-diabetic Lumbosacral plexopathy
- Clinical features
 - Asymmetric Proximal Weakness
 - Localized severe Pain (Hip, buttock, or thigh)
 - Usually lasts months after disease onset
 - Sensory loss: Distal
- Slow recovery over 6 to 24 months after diabetic control

Diabetic radiculopathy



- Trunk
 - Sensory
 - Acute, unilateral pain
 - Distribution: 1 or multiple thoracic nerves
 - Hypersensitive skin region
 - Motor: Weak abdominal wall muscles; May lead to herniation
 - Associations
 - Especially in patients > 50 years
 - Some patients with weight loss: r/o malignancy
 - Course: Spontaneous improvement over 1 to 2 years

4. Mononeuropathies



- Cranial nerve ; Especially in older diabetics
 - Third nerve > 7th nerve
 - Retro-orbital pain
 - Sparing of pupil involvement
- Limb
 - Vascular lesions: Major limb nerves
 - Onset: Abrupt & painful
 - Common location: Lumbosacral plexopathy
 - Damage at common compression sites
 - Carpal tunnel syndrome: 25% asymptomatic
 - Other: Ulnar; Posterior tibial (Tarsal tunnel)



5. Mononeuritis multiplex

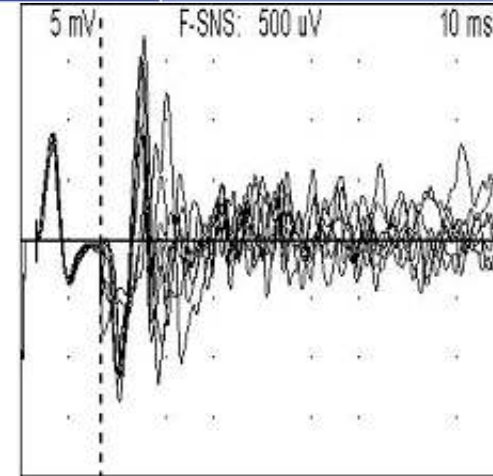


- Multiple mononeuropathies with polyneuropathy
- Coexisting focal compression neuropathies
 - Ulnar compression at elbow: More common in diabetes
 - Median at wrist: Often asymptomatic

Case 4 M/64



- DM 2yrs
- 2005-5 leg pain with insomnia(VAS 7.4)
- Decreased distal sensory function
- Absent DTR, ankle weakness G4
- 2007-3 no improvement, ataxia
- NCS; F-wave dispersion
- CSF protein 76.8mg/dl
- Immunofixation test abnormal IgA lambda



General rule of diagnosis of DPN



- DM by criteria
- Prolonged chronic hyperglycemia
- Predominantly distal symmetrical sensorimotor polyneuropathy of the lower limbs
- Exclusion of other causes of neurologic disease
- Retinopathy or nephropathy of similar severity

DIFFERENTIAL DIAGNOSIS



- Exclude other causes of neuropathy.
- Red flags: atypical of diabetic neuropathy
 - signs of a systemic disease such as vasculitis
- Exclude neuropathy commonly associated with diabetes
 - Chronic inflammatory demyelinating polyneuropathy (CIDP)
 - Neuropathy due to vitamin B12 deficiency
 - Hypothyroidism
 - Uremia

DDX: exclude other neuropathies



- **Distal symmetric polyneuropathy**
 - Uremia, VitB12 deficiency, Hypothyroidism, Porphyria
 - Alcohol, heavy metals, various drugs
 - Sarcoidosis, Leprosy, SLE
 - Paraproteinemia, Amyloidosis, Hereditary neuropathies
- **Painful neuropathies**
 - Small-fiber neuropathy
 - Psychologic disorders
- **Autonomic neuropathy**
 - MSA, Idiopathic OH
- **Motor polyneuropathy**
 - GBS, myopathies, MG
- **Cranial neuropathy**
 - Carotid aneurysm, intracranial mass
- **Mononeuritis multiplex**
 - Vasculitides, amyloidosis, Coagulopathies

