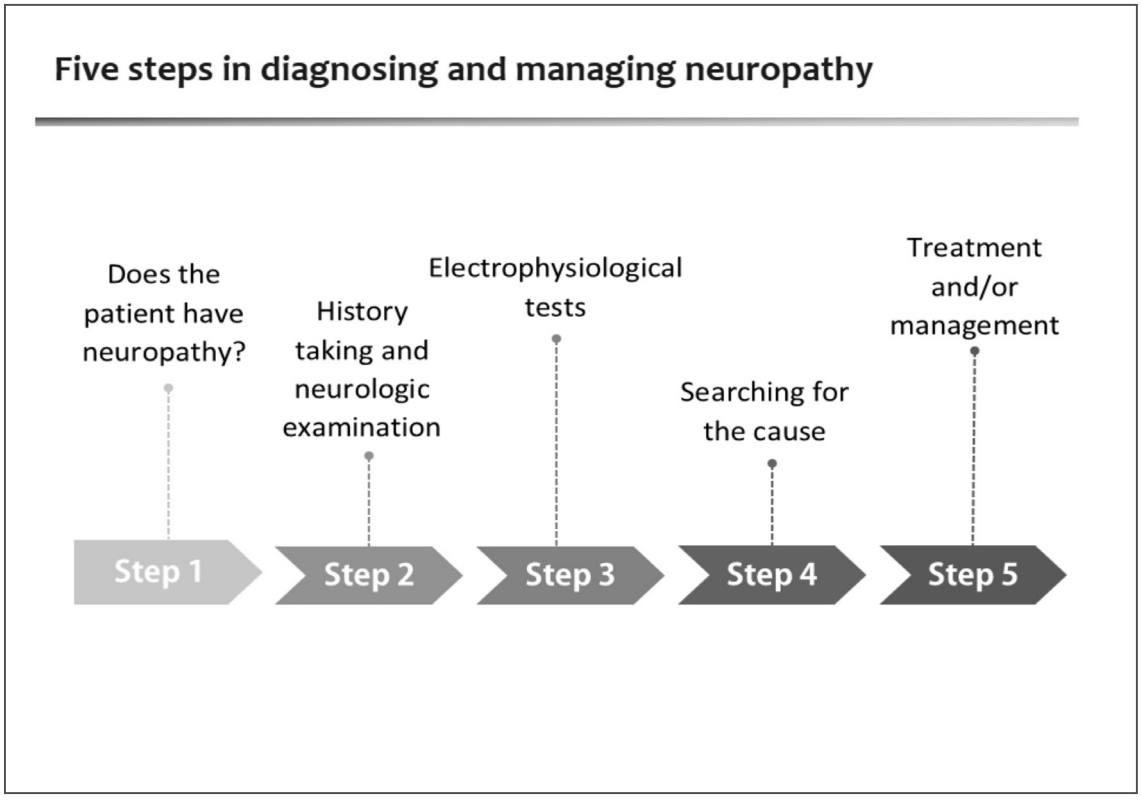
Tingling and numbness

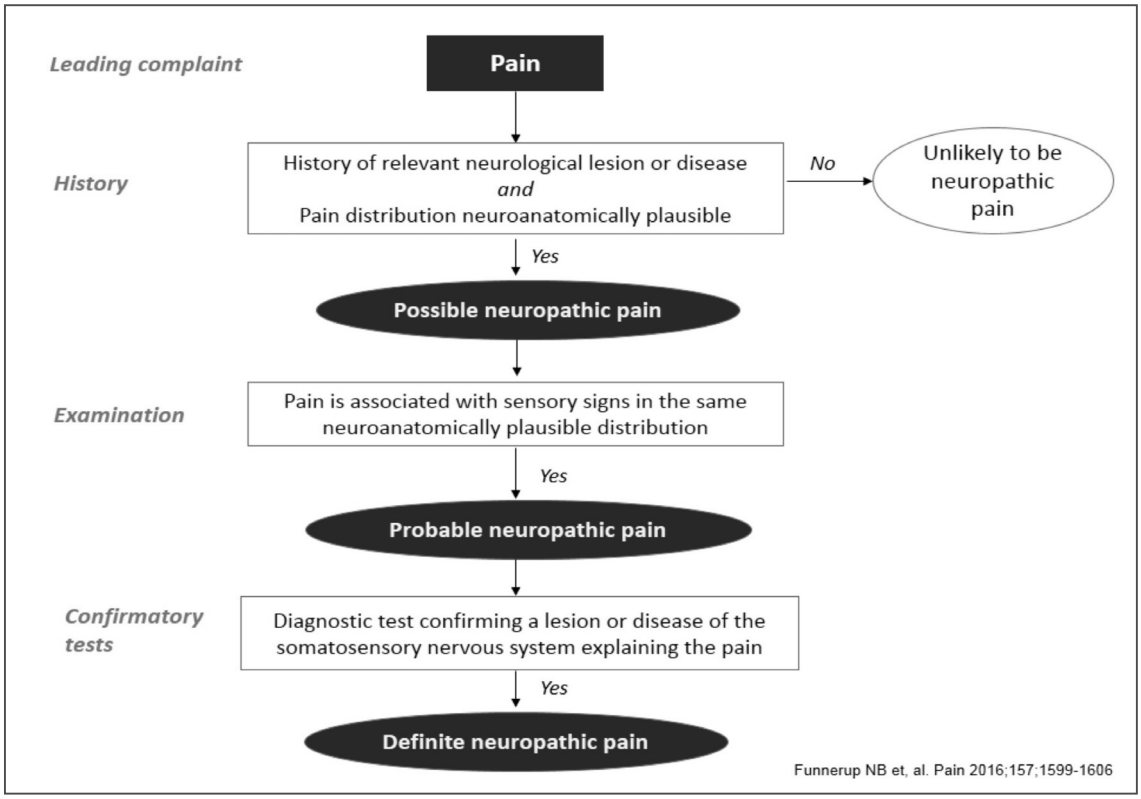
오 지 영
건국의대

Ten steps in diagnosing peripheral neuropathy

(1) Characterize anatomic-pathologic pattern of involvement
(2) Confirm the inferred anatomic-pathologic patterns by use of characterizing tests
(3) Infer the pathologic site and mechanism of nerve fiber alteration
(4) Consider the onset and course of neuropathy
(5) Decide whether the disorder is likely to be inherited or acquired
(6) Check for associations with present or past disease
(7) Perform hematologic, biochemical, serologic, imaging and other tests
(8) Evaluate skin
(9) Perform a cutaneous nerve biopsy
(10) Perform a therapeutic trial

Dyck PJ, et al. Neurology 1996;47:10-17.


Five steps in diagnosing and managing neuropathy
Does the patient have neuropathy?
History taking and neurologic examination
Electrophysiological tests
Searching for the cause
Treatment and/or management
Step 1
Step 2
Step 3
Step 4
Step 5


Leading complaint
Pain
History
History of relevant neurological lesion or disease
and
Pain distribution neuroanatomically plausible
No
Unlikely to be neuropathic pain
Yes
Possible neuropathic pain
Examination
Pain is associated with sensory signs in the same neuroanatomically plausible distribution
Yes
Probable neuropathic pain
Confirmatory tests
Diagnostic test confirming a lesion or disease of the somatosensory nervous system explaining the pain
Yes
Definite neuropathic pain
Funnerup NB et, al. Pain 2016;157;1599-1606

Korean Verbal Descriptor

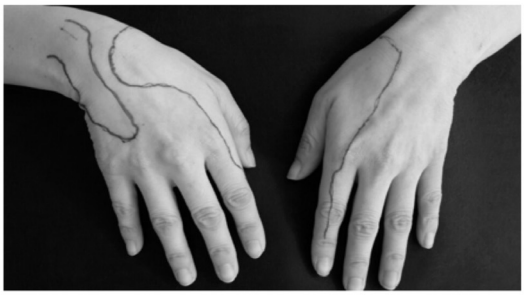
- 가물가물 아프다 – 지근덕거린다 – 욱신욱신하다 – 쿡쿡 쑤신다
- 깔끔거린다 – 뜨끔하다 – 쏘듯이 아프다 – 물어뜯듯이 아프다
- 바늘로 찌르듯 아프다 – 칼로 쑤시듯이 아프다 – 찢어발기듯 아프다
- 칼날로 스치듯 아프다 – 도려내듯이 아프다 – 난도질 하듯이 아프다
- 결린다 – 땅긴다 – 잡아떼듯이 아프다 – 끊어지는 듯이 아프다
- 따끈하다 – 얼얼하다 – 화끈거린다 – 불로 지지듯이 아프다
- 근질근질하다 – 서물서물하다 – 저리다 - 찌릿하다 – 전기오르듯이 아프다
- 조인다 – 빠지듯이 아프다 – 뒤틀리듯이 아프다 – 쥐어짜듯이 아프다
- 시리다– 선듯하게 아프다 – 오싹하게 아프다 – 에어내듯이 아프다
- 띵하다 – 묵적지근하다 – 뻐적지근하다 – 뻐개지듯이 아프다

