

Neuropathy in Diabetes

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GN 80 Male with painful feet

- Type 2 diabetes 1979
- Ischaemic heart disease
- Treated maculopathy
- Stage 3 CKD
- Rheumatoid arthritis
- Prostatic symptoms
- Risk of falls

On Examination

- Feet are burning, worse late afternoon and at night
- Made worse on walking
- Occasional shooting pain
- Severity 10/10, average 8/10
- LANSS 14
- Absent peripheral pulses
- Reduced pin price below ankle
- Hyperaesthesia lateral side of foot

D/D

- Neuropathic pain
- ? PVD
- ? Mechanical pain
- Tried on Gabapentin 300mg nocte
- Titrated up to: 0 - 0 - 300 - 300 mg to control pain

Admitted as emergency



X-Ray Showed Osteomyelitis



Angioplasty of common peroneal trunk and amputation of hallux



Needed Amputation of Hallux which healed after 3 months of antibiotics due to residual infected bone



Diabetic Neuropathy: Patient's View

- Most feared Amputation
- Most unpleasant Pain
- Most disliked Ulcer
- Most common Numbness

Diabetic Neuropathy: Clinician's View

- Most feared Intractable Vomiting
- Most unpleasant Wet Gangrene
- Most disliked Foot Examination
- Most common Abnormal NCV

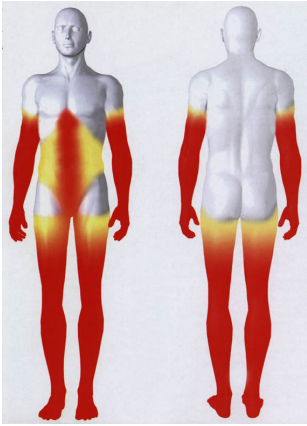
Epidemiology of Diabetic Neuropathy

- About 60-70% of people with diabetes have mild to severe forms of nervous system damage
- More than 60% of nontraumatic lower-limb amputations occur among people with diabetes.
- 30% of people with diabetes complain of pain

Risk Factors for Distal Symmetrical Neuropathy

- Hyperglycaemia
 - Duration/Age
 - Height
 - Cardiovascular Risk factors:
Hypertension, Cholesterol, Triglycerides, BMI, Smoking

Distal Sensory Motor Neuropathy



Typical 'glove & stocking' sensory loss

Significant motor deficit is not common

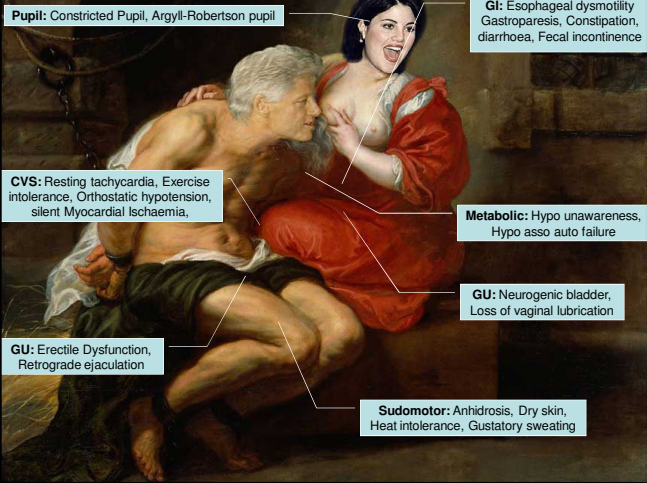
Symptoms may not match signs of nerve damage

Complications of Polyneuropathy

- Deformity
- Callus
- Ulcers
- Amputation - Risk factors include:
 - Peripheral vascular disease
 - Infection
 - Recurrent ulcers
 - Renal Failure

Less Common Clinical Presentations of Neuropathy

- Proximal myopathy
- Mononeuritis multiplexa
- Charcot foot
- Sensory ataxia (with diminished vision)
- Autonomic neuropathy