Monitoring for Early detection



- Early detection can decrease the morbidity of diabetic neuropathy.
- American Diabetes Association practice statement (2005)
 - screening for neuropathy
 - at diagnosis of type 2 diabetes
 - five years after diagnosis of type 1 diabetes
 - screening at least annually
 - Pinprick / Temperature
 - Vibration perception (using a 128 Hz tuning fork)
 - Pressure sensation (using a 10 g monofilament pressure sensation at the distal halluces)

Tuning fork test



- 128 Hz tuning fork
 - placed on the interphalangeal joint of the right hallux
 - no vibration: 2 points
 - stronger at the wrist: 1 point, if the vibration feels
 - no different at the wrist: 0 points
1. Normal 0
 2. Mild to moderate deficit 1
 3. Severe deficit 2
- Widespread utility in clinical practice
 - simple, brief, valid and reliable

Objective tests for DPN



- **Clinical assessment of sensory signs**
 - Clinical scale
- **Electrophysiologic methods**
 - NCS
 - QST
- **Direct morphologic evaluation of nerves**
 - Skin biopsy

Clinical Scales



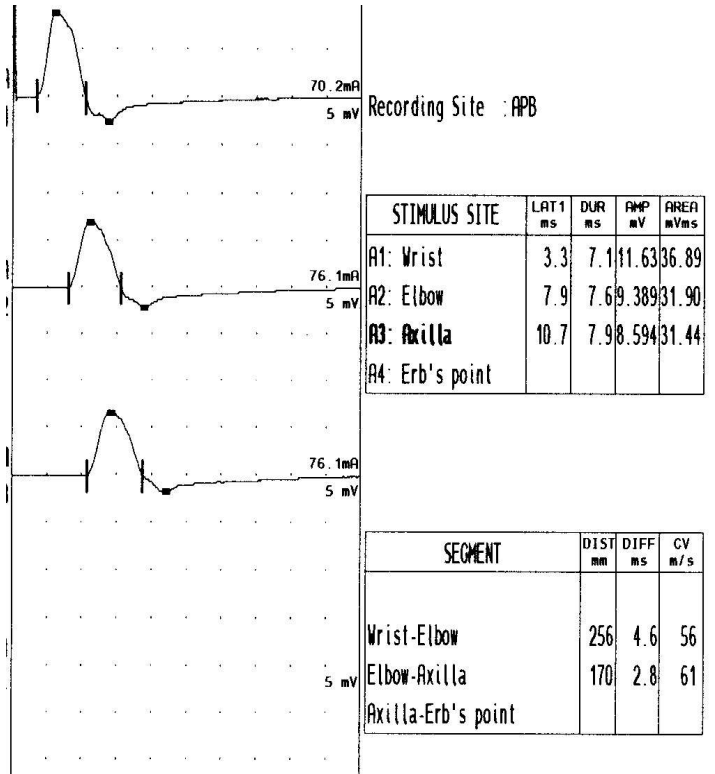
Clinical Symptoms

1. McGill pain questionnaire
2. Visual analog Scale (VAS)
3. Neuropathy Symptom Score (NSS)
4. Neuropathy Symptom Profile (NSP)
5. Simplified Neuropathy Symptom Score