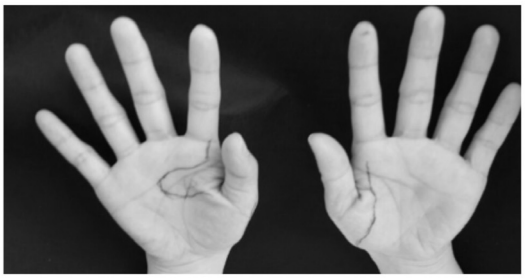
Korean Verbal Descriptor

	Peripheral 36, n (%)	Spinal Cord 10, n (%)	Brain 13, n (%)	Neuralgia 18 , n (%)
따가움	15 (41)	1 (10)	3 (23.0)	13 (72)
전기오듯 찌릿함	24 (67)	4 (40)	7 (53.8)	9 (50)
뻐근함,묵직함	14 (39)	7 (70)	7 (53.8)	7 (39)
꽉 조임	14 (39)	5 (50)	4 (30.7)	2 (11)
저림	25 (71)	7 (70)	10 (76.9)	7 (39)
남의 살 같음	25(71)	8 (80)	9 (69.2)	8 (44)
감각저하 (건드릴 때)	14 (39)	5 (50)	8 (61.5)	5 (28)

(n=77)

Song SH, et al. J Pain Auton Disord 2014;3:78-82



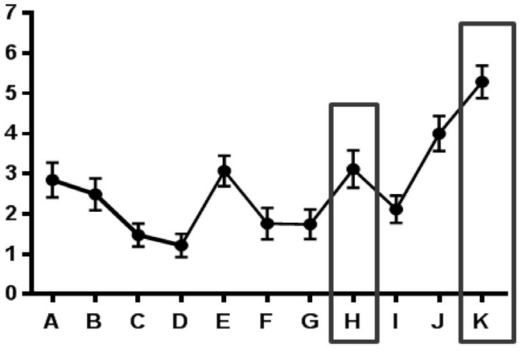


Spontaneous burning pain

Prickling pain

Pressure allodynia

Symptoms of Korean Patients with Small Fiber Neuropathy



A: 화끈거리는 통증

B: 쥐어짜는 듯한 통증

C: 눌리는 듯한 통증

D: 칼이나 송곳으로 찌르는 통증

E: 전기오는 듯 찌릿한 통증

F: 가볍게 닿으면 통증 유발/악화

G: 누르면 통증 유발/악화

H: 차가운 것이 닿으면 통증 유발/악화

I: 핀이나 바늘로 찌르듯 따끔한 통증

J: 피가 안 통하는 듯 저린 통증

K: 시린 통증

Courtesy of Cho EB

Small Fiber Neuropathy and Symptoms Inventory Questionnaire (SFN-SIQ)

	Do you	Score
1	experience changes in sweating pattern (diminished or increased sweating)?	
2	have sudden diarrhea?	
3	have constipation?	
4	have urination problems (incontinence or hesitation)?	
5	have dry eyes?	
6	have a dry mouth?	
7	experience dizziness when standing up from sitting or lying position?	
8	have palpitations?	
9	hot flashes?	
10	experience extreme skin sensitivity of the legs?	
11	have burning feet sensation?	
12	experience sheet intolerance?	
13	experience restless leg?	

Scoring: Never = 0, Sometimes = 1, Often = 2, Always = 3

Cold sense in the foot

M/37

외래초진기록 /오지영(확정) [기록일:2012-04-03] 2012-04-03 11:30

현병력>
2달전부터 오른 발등의 냉기가 느껴짐
local 신경과 --> X-ray는 이상이 없고 다리에 주사, 차도가 없음
한의원에서 한달 동안 침맞음 -차도가 없다
이들전부터는 왼발등도 약간
과거력>
None(-)
사회력>

Smoking(+)
현재흡연 0.5 갑/일
시작시기 20
신체검진>
dorsalis pedis pulse -weak, bilatetral
SLRT-full
motor, sensory-OK
Kj ++/++ AJ +/+

계획>
CT Lower Extremity (++) A 【 Angio + 3D Lower Ext. 】
CBC with diff count & ESR 【 WB, EDTA 】
Prothrombin Time 【 Plasma, Sodium Citrate 】
aPTT 【 Plasma, Sodium Citrate 】
Fibrinogen 【 Plasma, Sodium Citrate 】

외래경과기록 /오지영(확정) [기록일:2012-04-10] 2012-04-10 15:31

S>
양 다리 근력이 약간 떨어지는 것 같다

O>
BP 118/76 mmHG

heel, toe gait, hopping -OK

P>
[원외] Niferon CR 40mg (nifedipine) 【 1 T * 1 회 * 30 일 (QD PC) 】
[원외] Pletaal 50mg (cilostazol) 【 1 T * 2 회 * 30 일 (BID PC) 】
stop smoking

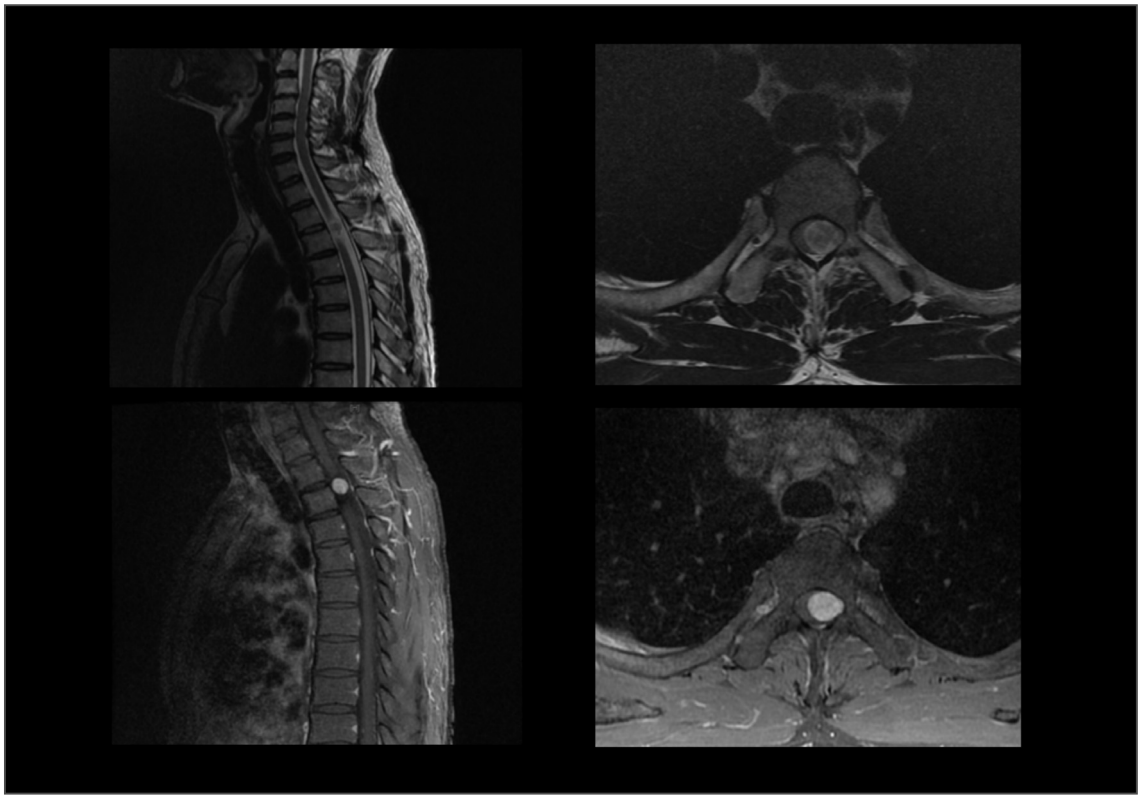
외래경과기록 /오지영(확정) [기록일:2012-05-08] 2012-05-08 16:23

S>
약복용후 두통으로 중단
허리 아래까지 감각이 이상하다
만지면 무언가 씌어있는 느낌
발등은 시리고 양 발바닥은 화끈거린다
다리힘도 풀리는 느낌
소변줄기가 힘이 없어짐

O>
paravertenral tenderness -
heel, toe gait - OK
decreased vibration, below knee
Bj +/+ Kj +/++
babinski -/equivocal

P>
MRI (흉추) + 【 T-Spine(+) 】
--> subacute progressive sensory abnormality with bladder dysfunction으로 spinal cord disease 감별이 필요함