Pupil: Constricted Pupil, Argyll-Robertson pupil

GI: Esophageal dysmotility, Gastroparesis, Constipation, diarrhoea, Fecal incontinence

CVS: Resting tachycardia, Exercise intolerance, Orthostatic hypotension, silent Myocardial Ischaemia,

Metabolic: Hypo unawareness, Hypo asso auto failure

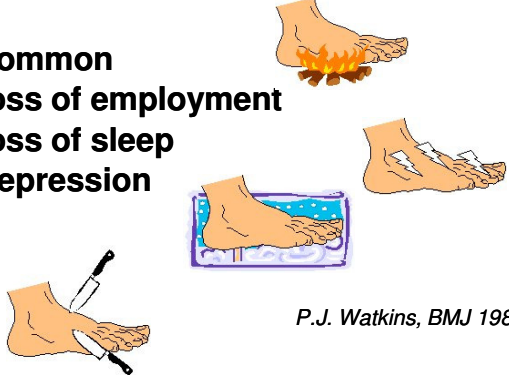
GU: Erectile Dysfunction, Retrograde ejaculation

GU: Neurogenic bladder, Loss of vaginal lubrication

Sudomotor: Anhidrosis, Dry skin, Heat intolerance, Gustatory sweating

Painful neuropathy of diabetes

- common
- loss of employment
- loss of sleep
- depression



P.J. Watkins, BMJ 1984

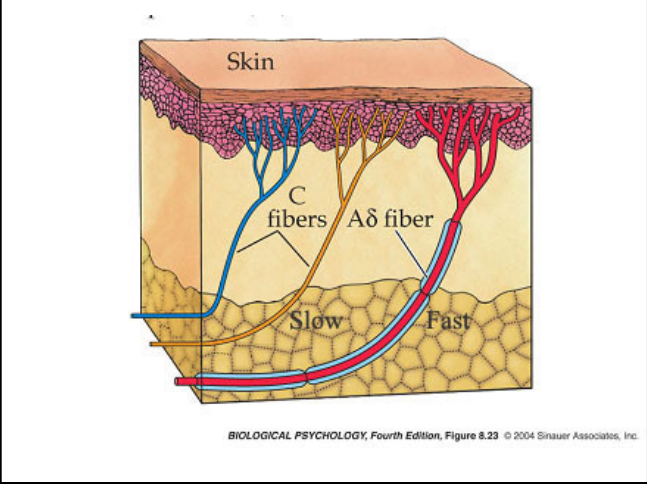


Diagram illustrating the structure of the skin and the pathways of C fibers and Aδ fibers. The diagram shows the skin layers (epidermis and dermis) and the underlying tissue. C fibers are labeled as 'Slow' and Aδ fibers as 'Fast'.

BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 8.23 © 2004 Sinauer Associates, Inc.

Peripheral Nerve Fibre

- **Myelinated**
 - A alpha (12-20µm) Motor
 - A beta (10 -15 µm) sensory
 - A gamma (5 - 15 µm) Motor for posture
 - A delta (3-8 µm) cold & pain
 - B (1-3 µm) Autonomic
- **Non myelinated**
 - C (0.2-1.5 µm) Heat, pain & Autonomic

Assessment of Neuropathy & Painful Neuropathy

- Detailed History
- Clinical examination
- Psychological assessment
- Investigations
- Other complications of diabetes

Investigations rarely needed

- Nerve conduction
- Qualitative Sensory Test
- Post exercise ABPI
- X-Ray
- MR Scan spine

Treatment of pain in DN

Tricyclic compounds

Mechanism of action:

- Blockade of NA reuptake
 - Not through anti-depressant effect
1. Effectiveness independent of mood
Max et al., Neurology; 1987
 2. Effective at lower [plasma] imipramine 400-500 nmol/l
Sindrup et al., 1990
 3. Onset of action - 1 day
Young & Clarke, 1985

Treatment of pain in DN

Anticonvulsants

- **Carbamazepine** - starting 100 mg bd (800-1000 mg/day)
 - *Rull et al., 1969*
 - *Ocaranza Ochoa et al., 1968*
 - *Wilton, 1974*
 - no change in NCV
Chakrabarti et al., 1976
 - **Phenytoin** - 100-400 mg nocte
 - *Chadda & Mathur, 1978*
 - **Sodium valproate** 100-500 mg tds
- Side effects: drowsiness, dizziness, GI disturb., ataxia etc...