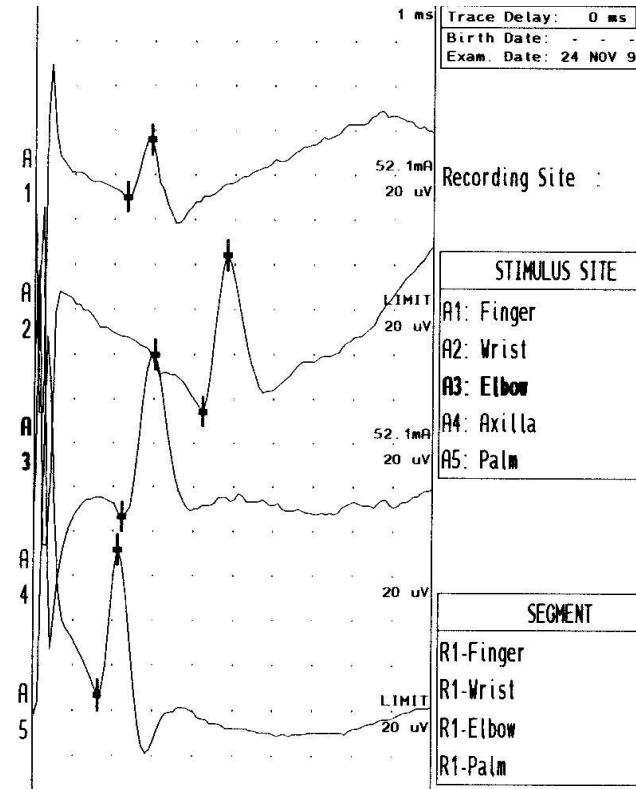
Clinical signs

1. Neuropathy Disability Score (NDS)
2. Modified NDS
3. Michigan Neuropathy Screening Instrument (MNSI)
4. Total Neuropathy Score (TNS)
5. Diabetic neuropathy Examination (DNE)
6. Neuropathy Impairment Score (LL) + n Tests Score

Nerve conduction study



Motor Nerve Conduction



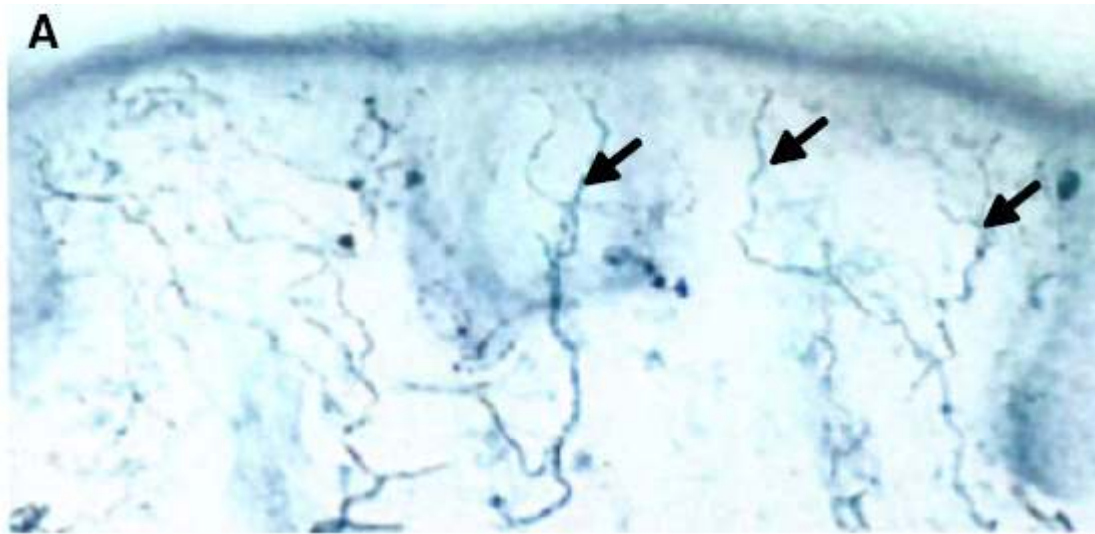
Sensory Nerve Conduction

Electrophysiologic features of axonal degeneration vs. segmental demyelination

	Axonal degeneration	Segmental demyelination
NCS		
Latency	Normal	Increased
Amplitude	Decreased	Normal
Velocity	Normal	Decreased
F-latency	Normal	Increased
EMG		
SPA	Present	Absent
MUP amp	Increased	Normal
Recruitment	Decreased	Normal