내일 검사후 진료



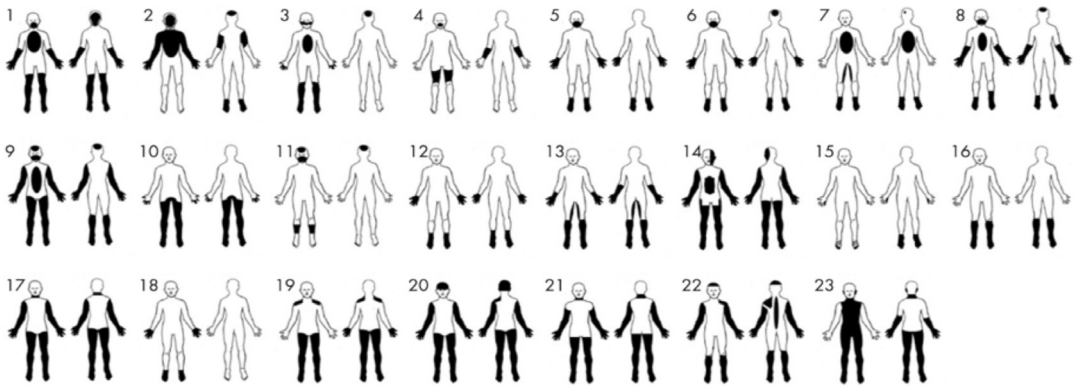
History taking

- Onset and tempo of the symptoms
- Pattern of the symptom progression
- Autonomic symptoms and signs
- Medical or surgical history
- Family history
- Medication history

Patterns of polyneuropathy

- Lower extremities → upper extremities
- Anterior compartment of L/E → posterior compartment
- "Teardrop" in anterior torso
- "Beanie cap" in trigeminal nerve

Patterns of small fiber neuropathy



Gorson KC, et al. JNNP 2008;79:163-169

Autonomic symptoms

Cardiac
- Resting tachycardia
- Orthostatic intoletance
- Exercise intolerance
- Light headedness/syncope
- Arrhythmias

Sudomotor
- Anhidrosis
- Gustatory sweating

Pupilomotor/secretory
- Dry eye/mouth
- Difficult adaptation to light/darkness

Gastrointestinal
- Nausea/vomiting
- Bloating
- Nocturnal diarrhea
- Increased variability in blood sugar

Urogenital
- Nocturnal frequency, urgency
- Urinary hesitancy, incontinence
- Sexual dysfunction

Past history

- **Diabetes mellitus**
- **Hypothyroidism**
- **Dyslipidemia**
- **Cardiac disease**
- Tuberculosis
- Kidney disease
- Hepatitis
- Cancer
- HIV
- Leprosy

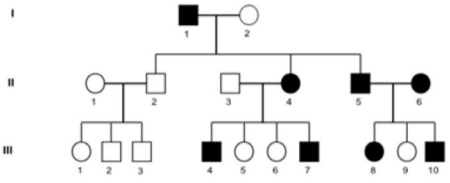
- Rheumatologic diseases
- Syphilis
- Vitamin deficiency (B1,6,12)
- Vitamin B6 overdose

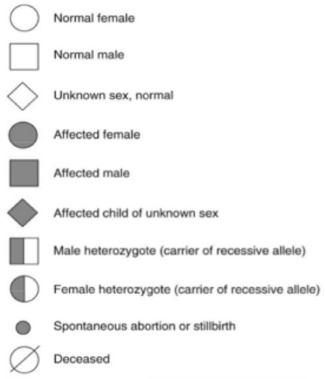
- Gastric or bowel surgery
- Repeated anesthesia

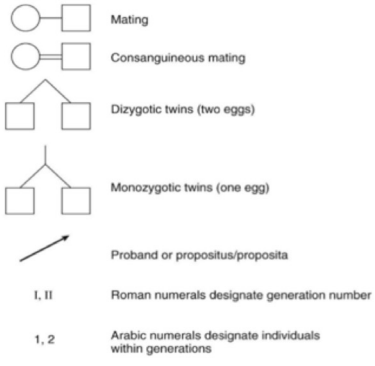
- Alcohol
- Smoking

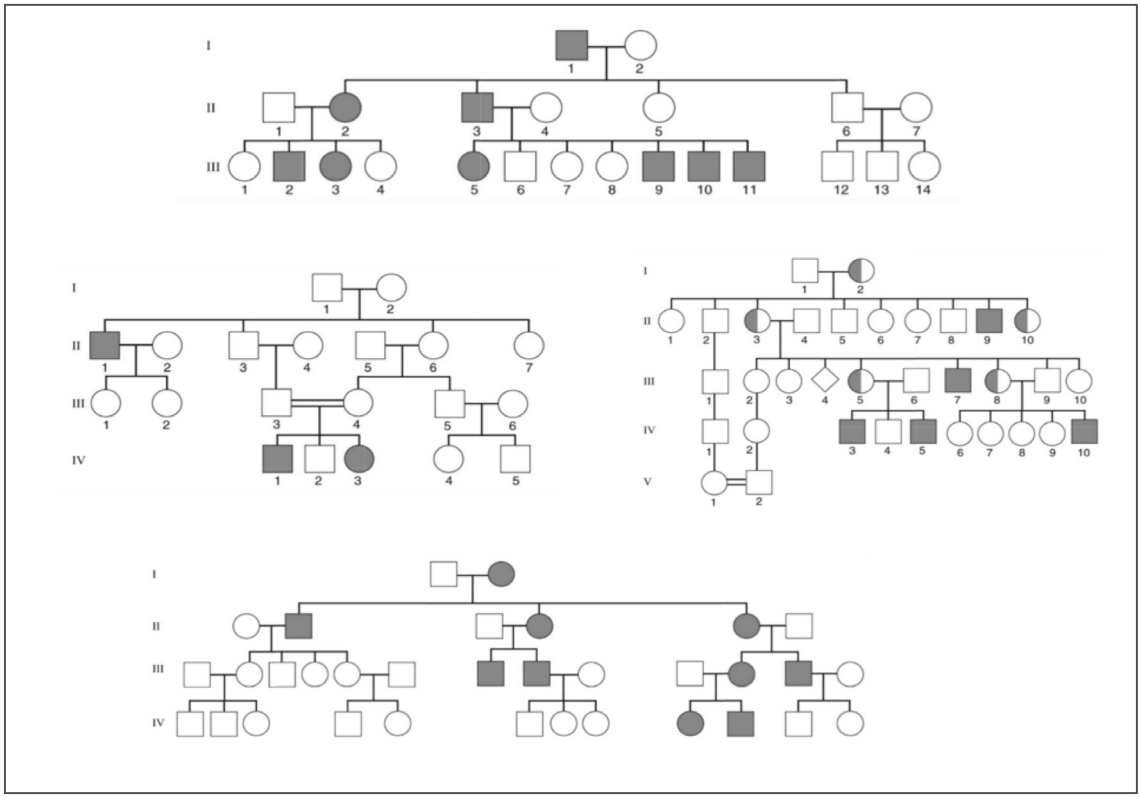
Family history

- Drawing pedigree









Medication history

Category	Medications
Antibiotics	Chloroquine, dapsone, isoniazid, metronidazole, nitrofurantoin
Antiarrhythmia drugs	Amiodarone, perhexilline, hydralazine
Chemotherapeutics	Paclitaxel, cisplatin, oxaliplatin, bortezomib, thalidomide
Other medicaitons	Colchicine, phenytoin, disulfiram, pyridoxine

Major chemotherapeutics causing toxic neuropathy

Platinum	Cisplatin	lung, stomach, breast, esophagus, head and neck
	Carboplatin	lung, ovary
	Oxaliplatin	stomach, colon
Taxane	Paclitaxel	lung, esophagus, stomach, ovary
	Docetaxel	lung, esophagus, stomach, head and neck
others	Vincristine	lymphoma, hematologic malignancies
	Bortezomib	multiple myeloma
	Thalidomide	multiple myeloma

Physical examination

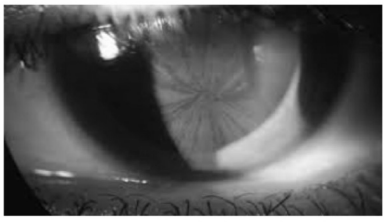
Observation

- Deformity
- Skin texture, color, temperature
- Sweating
- Nails

Palpation

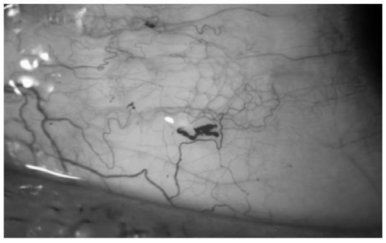
- Pulse – dorsalis pedis, radial artery
- Tinel along the nerve

