Neuropathy:
Diagnosis & Management

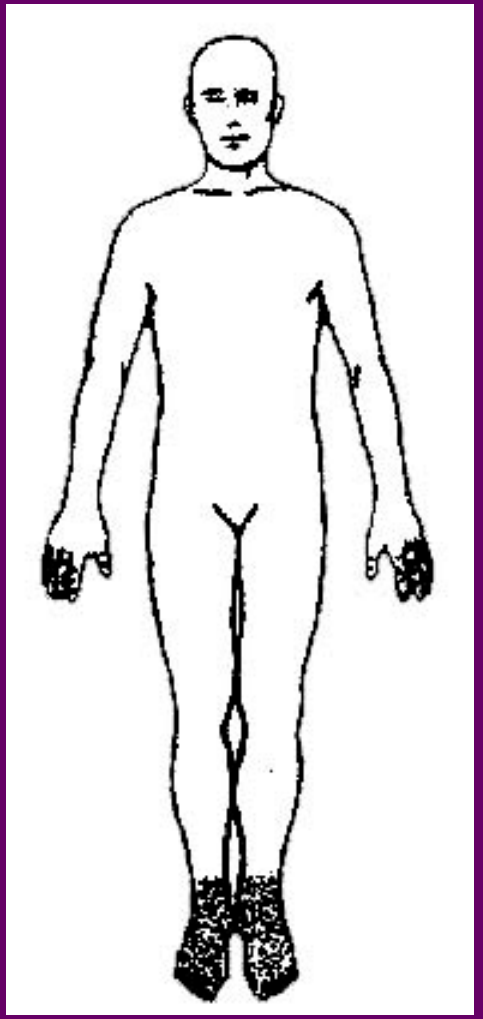
- http://homepage.ntu.edu.tw/~anatomy/teacher/hsieh/hsieh.html
  - **周邊神經教學**
- Topics
  - Etiology approach
  - Common neuropathies:
    - Diabetic neuropathy vs. Neuropathy in diabetes
  - Diagnosis of painful neuropathy
    - Skin biopsy and neuroimaging
  - Treatment:
    - Inflammatory neuropathies
    - Neuropathic pain

Overview of Neuropathy

- Typical presentations of neuropathy
  - Neurological deficits (motor, sensory, autonomic) in the territory of peripheral nerves
    - Motor: lower neuron type (vs. myopathy, myelopathy)
- Patterns of neuropathy and etiology
  - Single nerve (mechanical compression)
    - Mononeuropathy; Radiculopathy
  - Multiple nerves (systemic etiology)
    - Polyneuropathy (length-dependent, symmetric absence of ankle jerk): metabolic, toxic, autoimmune
    - Mononeuropathy multiplex: vascular (ischemic, inflammation), autoimmune

Diabetic Sensory neuropathy: Clinical presentations

- 45 y/o male with diabetes for 2 years under control with oral hypoglycemic agents; HbA1c=8.0%
- Tingling, prickling, burning over feet for 4 months
- Paresthesia over fingers for 1 months
- Sensory neuropathy (symptoms, NE, Lab tests)
  - Large-fiber neuropathy
  - Small-fiber neuropathy



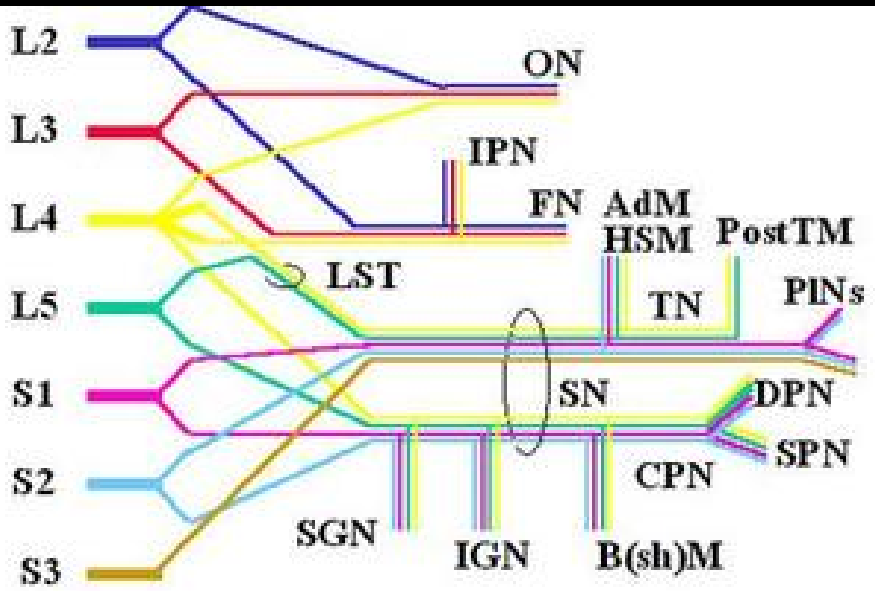
Neuropathy in diabetes?

- 75 y/o female with diabetes for 6 years under regular medications of oral hypoglycemic agents; HbA1c = 7.2%
- Mild paresthesia over both feet for 2 years
- Subacute onset of pain and weakness involving the right thigh muscles with progression over 2 months

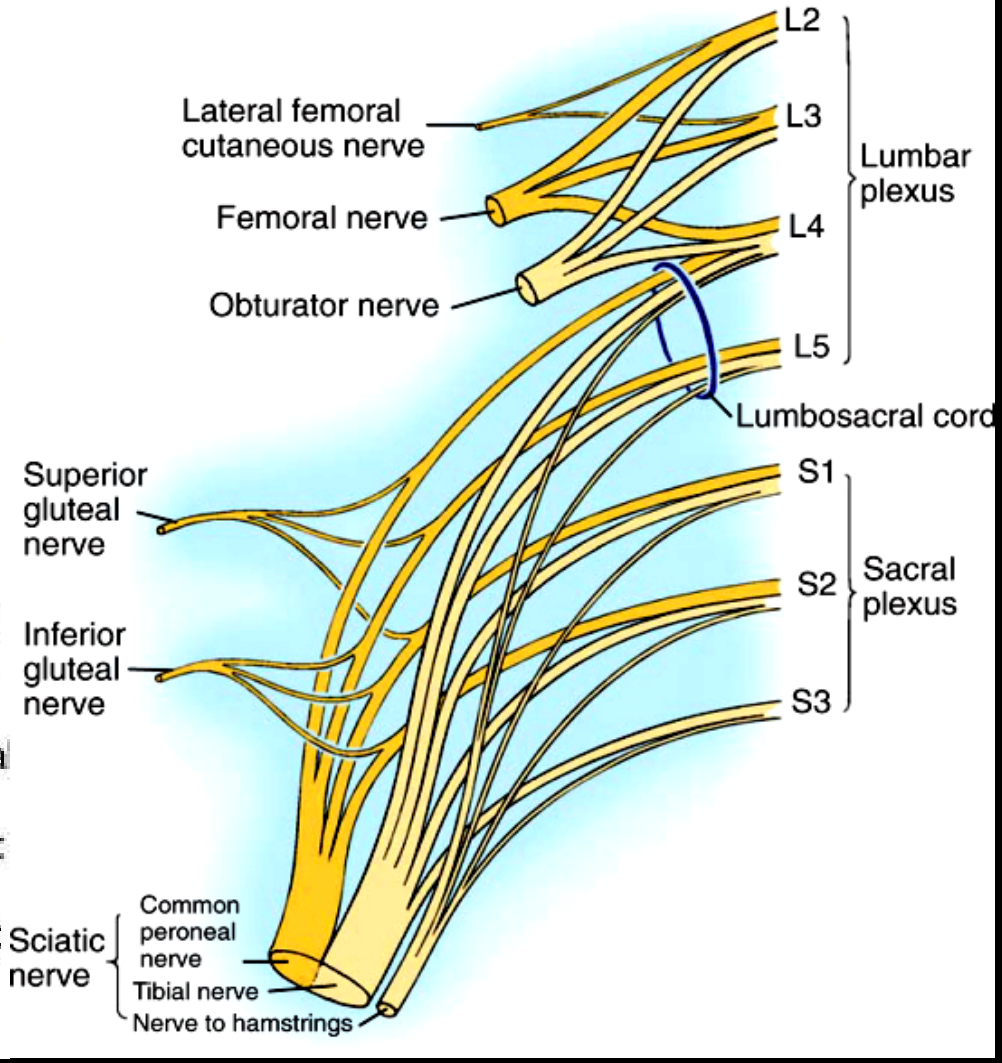
NE: Neuropathy in diabetes?