❖ Less representing small fiber function

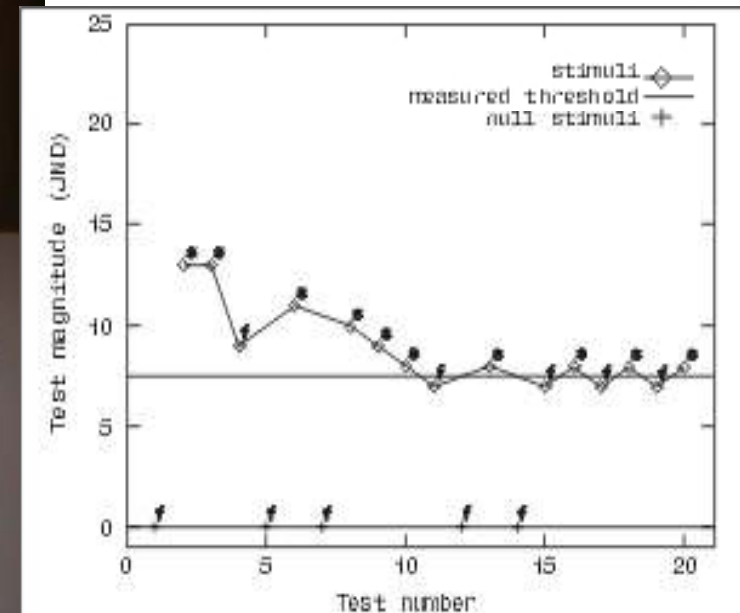
Skin-punch biopsy



Quantitative sensory testing



- Early detection of small and larger fiber dysfunction



Treatment of symptoms



No single satisfactory treatment for any of the neuropathic syndromes

- analgesics in mild pain
- *amitriptyline:*
- *nortriptyline, desipramine*
- *Anticonvulsants:*
phenytoins/carbamazepine/clonazepam/lamotrigine
- *baclofen:*
- *clonidine:*
- *Lidocaine*
- *Mexiletine*
- *topical use of capsaicin-containing creams*
- *tramadol HCL*
- *decompression of tarsal tunnel*