Clue for rare disease – Fabry disease



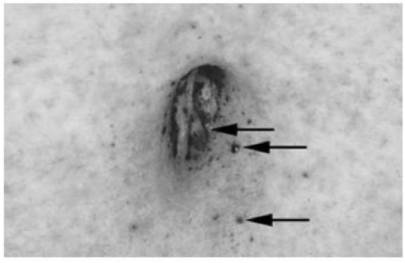
Corneal opacity

"Cornea verticillata"



Conjunctival telangiectasia

Angiokeratoma



Tingling in the toes

M/66

외래초진기록 /오지영(확정) [기록일:2015-03-04] 2015-03-04 16:01

주호소>
- 발가락이 저리다 발생일 : 1 yr

통증>
통증정도 6

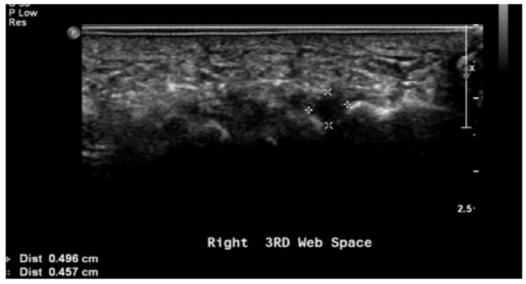
현병력>
양 발바닥이 무감각하고 찌릿찌릿하다
1년전부터 시작

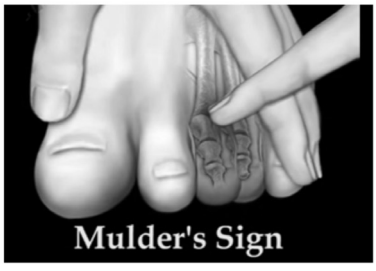
정형외과에서는 허리 척추문제라고 듣고 물리치료
효과가 없다

신체검진>
BP 142/85

tenderness (+) both 3-4, 4-5 interdigital space
Tinel+
hypoalgesia, both 3,4th toe

계획>
US Lower Ext(Foot Joint) 【 Rt Foot 】 (R/O Morton's neuroma)
NCV 하지(편측)(신경과) (plantar nerve)
Foot 1P [B.] 【 AP 】
Foot 1P [B.] 【 Standing Lat 】





Tinel sign is important

- F/51
- Diffuse B cell lymphoma로 항암치료 중
- Previous EDX – c/w tarsal tunnel syndrome
- Ankle MRI – swelling and increased signal intensity of tibial nerve, no space occupying lesion of tarsal tunnel

현병력>
2014.3 왼쪽 안쪽 발바닥으로 먹먹한 느낌
2014.5월부터 왼발에 힘을 줄 때마다 통증, 저린감
먹먹한 느낌은 엄지 발가락까지 진행

발가락이 굽혀지지 않는다

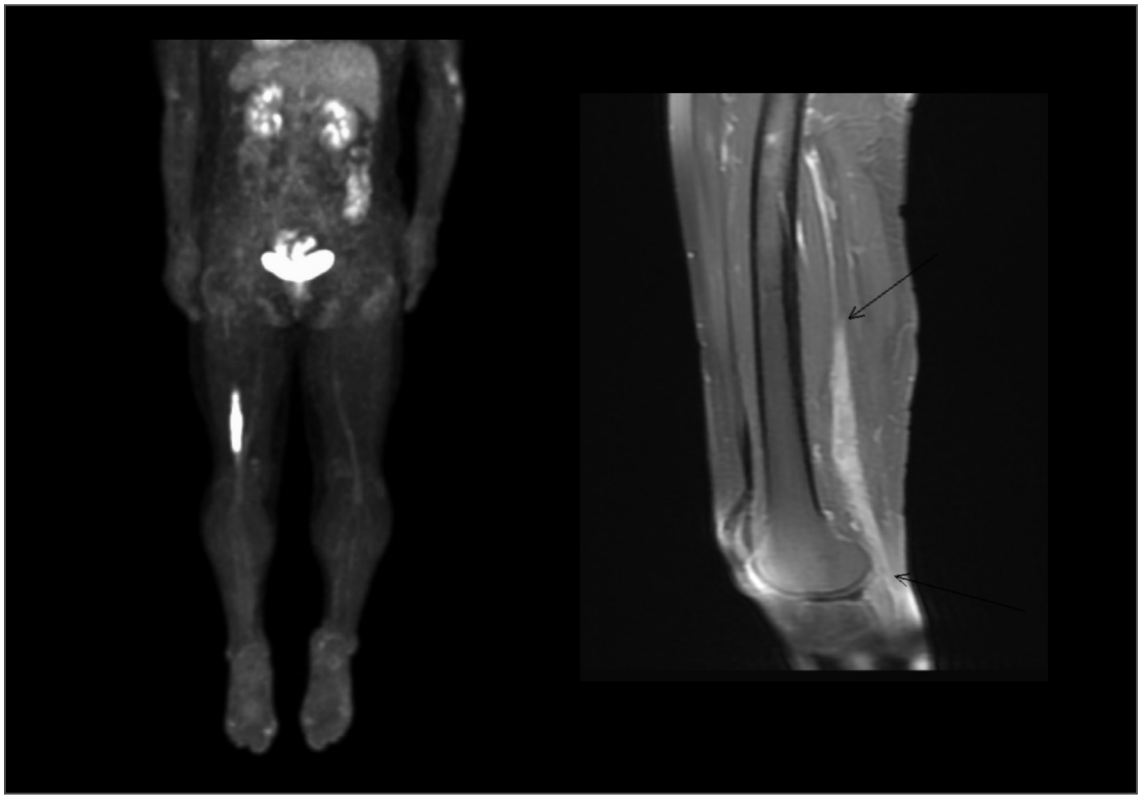
EDX - c/w tibial neuropathy

cymbalta + lyrica --> 저린감은 조금 완화
Lyrica 남아있음
신체검진>
BP 107/81

Tinel at popliteal fossal - equivocal
Tinel at ankle -

heel gait +/-
toe gait +/+
greater toe dorsiflexion G5
plantar flexion G3
gr toe flexion G1

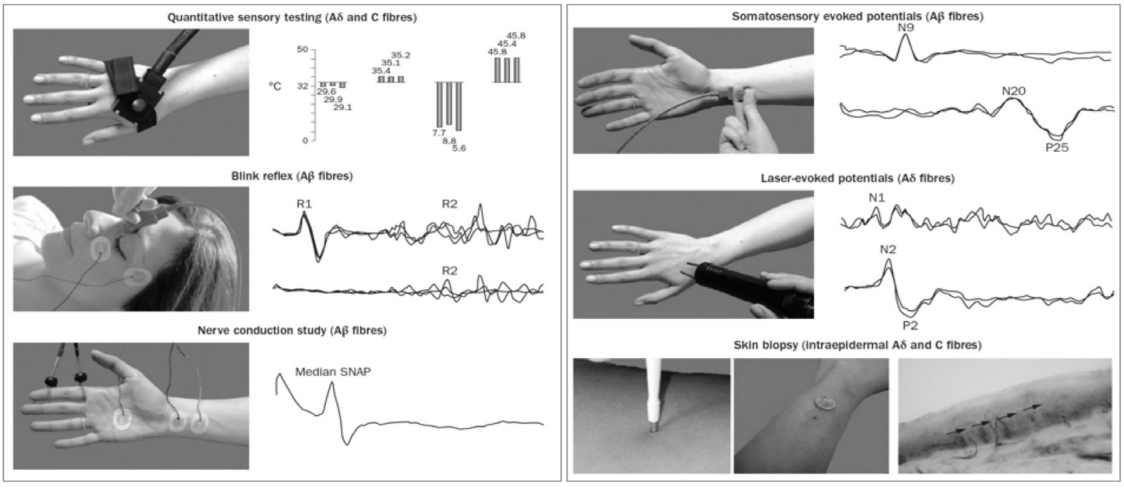
hypoalgesia, medial and lateral plantar nerves
계획>
Total Whole Body FDG Fusion PET(머리끝-발끝) (left tibial neuropathy - lymphoma infiltration 여부 확인 필요합니다)
[원외] Cymbalta 60mg(Duloxetine) 【 1 C * 1 회 * 7 일 (QD PC) 】



Neurologic examination

- Functional – heel and toe gait, hopping
- Romberg
- Motor – distal muscles
- Sensory – pinprick, vibration
- Pathologic sign
- Tendon reflex