- Motor system
  - Muscle strength (R/L):
    - Hip flexor: 3+/5
    - Knee extensor: 3+/5; Knee flexor: 4/5
    - Plantar dorsiflexor: 4/5; Plantar flexor 4/5
  - Deep tendon reflex (R/L):
    - Knee jerk: -/+
    - Ankle jerk: -/-
- Sensory system
  - Vibration: reduced in bilateral lateral malleoli
  - Pin-prick: reduced over bilateral foot dorsum
- Sphincters for urine and stool: intact

Laboratory examinations: Neuropathy in diabetes

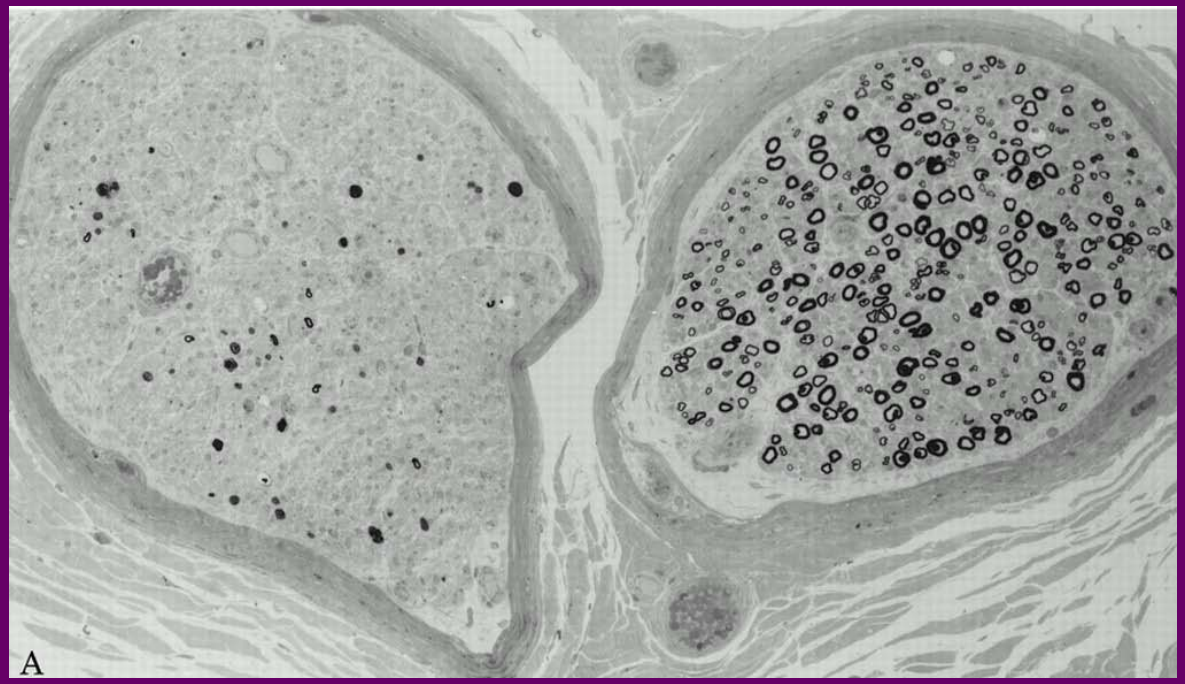


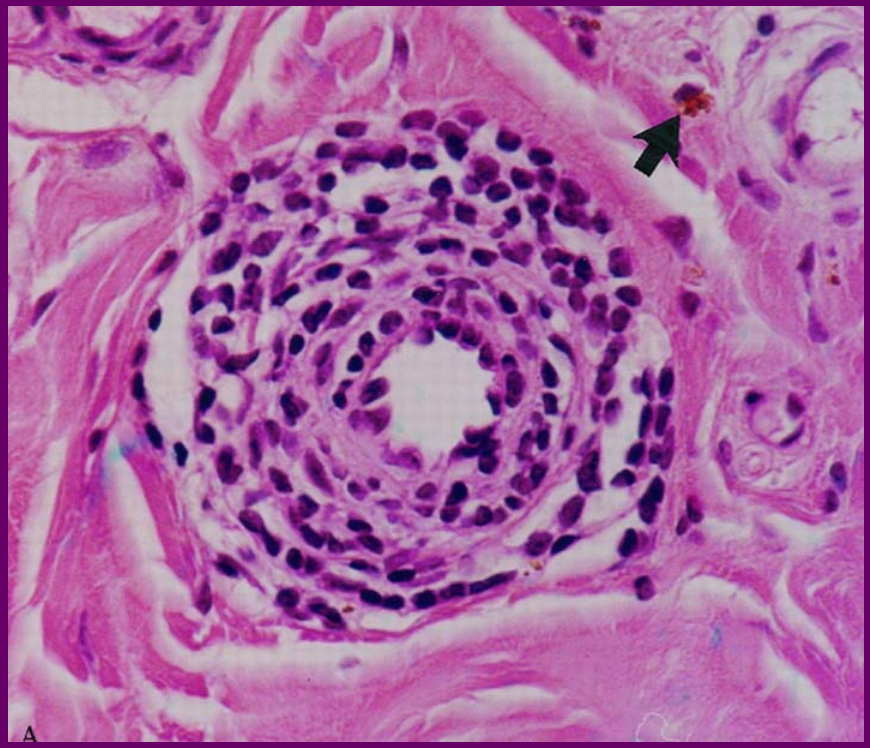
Schematic representation of the lumbosacral plexus and most important intermedial nerves. IPN: iliopsoas nerve; SGN: superior gluteal nerve; IGN: inferior gluteal nerve; ON: obturator nerve; FN: femoral nerve; LST: lumbosacral trunk; SN: sciatic nerve; TN: tibial nerve; CPN: common peroneal nerve; AdM: adductor muscle of the thigh; HSM: hamstring muscles; PostTM: posterior tibialis muscle; B(sh)M: short head of the biceps femoralis muscle; PINs: plantar nerves; DPN: deep peroneal nerve; SPN: superficial peroneal nerve.



Pathology of lumbosacral plexoradiculopathy: microvasculitis Dyck PJ, Neurol 53:2113, 1999

- Focal fiber loss
- Perivascular mononuclear infiltration
- Destruction of vascular wall





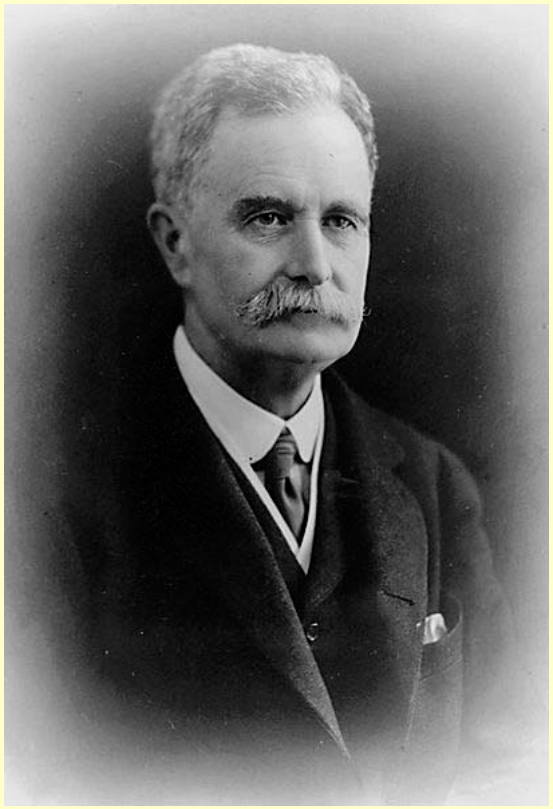
Spectrum of Diabetic Neuropathies

- **Mononeuropathy**
  - Carpal tunnel syndrome
- **Symmetric/Systemic polyneuropathy**
  - **Sensory-predominant polyneuropathy**
  - Autonomic neuropathy
- **Asymmetric neuropathy**
  - Mononeuropathy multiplex
  - **Lumbosacral plexoradiculopathy (“DM amyotrophy”)**