Treatment of pain in DN

Gabapentin

- Backonja et al. JAMA 1998.
- Gabapentin 900 - 3600mg/day (n=70)
Placebo (n=65)
- Trial time - 8 weeks
- Gabapentin improved:
 - pain scores (↓ 40% vs 22%) p<0.001
 - QOL (SF - 36)
- Side effects: dizziness and somnolence

Treatment of pain in DN

- Pregabalin
 - 300 – 600mg daily
 - Reduce pain and improve sleep quality
(Freyenhagen Pain 2005)
- Lamotrigine
- Topiramate
- Levodopa
 - Single study on 25 patients
 - Reduction in pain by 100mg TDS
(Ertas, Pain 1998)

NICE Guideline (CG96)

NHS
National Institute for
and Clinical Excellence

- Duloxetine as first choice
- Amitriptyline if not tolerated
- Change to or add pregabalin

Start low, go slow

Issue date: March 2010

Neuropathic pain

The pharmacological management of neuropathic pain in adults in non-specialist settings

Step up Treatment

Tramadol

- Harati Y et al. Neurology 1998.
- Tramadol (n=65),
average dose 210mg/day (four divided doses)
Placebo (n=66)
- Trial time - 42 days
- Tramadol improved:
 - pain scores (p<0.001)
 - 'physical / social functioning' (p<0.05)

Morphine & Gabapentine

- 57 painful neuropathy patient
- Pain score:

| | |
|-----------------|------|
| – Baseline | 5.72 |
| – Placebo | 4.49 |
| – GBP | 4.15 |
| – Morphine | 3.7 |
| – Morphine +GBP | 3.06 |
- Maximum tolerable dose for combination was lower

Gilron NEJM 2005

For more localised pain

Topical capsaicin - (0.075%)

- depletes substance P
- marked placebo effect (69.5% - C Vs 53.4% -P)
- questionable blindness *Capsaicin Study Group, 1992*
- initial burning pains, skin rashes, erythema, cough, sneezing
- More concentrated compound on clinical trial

Topical lignocaine 5%

- Tradename Versatis
- Up to 3 patches per day that can be cut if needed (700mg per patch)
- 12 hours off period
- Expensive

Occasionally tried treatment

- Clonazepam
- Dextromethorpan (over the counter cough medicine)
- Clonidine
- Sativex nasal spray
- Topical ISDN

B Vitamins

- Only limited data in randomised trials
- The evidence is insufficient to determine whether vitamin B is beneficial or harmful.
- Water soluble vitamin so possibly no harm
- Placebo effect

Ang D et al. *Cochrane Database Syst Rev.* 2008 Jul 16;(3):CD004573.

Experimental treatment

- α Lipoic acid (Can import)
- NGF (Roche)
- PKC beta inhibitors (Lilly)

Feet Screening in Diabetes

- Check for sensation
 - 10 gm monofilament most reproducible
- Check for deformity
 - Callus
- Check pulses
- Condition of skin & nail

Prevention of Ulcer

- Good fitting shoes
- Daily examination of feet
- Regular foot carer if high risk feet
- Nail hygiene
- Prompt treatment of any infection

Conclusions

- Glycaemic control essential
- Control of cardiovascular risk factor
- Pharmacological treatment for pain
 - Tricyclic compounds
 - Pregabalin, Gabapentin
 - Duloxetine
 - Combination
 - Tramadol
- Annual screening of feet