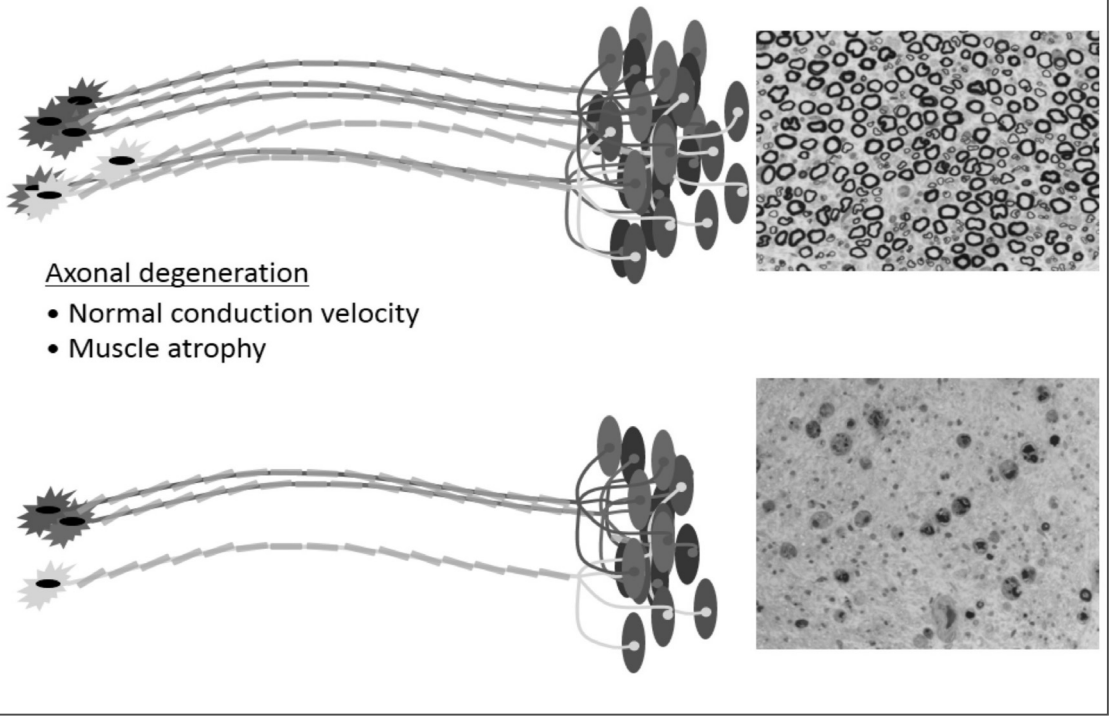
Electrophysiological tests for neuropathy



Truini A, et al. Nat Rev Neurol 2013;9:572-582

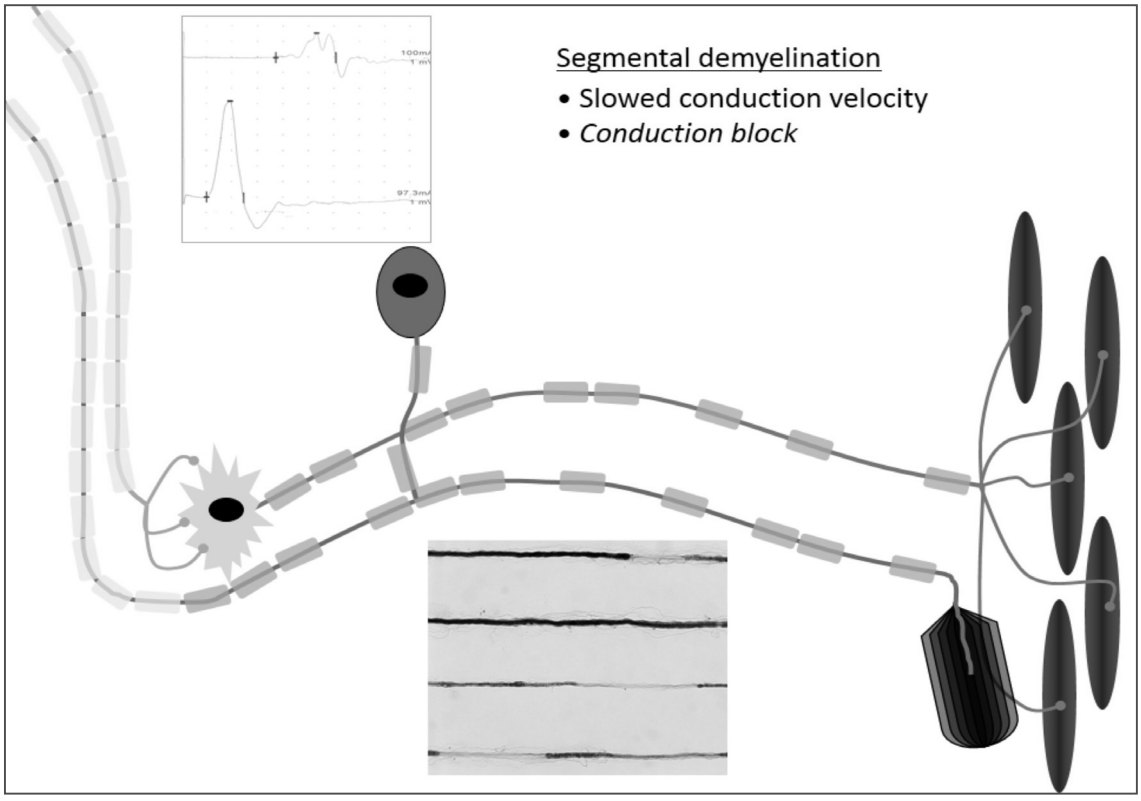
Advantage and disadvantage of tests

Methods	Advantage	Disadvantage
Neurological examination	Simple, easy to perform, does not require special equipment	Not sensitive, not reproducible
Nerve conduction studies	Sensitive, objective, currently the 'gold standard' for diagnosis	Assesses only large fibers, moderate reproducibility, requires special equipment
Quantitative sensory testing	Evaluates both large and small nerve fibers, quantitative, relatively easy to perform	Subjective, moderate reproducibility, requires special equipment
Quantitative sudomotor axon reflex test	Sensitive, objective, reproducible	Requires special equipment, time-consuming
Autonomic testing	Objective, quantitative	Moderate sensitivity, requires special equipment
Sural nerve/skin biopsy	Quantitative, sensitive, currently the gold standard to quantify small fibers	Invasive, costly, risk of infection at the site of biopsy, requires specialist histological Technique (IENFD)



Axonal sensorimotor polyneuropathy

- Diabetes Mellitus
- Alcoholism
- AIDS
- Thiamine deficiency
- Malabsorption
- Connective tissue diseases
- Sarcoid
- Behcet's
- Lyme's disease
- Copper deficiency
- Hypothyroidism
- Amyloid
- Polycythemia
- Hypereosinophilia
- Cryoglobulinemia
- Paraneoplastic
- Ataxia telangectasia
- Celiac Sprue



Demyelinating polyneuropathy

- Charcot-Marie-Tooth disease type 1,3,4
- Hereditary neuropathy with liability to pressure palsy (HNPP)
- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)
- Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
- Distal acquired demyelinating symmetric neuropathy (DADS)
- Toxins (diphtheria, amiodarone, n-hexane, arsenic)

Criteria for SFN

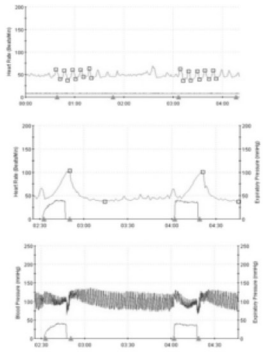
Lauria criteria

- At least 2 of the following
- ***Clinical signs*** of small fiber impairment (pinprick and thermal sensory loss and/or hyperalgesia) with distribution consistent with peripheral neuropathy (length or non-length dependent neuropathy)
- ***Abnormal warm and/or cooling threshold*** at the foot assessed ***by QST***
- ***Reduced IENF density*** at the distal leg

Hermann criteria

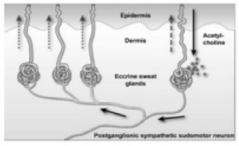
- ***Compatible sensory symptoms*** without motor weakness or UMN signs
- ***Normal EMG/NCS***
- At least two abnormalities of ***QST, QSART, skin biopsy***

Tests for autonomic nervous system



- **Cardiovascular**
  HRV in deep breathing
  Valsalva maneuver
  Head-up tilt test

- **Gastrointestinal**
  Gastric emptying time
  Esophageal manometry
- **Urogenital**
  Urodynamic study



- **Sudomotor**
  Quantitative sudomotor axon reflex
  Thermoregulatory sweat test

Serological tests for typical polyneuropathy

- Blood glucose, HbA1c
- 75-g oral glucose tolerance test
- Thyroid function test
- Serum vitamin B12, methylmalonic acid w/wo homocysteine
- Serum protein electrophoresis/ immunofixation

Serological tests for atypical neuropathies (1)