Charcot-Marie-Tooth

Jean-Martin Charcot

Pierre Marie

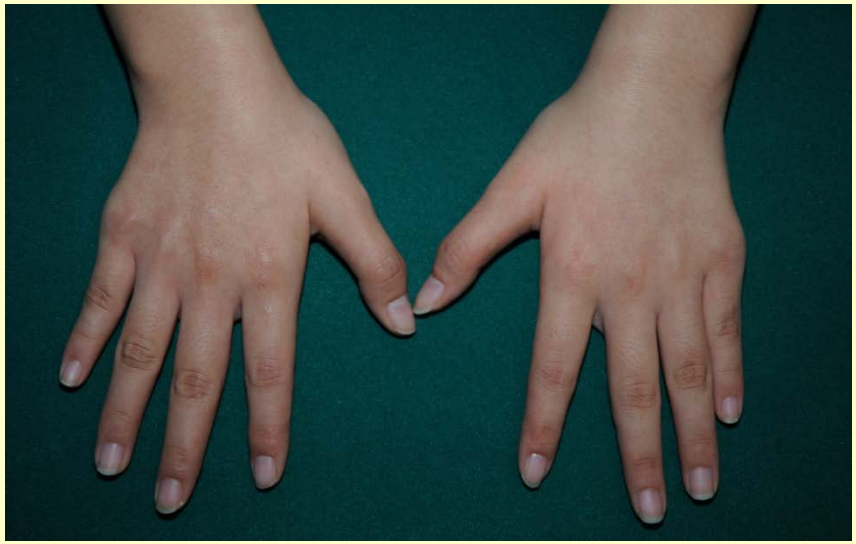


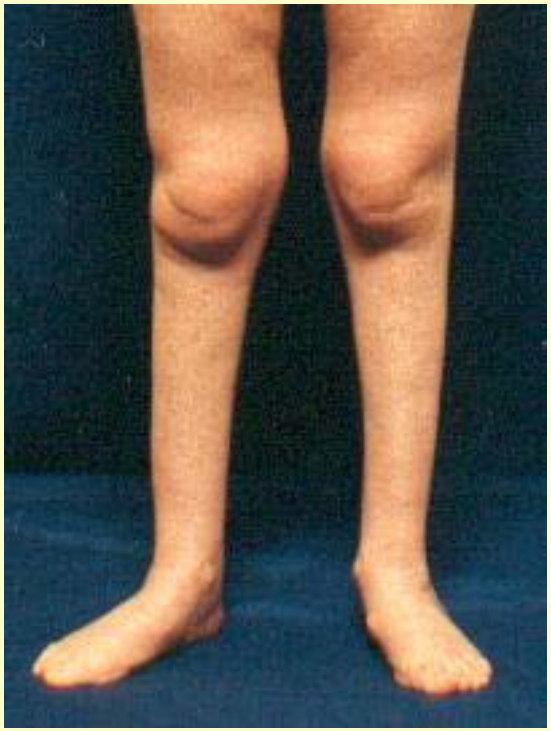
Howard Henry Tooth

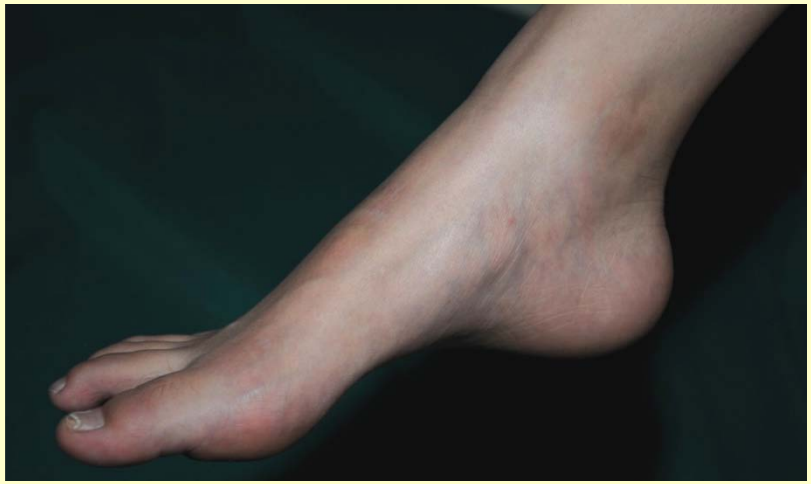
Charcot-Marie-Tooth (CMT)

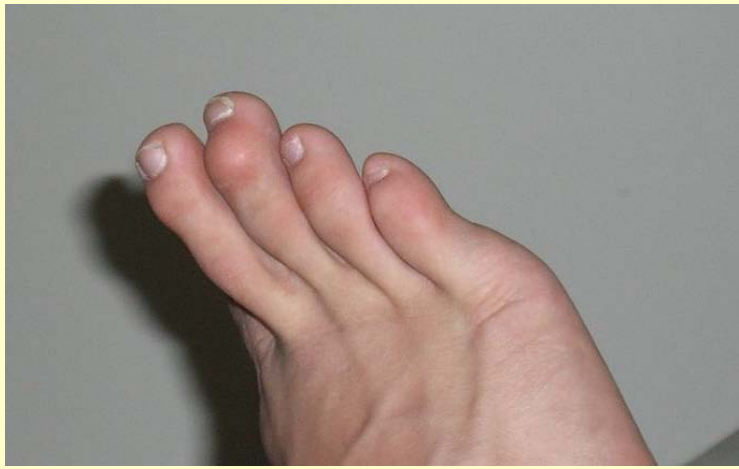
- The most common form of hereditary neuropathies
- Hereditary motor and sensory neuropathy (HMSN)
- Presentations
  - "Peroneal muscular atrophy", "inverted bottle"
  - pes cavus, high-arched foot
- Pathology and electrophysiologic phenotypes
  - type 1 (demyelination)
  - type 2 (axonal degeneration)
- Genotype: CMT1A (peripheral myelin protein 22, PMP22); CMT1B (myelin protein zero, MPZ, P0); CMTX (connexin 32) et al

Charcot-Marie-Tooth: Clinical presentations









Clinical presentations and skin denervation in amyloid neuropathy due to transthyretin Ala97Ser

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ABSTRACT

Objective: Familial amyloid polyneuropathy (FAP) due to amyloidogenic transthyretin (TTR) is often associated with impairment of thermonociceptive functions. This study investigated skin innervation and its clinical significance in genetically defined FAP due to a hot-spot Ala97Ser TTR mutation (Ala97Ser).

Methods: Skin biopsies were performed on the distal leg of patients with Ala97Ser, and intraepidermal nerve fiber (IENF) densities were quantified.

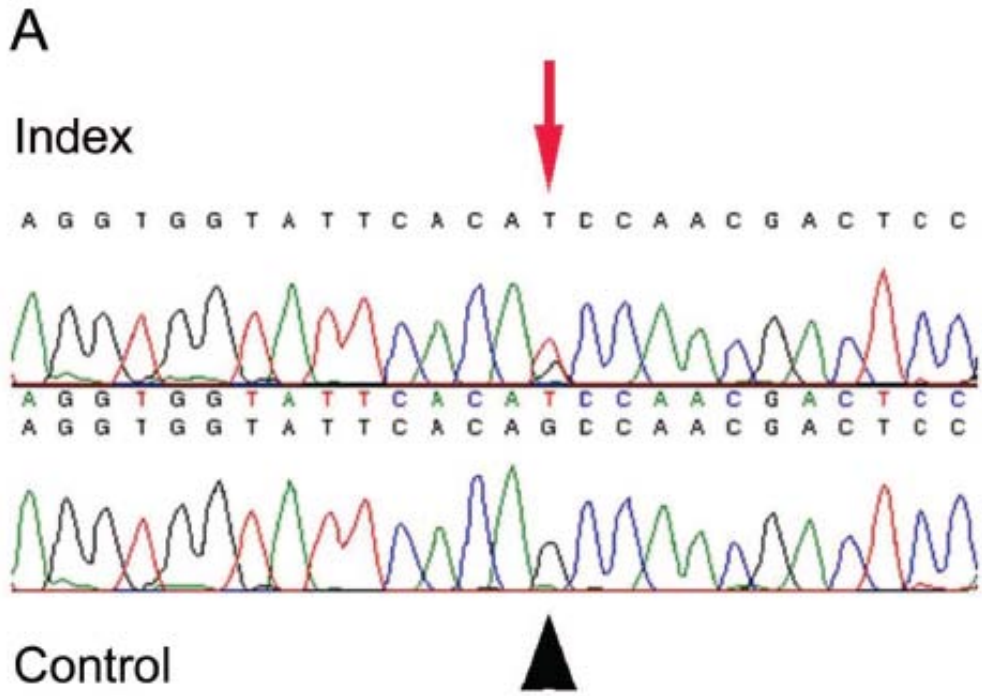
Results: There were 19 unrelated patients with Ala97Ser manifesting a late-onset (59.47 ± 5.70 years) generalized neuropathy with disabling motor, sensory, and autonomic symptoms. Against a background of a slowly progressive course, 7 patients (36.8%) exhibited additional rapid declines in neurologic deficits, which were associated with elevation of the protein content in the CSF ($p < 0.001$). The IENF density was markedly reduced in Ala97Ser patients compared to age- and gender-matched controls (0.99 ± 1.11 vs 8.31 ± 2.87 fibers/mm, $p < 0.001$). Skin denervation was present in all patients and was lower in patients with a higher disability grade (0.17 ± 0.26 vs 1.37 ± 1.16 fibers/mm, $p = 0.003$). Albuminocytologic dissociation in the CSF was observed in 14 patients (73.7%), and the IENF density was negatively correlated with the CSF protein concentration ($p = 0.015$).

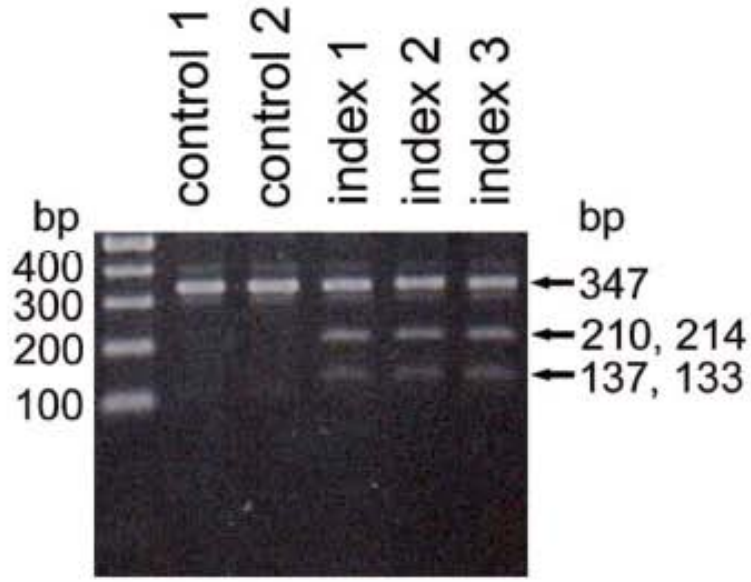
Conclusions: Skin denervation was common in Ala97Ser, and degeneration of cutaneous nerve terminals was correlated with the severity of clinical phenotypes and the level of CSF protein.