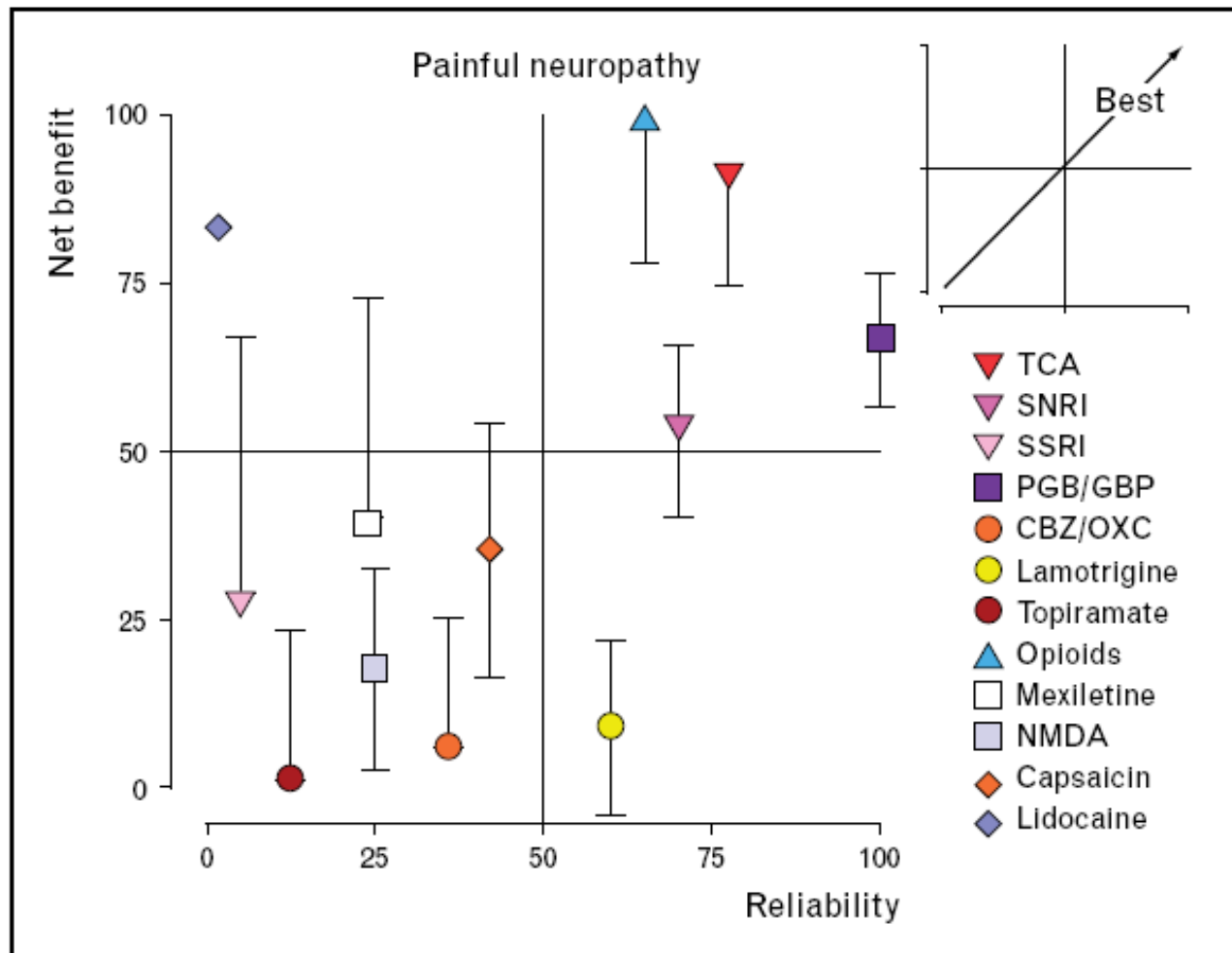
Placebo-controlled, double-blind trials, n>50



- 19 RCT's

Drug class	Drug	Daily dose (mg)	NNT	NNH	Side effects
Tricyclics	Amitriptyline	25–150	2.4 (2.0–3.0)	2.7 (2.1–3.9)	++++
	Imipramine	25–150	2.4 (2.0–3.0)	2.7 (2.1–3.9)	++++
SSRIs	Paroxetine	40	ND	ND	+++
	Citalopram	40	ND	ND	+++
Anticonvulsants	Gabapentin	900–1,800	3.7 (2.4–8.3)	2.7 (2.2–3.4)	++
	Pregabalin	150–600	3.3 (2.3–5.9)	3.7	++
	Carbamazepine	200–400	3.3 (2.0–9.4)	1.9 (1.4–2.8)	+++
	Topiramate	Up to 400	3.0 (2.3–4.5)	9.0	++
Opioids	Tramadol	50–400	3.4 (2.3–6.4)	7.8	+++
	Oxycodone CR	10–60	ND	ND	++++

DIABETES CARE, VOLUME 28, NUMBER 4, APRIL 2005



Summary and conclusions



- There are many forms of diabetic neuropathy including symmetric polyneuropathy, autonomic neuropathy, radiculopathies, mononeuropathies, and mononeuropathy multiplex.
- It is important to appreciate that there are other causes of neuropathy.
- Because of the potentially severe complications, early detection of diabetic polyneuropathy followed by therapeutic interventions is important.
- Careful neurologic examination is the mainstay to detect DPN, and can be complemented by nerve conduction study, quantitative sensory test, and/or skin biopsy.



감사합니다.