Features	Differential diagnosis	Evaluation
Asymmetric	Vasculitic syndrome HNPP Infectious	FANA, p-ANCA, c-ANCA, HbA1c, ESR, anti-HIV Ab, cryoglobulin, HCV, ACE, CMV PCR, HTLV-1
Proximal involvement	AIDP/CIDP, diabetic radiculoplexoneuropathy Radiculitis (cancer, lymphoma, sarcoid, infectious)	CSF analysis (cell, protein, glucose, stain and culture, etc.) Gd-enhanced MRI
Acute/subacute progression	Toxic, infectious, porphyria, paraneoplastic	Vitamin B6, heavy metals, paraneoplastic panels, urine PBG, rheumatologic screen
Motor dominant	Motor neuron disease, POEMS, lead intoxication, acute porphyria, CMT, AIDP	CSF analysis, ganglioside panel, urine PBG, heavy metal panel, gene study

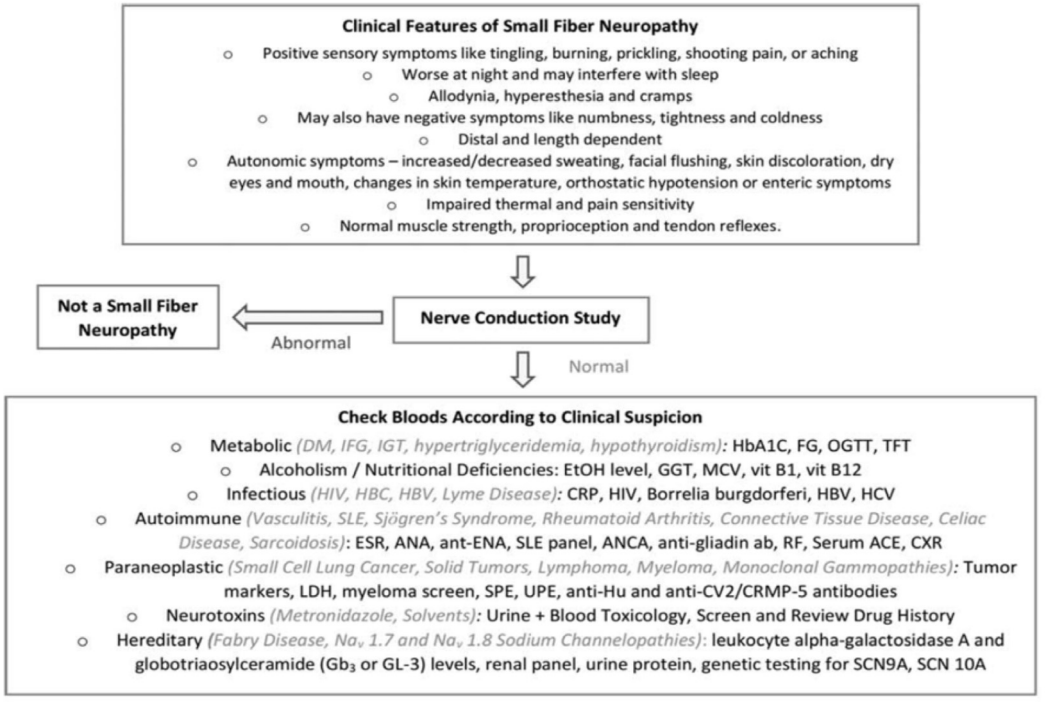
Serological tests for atypical neuropathies (2)

Features	Differential diagnosis	Evaluation
Prominent autonomic features	Diabetic neuropathy, amyloidosis, porphyria, paraneoplastic, hereditary	HbA1c, OGTT, protein electrophoresis, free light chain, pareneoplastic panel, urine PBG
Non-length dependent sensory	Sjogren syndrome CIPN, parneoplastic Vitamin B6 toxicity, HIV, sarcoidosis	ACE, rheumatologic screen, paraneoplastic panel, vitamin B6 level, HIV
Young age onset	CMT, toxic exposure, vitamin deficiency	Genetic screening, heavy metals and vitamin levels

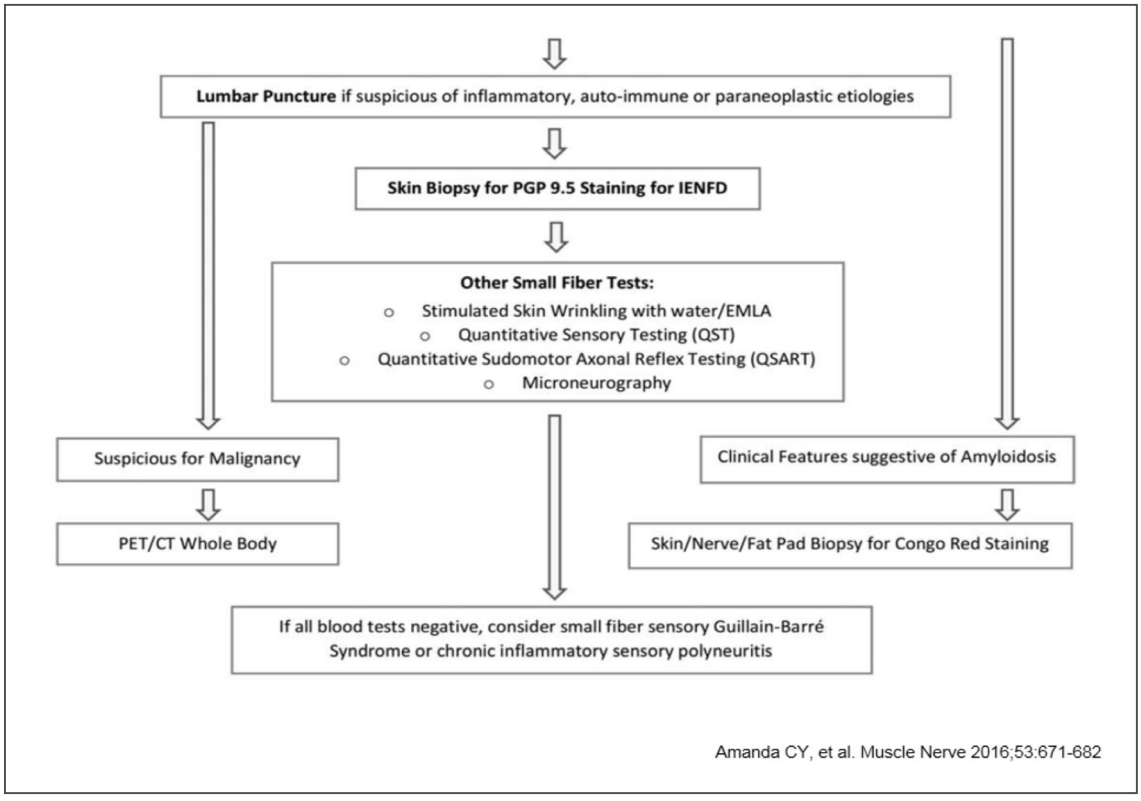
IGT-related neuropathy

- High prevalence (40-50%)of IGT in the patients with cryptogenic polyneuropathy
- Burning or tingling foot pain in the patients with IGT
- Lifestyle intervention improves metabolic parameters resulting in recovery of small fiber function