Neurology® 2010;75:532–538

Familial amyloid polyneuropathy with mutated transthyretin (TTR Ala97Ser)

- Mutation of G to T to cause transthyretin (Ala97Ser): unique in Taiwan
- Val30Met: the most common in Portugal, Sweden, and Japan





Familial amyloid polyneuropathy with mutated transthyretin (Ala97Ser) in Taiwan

- The most common genetic neuropathy of adult-onset with pan-modality involvement and axonal degeneration in Taiwan
- Marked neuropathic pain as a major symptom
- Progressive weakness of muscle strength
- Dysautonomia, especially diarrhea, frequently as one of initial symptoms
- Some exhibited rapid decline on a background of slowly progressive course

(Yang et al, Neurol, 2010)

Guillain-Barré syndrome (GBS)

Ascending paralysis in 1859

Jean Baptiste Octave Landry de Thézillat

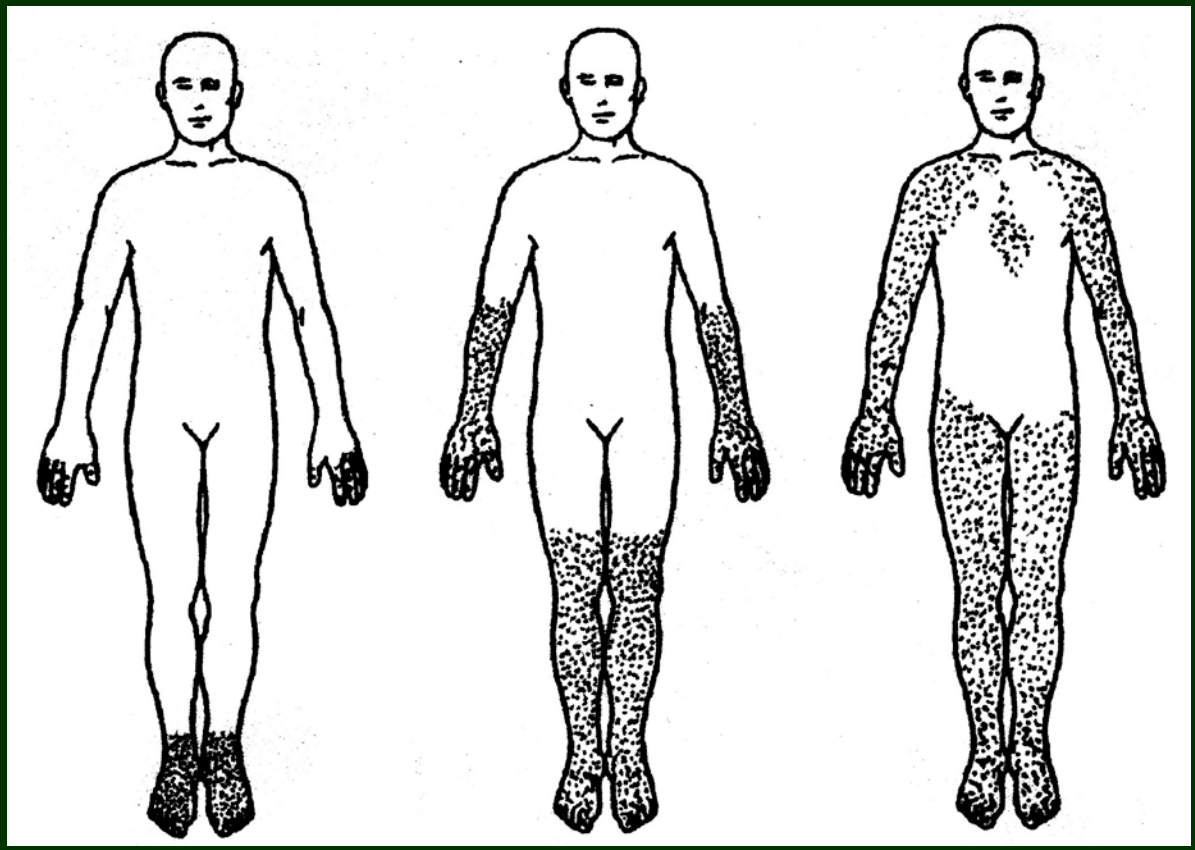
Reduced reflexes, Increased CSF protein
Without pleocytosis, in 1916

Georges Charles Guillain

Jean-Alexandre Barré

André Strohl

Guillain-Barré syndrome (GBS)



Progressive weakness

Day 1
Lower limbs

Day 3
Upper limbs

Day 7
Respiratory failure

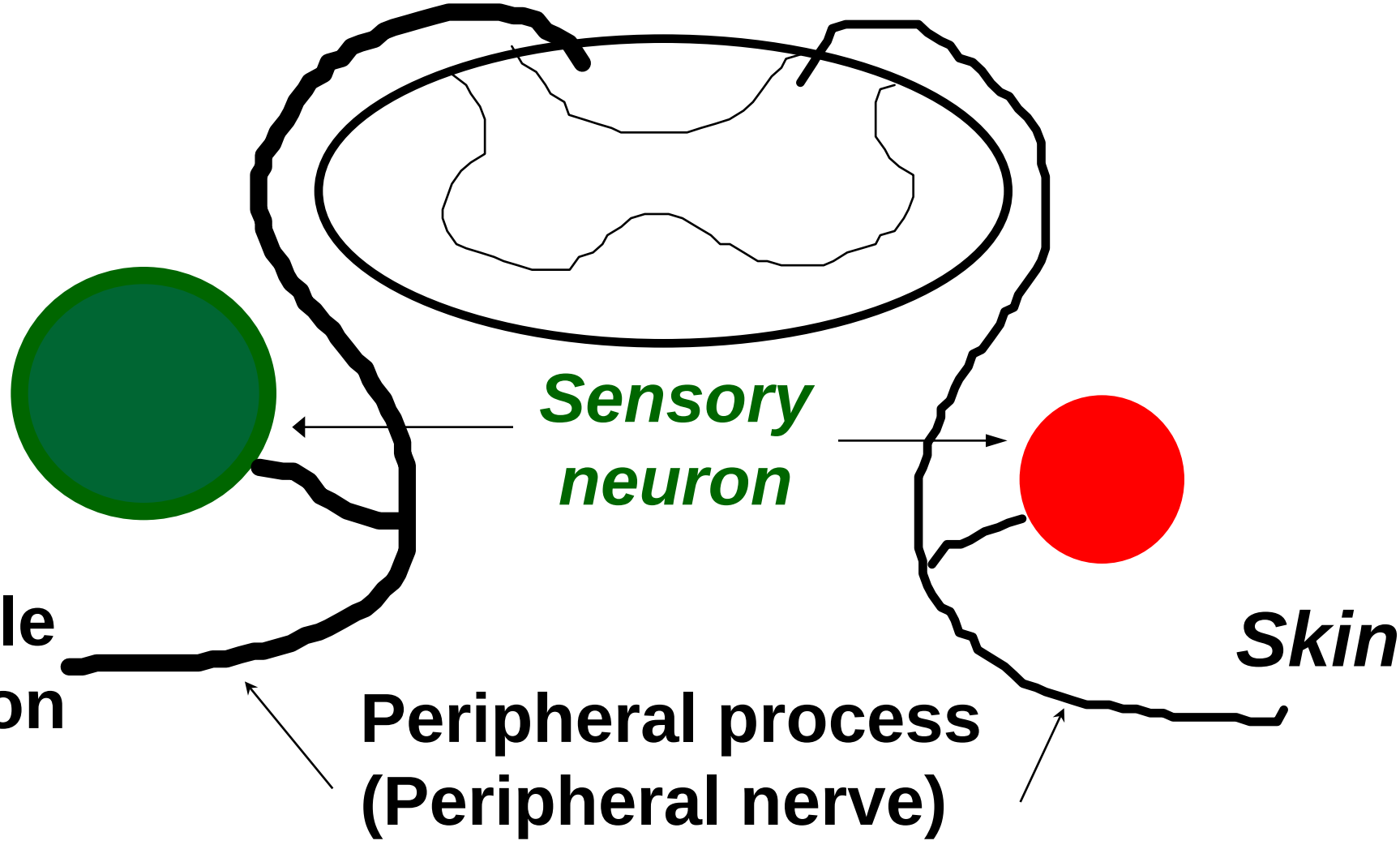
Inflammatory neuropathies: GBS and CIDP

- Guillain-Barré syndrome (GBS)
  - 20-30% associated previous infections, *Campylobacter jejuni* et al; usually < 4 weeks to reach peak and monophasic
  - molecular mimicry: autoantigen (gangliosides et al)
  - variants of (limb/bulb weakness and respiratory failure):
    - acute inflammatory demyelinating polyneuropathy (AIDP)
    - acute motor axonal neuropathy (AMAN)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - course: > 2 months
  - with underlying immune dysregulations