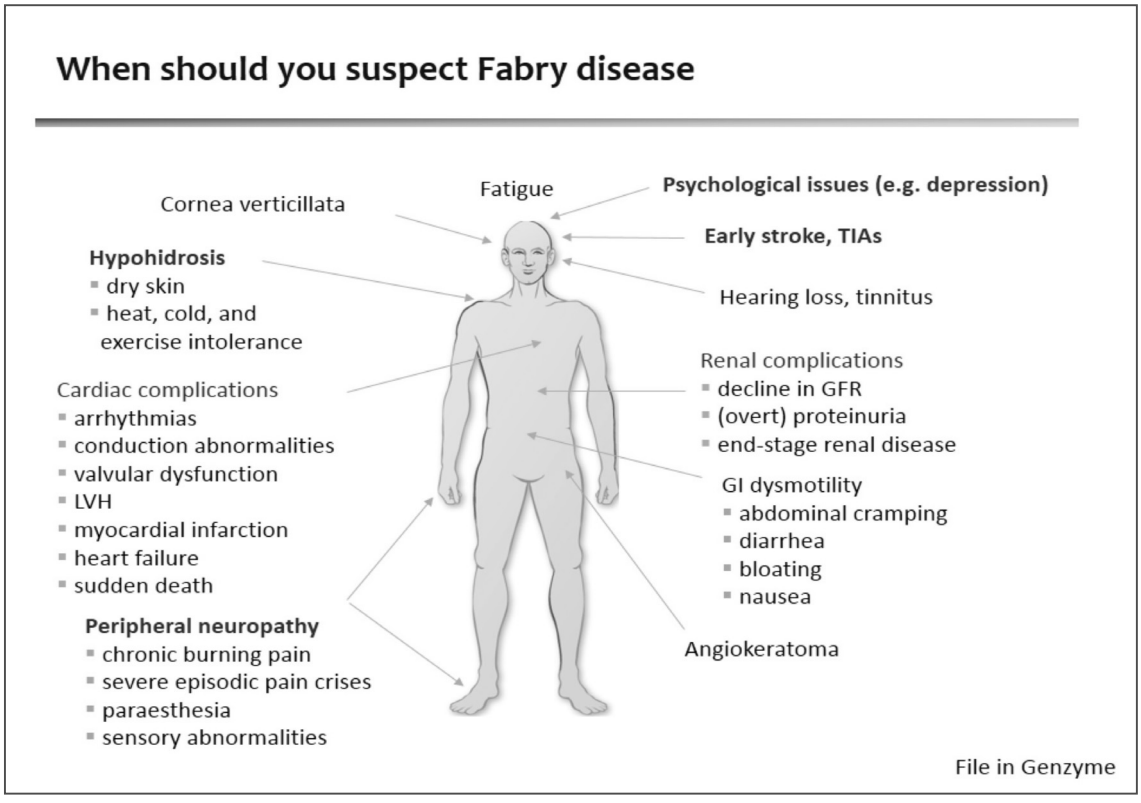
Diagnosis	FPG (mg/dL)	2-hr OGTT (mg/dL)	HbA1c (%)
Normal	< 100	< 140	< 5.7
Diabetes	≥ 126	≥ 200	≥ 6.5
IGT	**100 - 125**	**140 - 199**	**5.7-6.4**



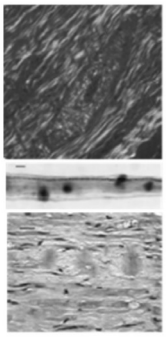
Amanda CY, et al. Muscle Nerve 2016;53:671-682

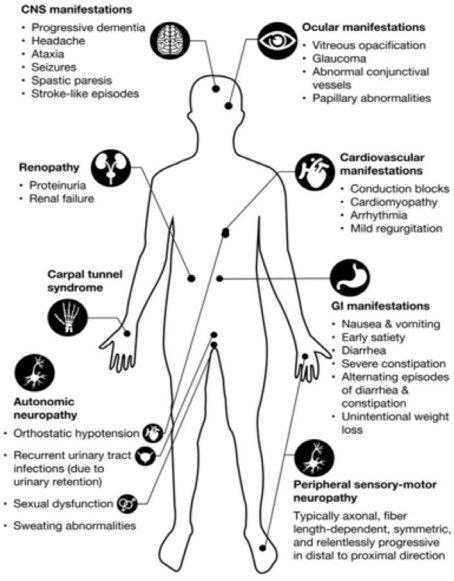


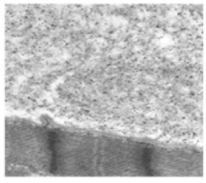
Amanda CY, et al. Muscle Nerve 2016;53:671-682

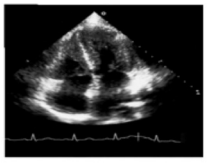


When should you suspect hATTR-PN ?









Amass et al, J Peri Ner Sys 2016;21:5-9

"Red Flag" symptom clusters for hATTR-PN

Progressive symmetric sensorimotor neuropathy

+ ≥1 of the following

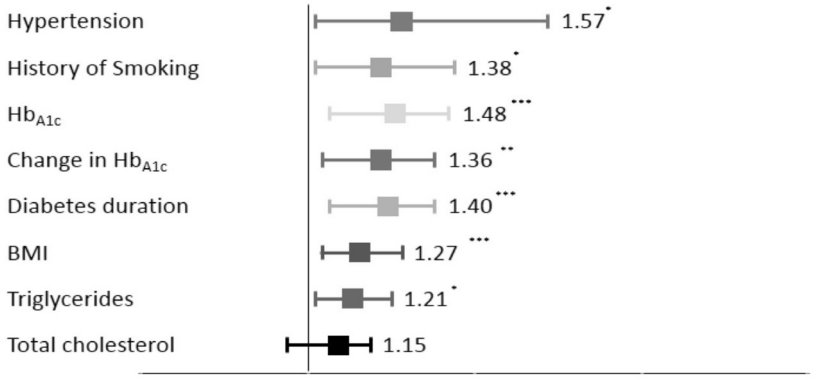
- **Family history**
- **Early autonomic dysfunction** (e.g. erectile dysfunction or postural hypotension)
- **GI complaints** (e.g. chronic diarrhea, constipation)
- **Unexplained weight loss**
- **Cardiac hypertrophy, arrhythmia, ventricular block or cardiomyopathy**
- **Bilateral carpal tunnel syndrome**
- **Renal abnormalities** (e.g., albuminuria or mild azotemia)
- **Vitreous opacity**

Additional alert signs:
- Rapid disease progression
- Failure of response to prior therapy

Conceicao I, et al. J Peri Nerv Sys 2016;21:5-9.

Risk factors for diabetic neuropathy

N=1,101 Follow-up: 7.3±0.6 yrs



*p=0.03; **p=0.001; ***p<0.001. BMI = Body mass index; CI = Confidence interval;

Tesfaye S, et al. N Engl J Med (2005)

Treatment induced neuropathy of diabetes

- Small fiber more than large fiber neuropathy
- Caused by rapid glycemic control
- Not exceed a 3% point change in the HbA1c in 3 months

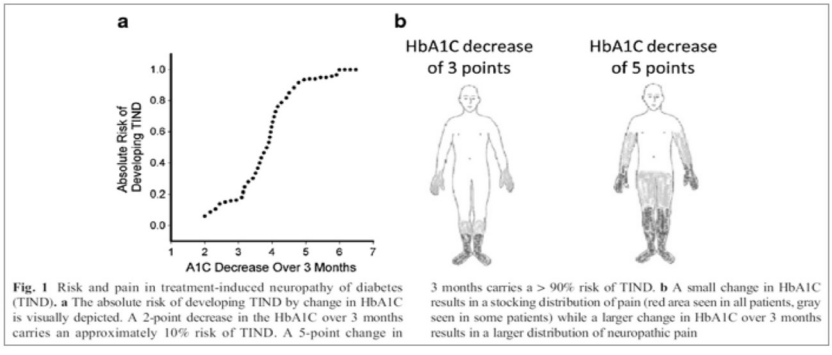


Fig. 1 Risk and pain in treatment-induced neuropathy of diabetes (TIND). **a** The absolute risk of developing TIND by change in HbA1C is visually depicted. A 2-point decrease in the HbA1C over 3 months carries an approximately 10% risk of TIND. A 5-point change in 3 months carries a > 90% risk of TIND. **b** A small change in HbA1C results in a stocking distribution of pain (red area seen in all patients, gray seen in some patients) while a larger change in HbA1C over 3 months results in a larger distribution of neuropathic pain

Indication for Metformin in IGT-related PN

- Age < 60
- BMI 35
- Family history of diabetes in the first-degree relatives
- Elevated TG, reduced HDL-C
- Hypertension
- HbA1C > 6.0

Exercise as a therapy of DPN

- Moderate endurance and aerobic exercise in both T1DM and T2DM improves heart rate variability, in favor of parasympathetic dominance.
- Supervised exercise improves cutaneous reinnervation
  (Singleton JS, et al. Ann Neurol 2015)
- At least 3 days per week (minimum of 150 min/week of aerobic exercise)