Therapy for inflammatory neuropathies

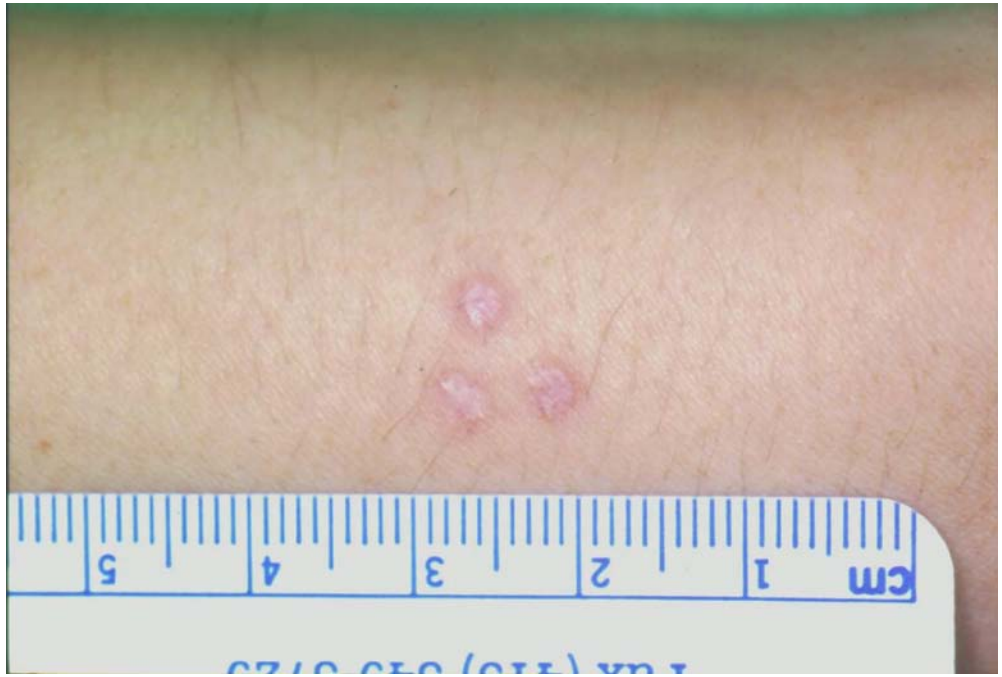
- Treatment strategies
  - Plasma exchange (PE) / Plasmapheresis
  - Intravenous immunoglobulin (IVIg)
  - Corticosteroid therapy
    - **Pulse methylprednisolone therapy**
    - **Oral prednisolone therapy**
  - Azathioprine (Imuran)
  - Cyclophasphamide (Endoxan)
- Guidelines
  - GBS: only PE or IVIG
  - CIDP: PE or IVIG followed by maintenance immunotherapy

Sensory neuron

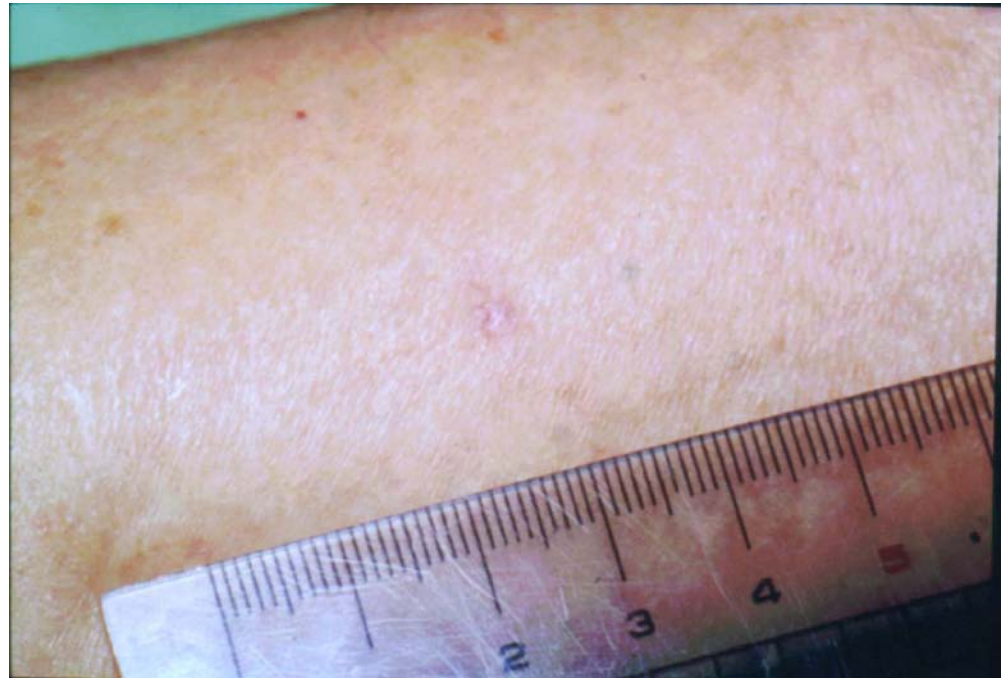


Skin biopsy (3 mm-punch)

Two weeks later

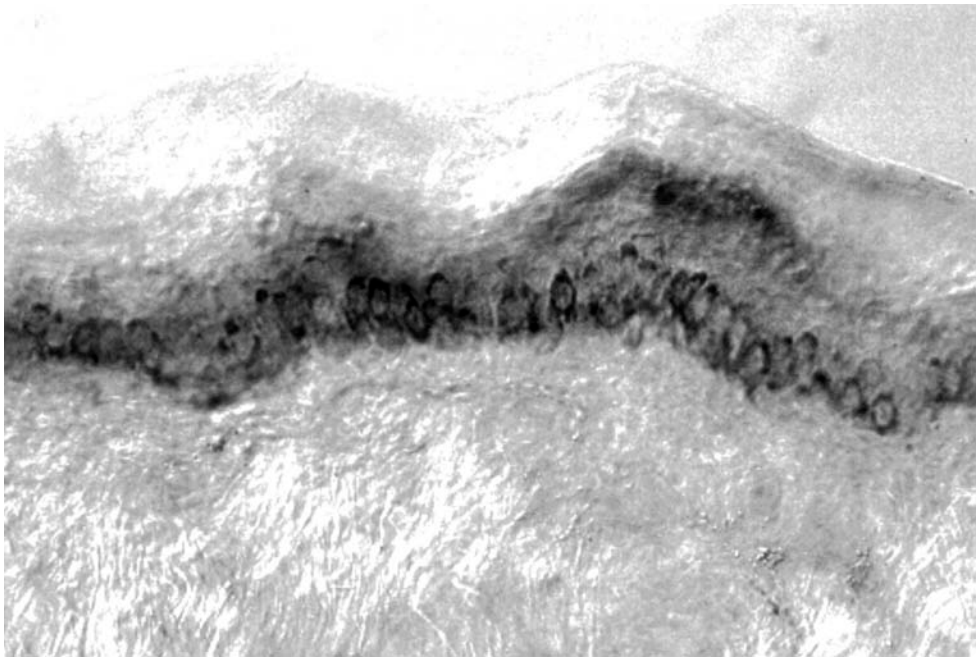


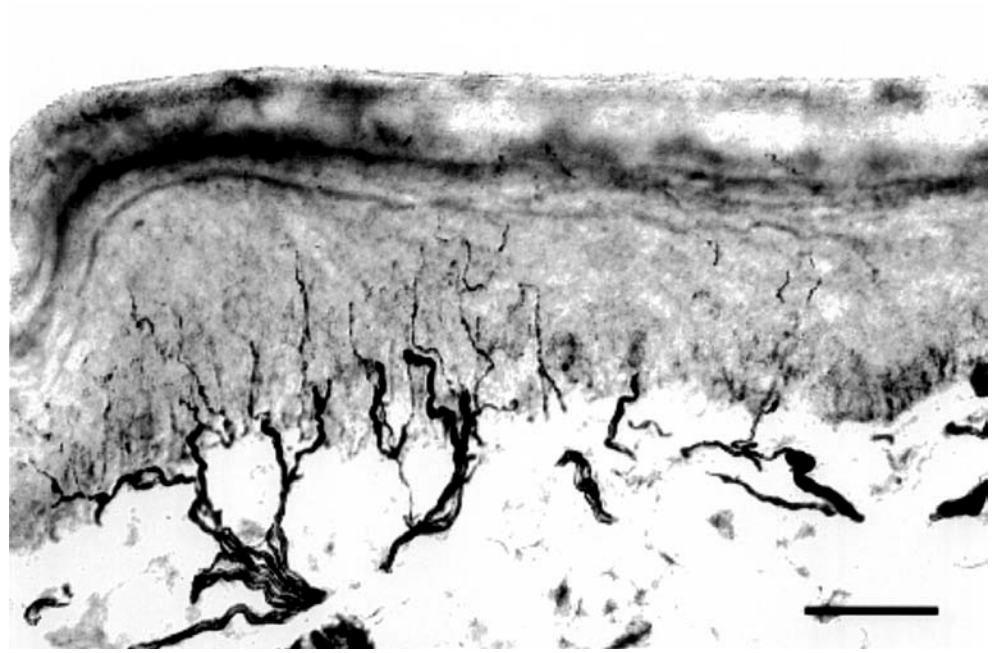
One year later



Sensory neuropathy (small-fiber type)

Normal subject





intra-epidermal nerve fiber (IENF)

IENF density: objective and quantifiable parameter of skin innervation
(European Federation of Neurological Societies Skin Biopsy Task Force, 2010)

Small-fiber neuropathy in Diabetes

DOI: 10.1093/brain/awh180 *Brain* (2004), **127,** 1593–1605

Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments

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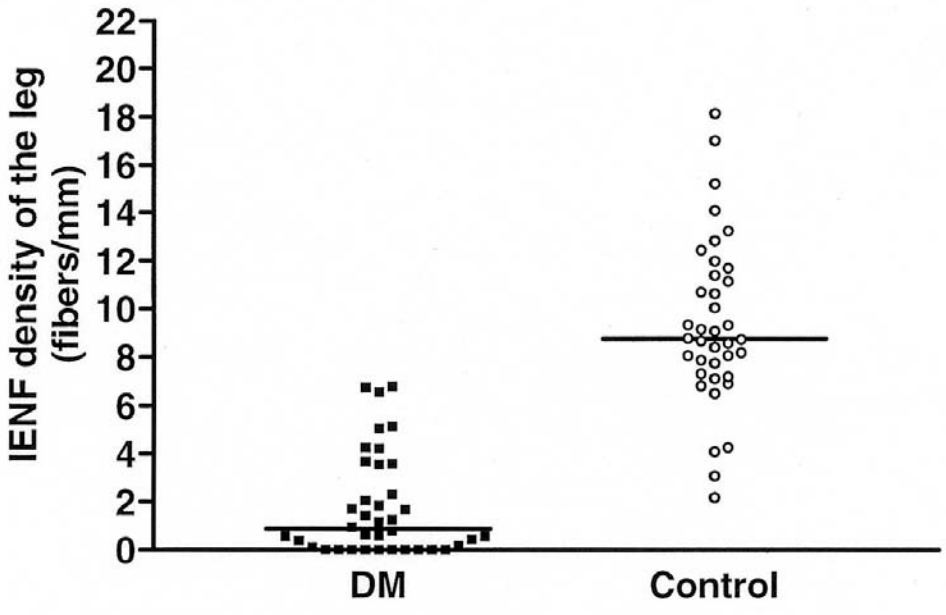
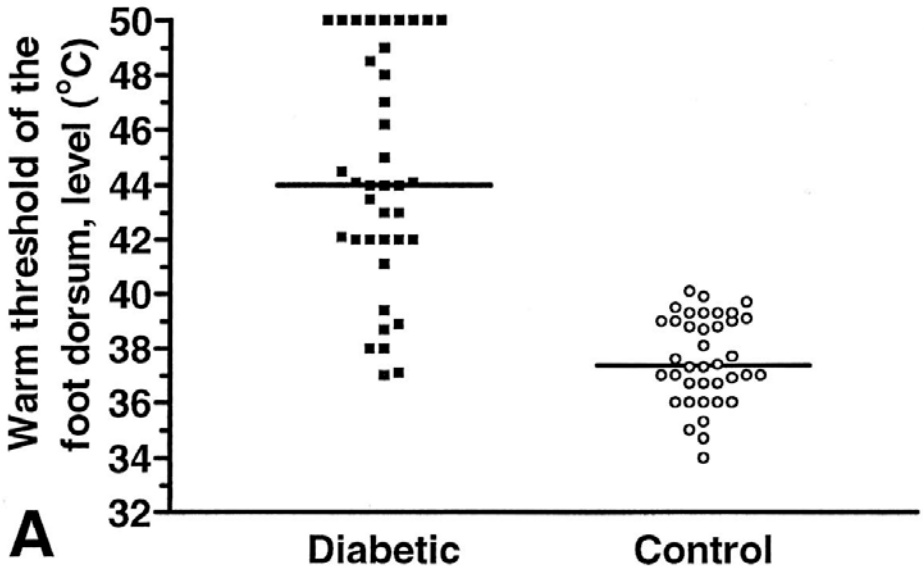
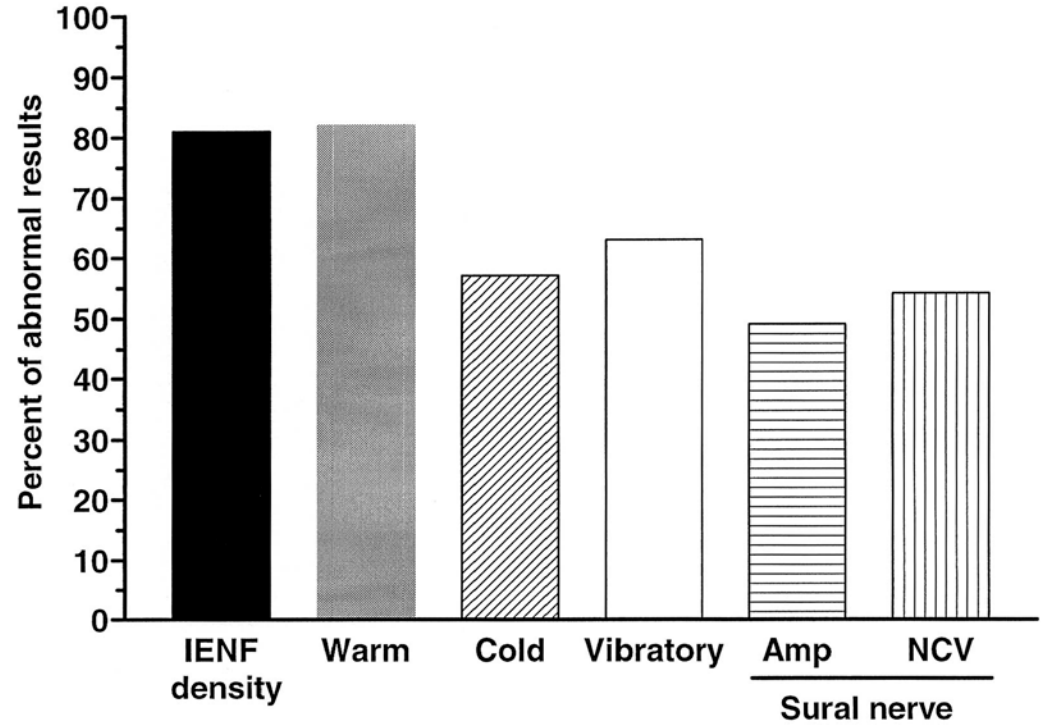
Skin innervation (IENF density) in DM







(Shun CT, Brain 127:1593-1605, 2004)

Relationship between skin innervation (IENF density) and pain

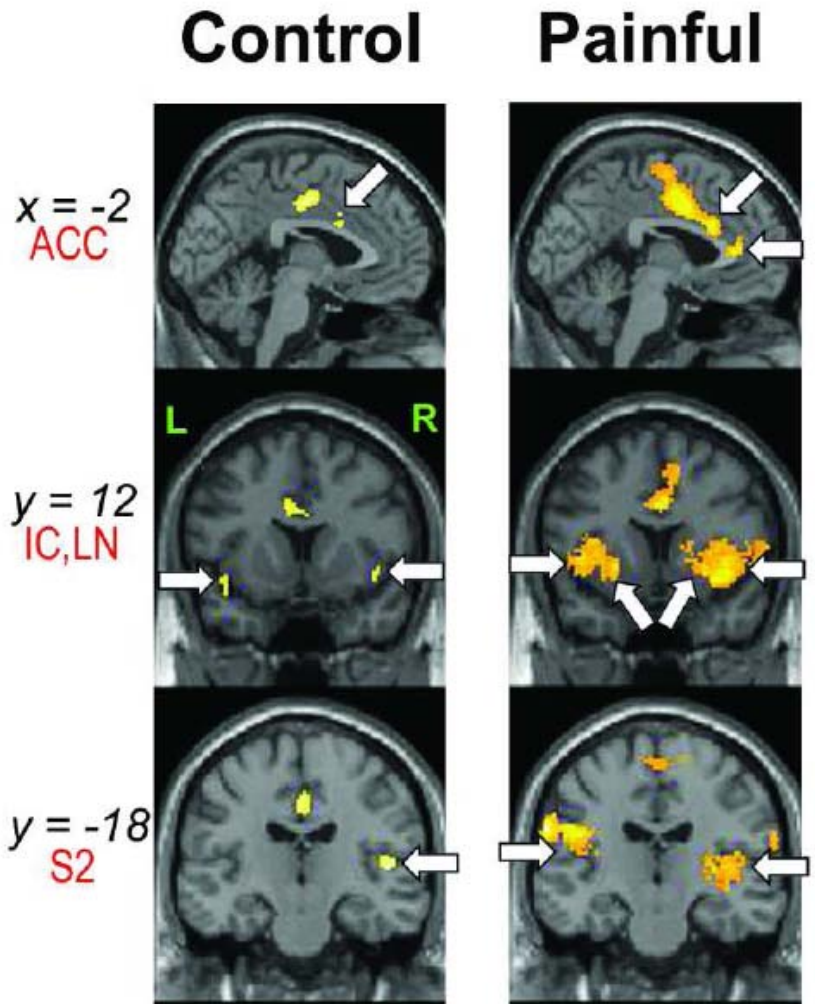
Table 7 *Relationship between intraepidermal nerve fibre density and amplitude of sural sensory action potential with clinical parameters*