IASP Guideline for NeuP

First line medication

- TCAs
- Gabapentin / Pregabalin
- SNRIs
- Lidocaine patch**

** in PHN

Second line medication

- Tramadol
- Opioids

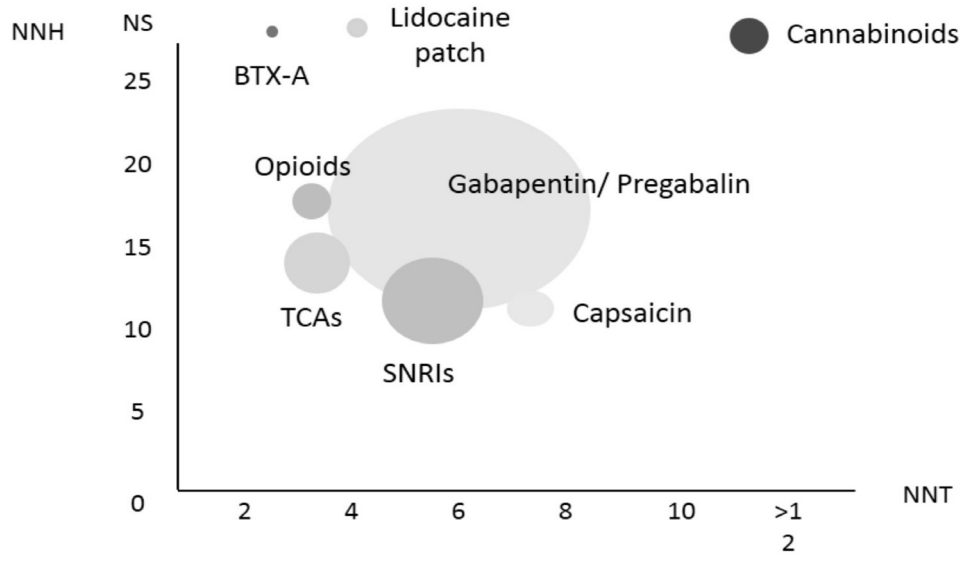
Third line medication

- Other AEDs
- SSRIs
- Capsaicin cream**

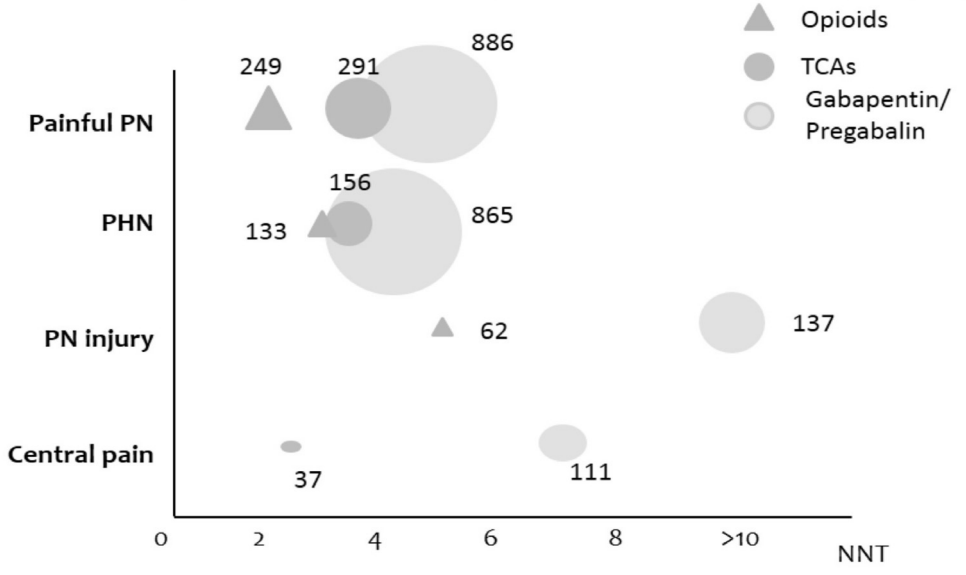
EFNS Guideline for NeuP

Etiology	Level A rating	Level C rating	Recommendation for first line
Diabetic NP	Duloxetine Gabapentin/Pregabalin TCA Oxycodone/Tramadol	Carbamazepine Phenytoin	Duloxetine Gabapentin/Pregabalin TCA Venlafaxine ER
PHN	Capsaicin 8% patch Gabapentin/Pregabalin Lidocain plaster TCA		Gabapentin/Pregabalin TCA Lidocaine plaster
TG	Carbamazepine	Baclofen Lamotrigine	Carbamazepine Oxcarbazepine
Central pain	Cannabinnoid (MS) Pregabalin (SCI)		Gabapentin/Pregabalin TCA

Overall NNT and NNH



NNT for specific etiology



Drug Effects on NeuP Symptoms

Studies using topical capsaicin model in human

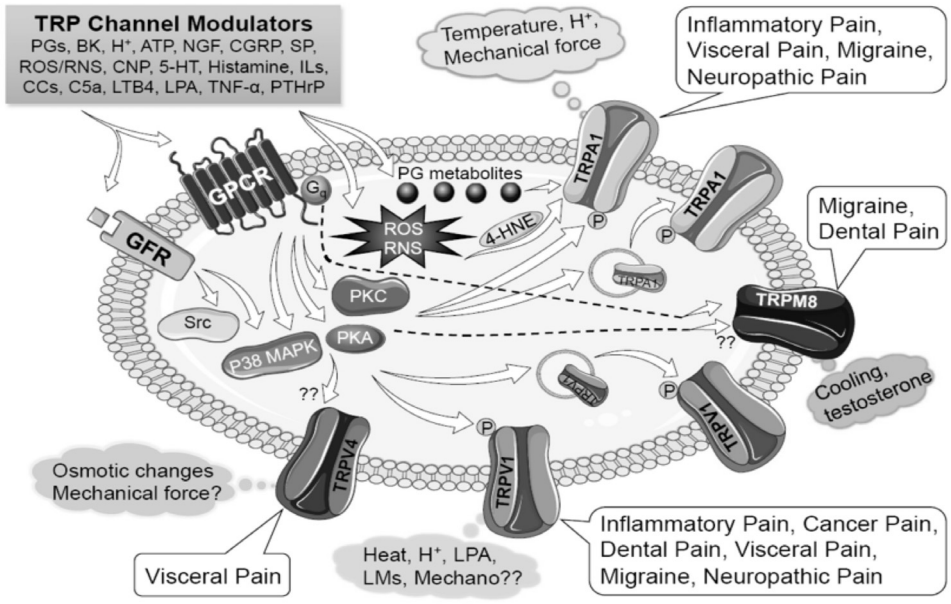
Drug class	Spontaneous pain	Heat hyperalgesia	Cold hyperalgesia	Punctate hyperalgesia	Mechanical allodynia
NSAIDs	1/1	0/1	0/1	1/1	½
TCA	0/2			0/2	0/2
Ca-channel blocker	1/3	0/1		1/3	2/3
NMDA receptor antagonist	4/8	0/2		3/8	1/1
Lidocaine	2/5	1/4		3/5	0/5
Lamotrigine	0/1	0/1		0/1	0/1
Opioid	4/6	0/1	1/2	0/1; 4/8	0/1; 4/8
Cannabinoids	1/2			1/2	1/2

Helfert SM, et al. Clin Pharmacol Ther 2015;97:135-141

Possible Targets for Pharmacological Therapy in NeuP

Symptoms	Mechanism	Target	Optimal compounds
Spontaneous and shooting pain	Ectopic impulse generation, oscillation in DRG	Na-channel	Carbamazepine, lidocaine, Lamotrigine, TCA
Heat hyperalgesia	Reduced activation threshold to heat	TRPV1 receptor	Capsaicin patch
Punctate mechanical hyperalgesia	Ongoing C-input induced increased synaptic transmission	Presynaptic μ-receptor, Ca-channels	Opioids, pregabalin, gabapentin
	Decreased inhibitory control	α2-receptor, NE receptor	Clonidine, TCA, duloxetine, venlafaxine
Dynamic mechanical hyperalgesia	Gating of Aβ-fiber input		

Reimer M, et al. Curr Opin Support Palliat Care 2014;8:124-129



Mickle AD, et al. Pharmaneuticals 2016;9:72

Combination treatment

Combination therapy or single drug with multiple mechanism?

Combination therapy

- Avoid drugs with no effect
- Can combine two route of administration
- Complicated assessment of efficacy and identification of optimal dose-ratio
- Non-compliance

Single drug with MM

- Easy administration
- Better compliance
- May have unnecessary side effects

Combination therapy in DPN

Combination	Study type	No. of patients	Periods	Results	Adverse effects
GBP vs NT vs CT	CT vs mono	56	6 weeks	Better with CT	Less with CT
GBP+VX vs GBP+PC	Add-on	60	8 weeks	Better with GBP+VX	Similar
GBP+OX vs GBP+PC	Add-on	338	12 weeks	Better with GBP+OX	Similar
PGB vs PGB+OX	CT vs mono	62	4 week	No better with CT	Similar
PGB vs 5% LP vs CT	Add-on	229	8 week	Better with CT	Fewer with 5% LP

GBP=gabapentin, NT=nortriptyline, CT=combined therapy, VX=venlafaxine, PC=placebo, OX=oxycodone, PGB=pregabalin, LP=lidocaine

Intervention for painful neuropathies

NeuPSIG recommendation

Intervention	Quality of evidence	Strength recommendation	Comment
Spinal cord stimulation	Low	Inconclusive	Weak evidence with small, positive case series with large effects in refractory DPN over long-term follow-up
Intrathecal medication delivery	Low	Inconclusive	Somewhat promising result in other type of chronic pain
Deep brain stimulation	Low	Inconclusive	Weak evidence but promising result in small, uncontrolled series
Surgical decompression	Low	Inconclusive	Most likely to be beneficial in patients with evidence of peripheral nerve compression