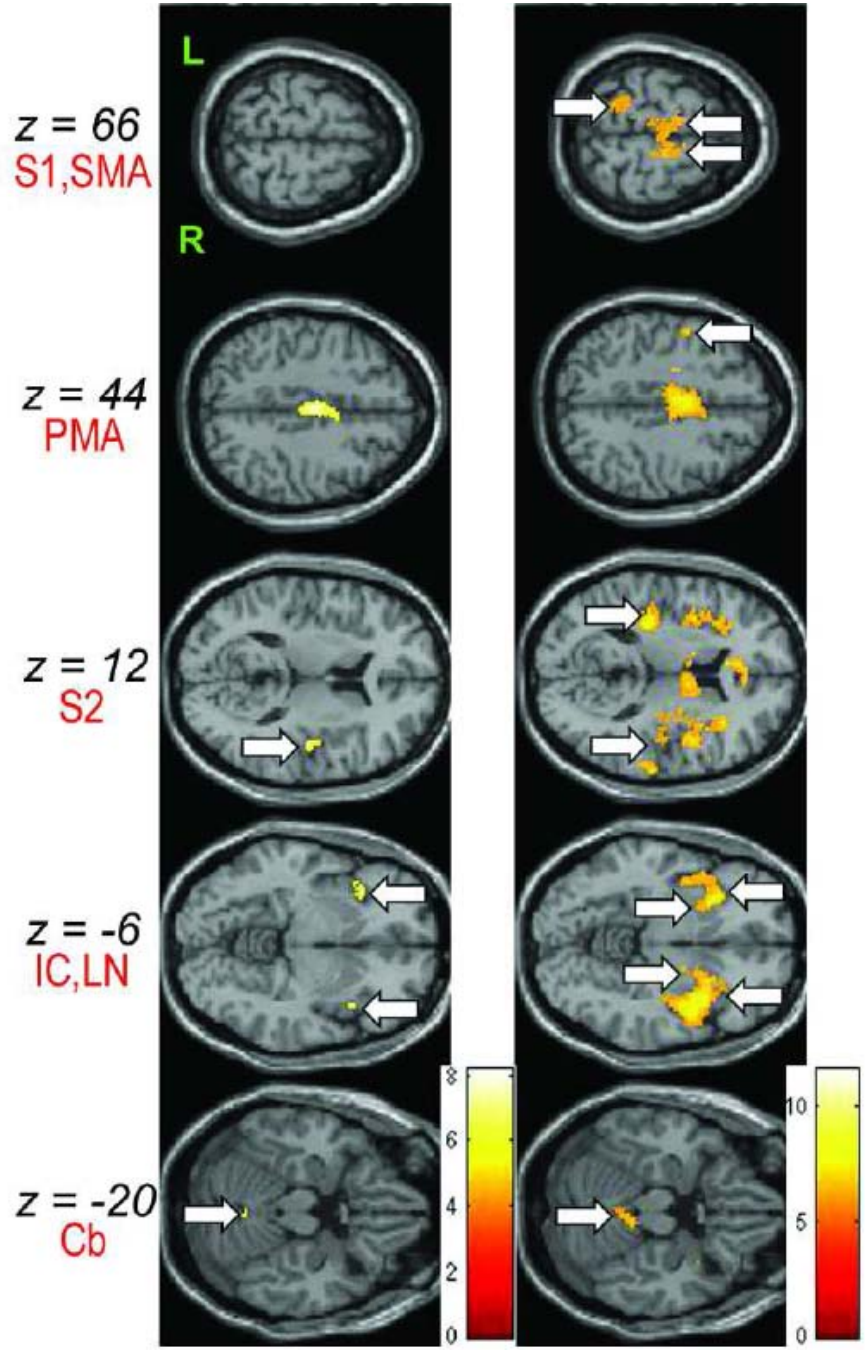
		IENF density (fibres/mm)		Sural SAP amplitude (μV)	
		Median (range)	*P*	Median (range)	*P*
Painful neuropathy	Yes (9)+	0.17 (0–4.23)	0.1137	4.2 (0–13.1)	0.1962
	No (29)	1.44 (0–6.80)		8.95 (0–18.65)	
Symptomatic site	Yes (7)	0 (0–1.68)	0.0116*	0 (0–4.96)	0.0034*
	No (31)	1.25 (0–6.8)		8.95 (0–18.65)	

+*n*. *Statistically significant.

(Shun CT, Brain 127:1593-1605, 2004)

Brain activations in pain due to diabetic neuropathy

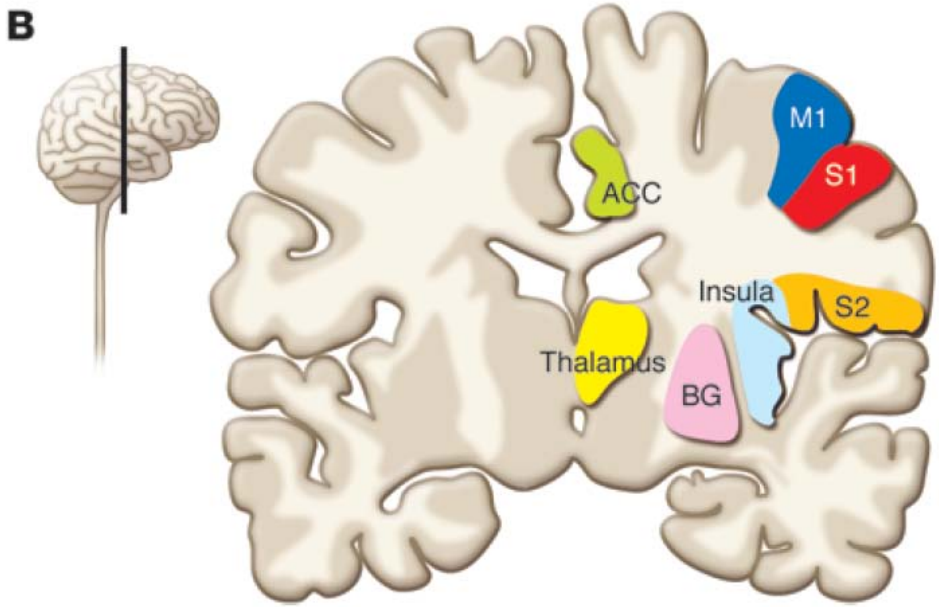


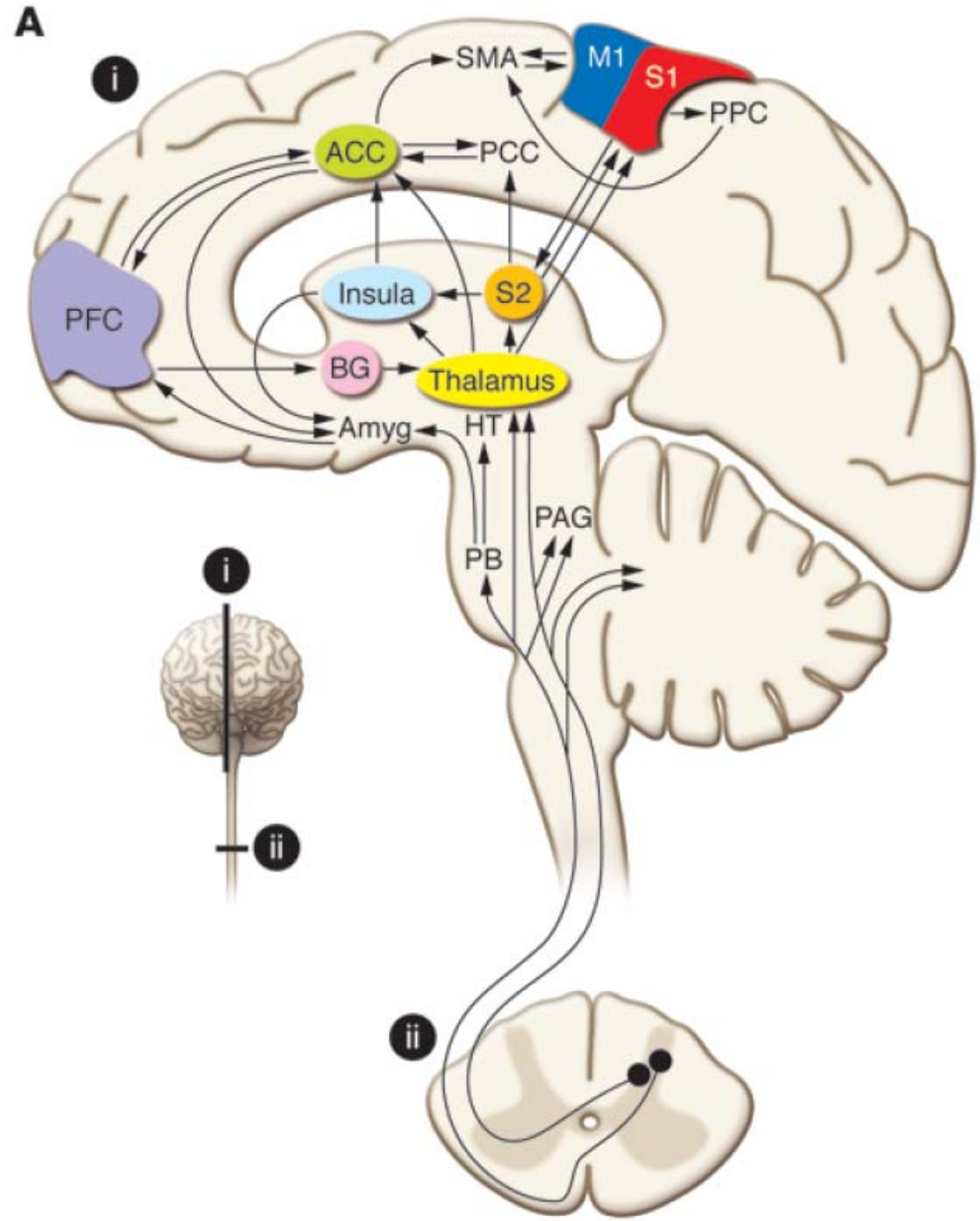


Tseng et al, Human Brain Mapping, 2013

Pain-activating system

- Lateral pain system
  - Discriminatory (Detecting) component
- Medial pain system
  - Affective component





(Schweinhardt and Bushnell, 2010)

Neuropathic pain

今年47歲的林小姐，4年前確診第3期乳癌，手術後因淋巴有多處癌細胞蔓延，開始化療，她直喊，治療的痛苦前所未有，打完針劑後，晚上回家開始感覺到**手腳末稍神經有刺痛感，像是有人拿著針不斷的戳我的指縫，彷彿滿清十大酷刑**。

http://www.nownews.com/n/2014/12/03/1530890

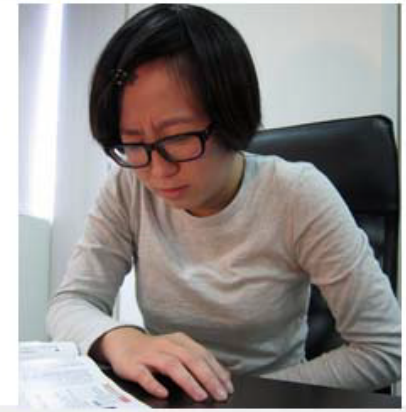
比死可怕！痛如「插針」酷刑　1/4癌友痛苦中死亡

陳鈞凱

2014年 12月 03日　11:12

記者陳鈞凱／台北報導

罹癌真的很「痛苦」！國外研究發現，有4分之1癌末患者，在人生的終點仍伴隨著痛苦，中華民國乳癌病友協會今（3）天公布最新「乳癌病友疼痛問題」調查，發現有8成8、不分癌症期別患者都經歷疼痛，有患者形容活像接受滿清十大酷刑的「插針」一樣，但有4成2的人選擇忍痛，還多於尋求醫師協助的4成。



▲（圖為模擬畫面）。

乳癌病友協會今年8月針對807位病友進行這項「乳癌病友疼痛問題」調查，結果發現，在治療期有高達8成8、不分癌症期別的病友經歷疼痛，其中超過6成是中度以上疼痛，但在全部重度疼痛的病友中，僅有3成6有接受疼痛治療。

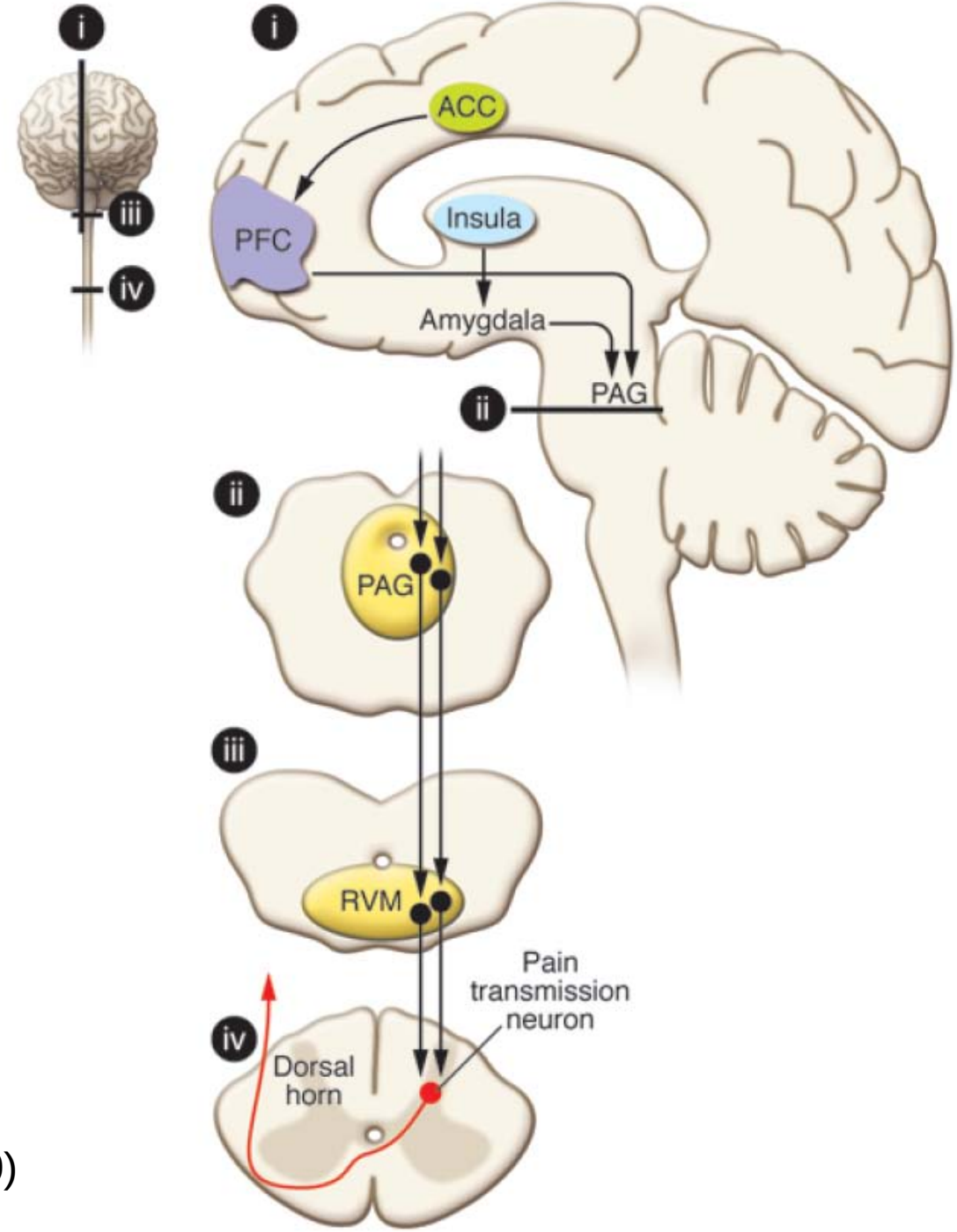
有時候疼痛比死亡更可怕！中華民國乳癌病友協會林葳婕秘書長表示，調查也顯示，選擇忍痛的病友，比率達42%，還多於尋求醫師協助的40%，顯示目前抗癌的疼痛控制還有很大進步的空間，且癌症疼痛不僅只發生在末期癌症患者身上。

今年47歲的林小姐，4年前確診第3期乳癌，手術後因淋巴有多處癌細胞蔓延，開始化療，她直喊，治療的痛苦前所未有，打完針劑後，晚上回家開始感覺到手腳末稍神經有刺痛感，像是有人拿著針不斷的戳我的指縫，彷彿滿清十大酷刑。

調查指出，雖然半數以上病友都曾有疼痛問題，但卻有4成4從未接受過疼痛評估，且7成2的病友沒有使用止痛藥物，另有超過3成使用止痛藥之後，仍有中度以上的疼痛，不是沒用藥，就是使用的藥物未能達到解除疼痛的效果。

Pain inhibitory system

- Descending pain-inhibition pathways
  - Periaqueductal gray matter (PAG)
- Monoaminergic
  - Serotonin (5-HT)
  - Norepinephrine (NE)



(Schweinhardt and Bushnell, 2010)

Specific Treatment of Neuropathic Pain

- Anti-depressants
  - Imipramine (Tofranil)
  - Despramine / Amitriptyline
  - Duloxetin (Cymbalta)
  - Venlafaxine (Efexor)
- Anticonvulsants
  - Clonazepam (Rivotril)
  - Pregabalin (Lyrica)
  - Oxcarbazepine (Trileptal)
  - Phenytoin (Aleviatin)
  - Gabapentin (Neurontin)
- Opioid
  - Tramadol, Ultracet
- Local patch
  - Cpsaicin
  - Lidocaine