Diagnostic approach to peripheral neuropathy

대구 가톨릭 대학병원 신경과
석정임

Diagnosis of neurologic disorders

- Anatomical localization
- Cause of responsible lesion

Does the patient actually have a neuropathy?

	Sensory	Weakness	DTRs
Central lesion	variable	Subtle atrophy	Increased
PN	Present	Distal / Wasting > weakness	Abolished, even early
NMJ ds.	Absent	Proximal	Variable
Myopathy	Absent	Proximal / Proportional to wasting	Proportional to weakness

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Symptomatology

	SENSORY SYMPTOMS	MOTOR SYMPTOMS	AUTONOMIC DYSFUCTIONS
Positive	Paresthesias Pain Burning -squeezing or tightness -electric-like -hypersensitivity	Fasciculations Cramps	Anhidrosis Orthostatic hypotension
Negative	Numbness Reduced or lack of sensation Postural instability	Weakness Atrophy	

Pattern recognition approach

- 당뇨환자 + 손발저림 → diabetic polyneuropathy
- Heavy alcoholic + 손발저림 → alcoholic polyneruopathy

- 효율적
- 진단오류를 범할 위험

Structured Approach (1)

- Since there are many etiologies of polyneuropathy, a logical clinical approach is needed

1. What systems are involved?
2. What is the distributions of weakness?
3. What is the nature of sensory involvement?
4. What is the temporal evolution?
5. Is there evidence for a hereditary neuropathy?
6. Axonal or demyelinating?

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Structured Approach (2)

Is a specific etiology suggested ?

↓

Yes → confirmatory study (laboratory test, biopsy)
No → screening laboratory study

↓

Etiologic diagnosis established (±80%)
Cryptogenic neuropathy (±20%)

Categorization

I. ***Pattern of involvement***
II. ***Fiber type is involved***
III. ***Temporal course***
IV. ***Axonal vs demyelinating***
V. ***Family history***
VI. ***Medical disease, toxin, drug***

1. Anatomical distribution

Focal	*Multifocal (Asymmetric)*	*Diffuse (Symmetric)*
Mononeuropathy Radiculopathy Plexopathy	Multiple mononeuropathies Polyradiculopathy Multifocal Motor neuropathy	Polyneuropathy Doral root ganglionopathy

- Polyneuropathy
  : Diffuse process, such as immune reaction, toxin, metabolic, deficency state
- Mononeuropathy or multiple(multifocal) mononeuropathy(mononeuritis multiplex)
  : Localized damage, vascular, granulomatous, neoplastic or other infiltrative disease

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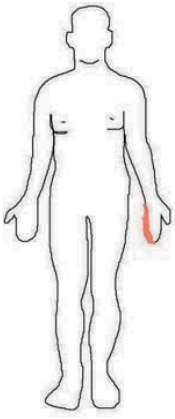
Mononeuropathy (focal)



mononeuropathy

Median neuropathy
Ulnar neuropathy
Radial neuropathy
Peroneal neuropathy
Sural neuropathy
:
:
:

Case 1

- 66/M
- C/C : 2주전부터 오른손에 힘이 빠진다.
- Brief history
  - sensory symptom 동반 안됨
  - neck discomfort 동반 안됨
  - progressive course
  - leg weakness와 bulbar symptom은 없음
- PMHx : n-s, medication(-)
- Social history: alcohol (-), smoking (+, 80PY), 농업

N/E

- CNE : n-s
- Motor : right finger abduction 3
  right finger adduction 3
  나머지 intact
  muscle atrophy (-)
- DTR ++/++
- Sensory : intact

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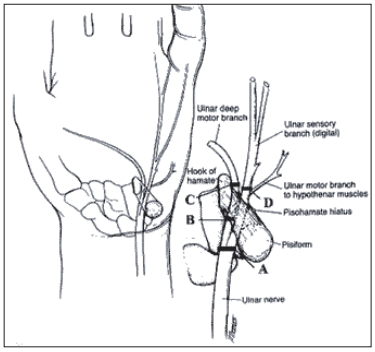
NCS/EMG

Nerve	Stimulation site	Motor			Sensory	
		TL	CV	Amp	CV	Amp
Median, Lt	Wrist	2.95		13.1	48.1	15.1
	Elbow		61.6	12.6		
	F-latency	25.95				
Median, Rt	Wrist	3.25		16.0	39.7	12.0
	Elbow		61.0	14.7		
	F-latency	26.75				
Ulnar, Lt	Wrist	2.3		14.4	47.9	11.2
	Elbow		66.2	12.4		
	F-latency	26.05				
Ulnar, Rt	Wrist	2.2		0.9	47.8	11.2
	Elbow		65.4	0.7		
	Axilla			0.4		
	F-latency	NR				

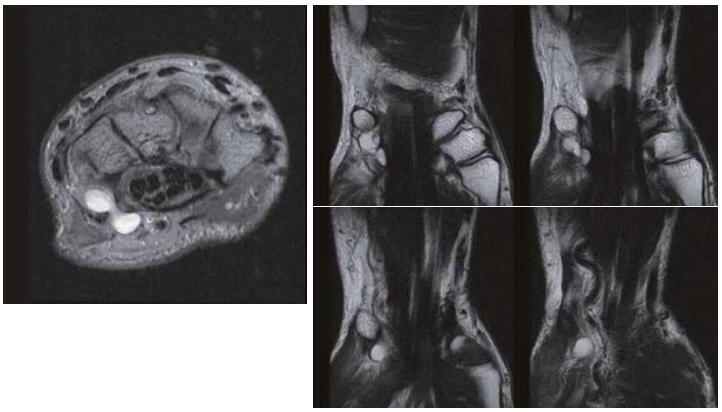
Muscle	Spontaneous activity	MUP	Recruitment
FDI	Increased IA, PSW(2+)	normal	reduced
FCU	N-S	normal	full
ADQ	Increased IA, FP(2+), PSW(2+)	normal	reduced
APB	N-S	normal	full
Paraspinal	N-S		

Ulnar neuropathy at the wrist

- 빈도 : 1/20 of ulnar neuropathy at the elbow
- 증상 : depend on lesion location
- 원인 : ulnar neuropathy at the elbow에 비해서 space occupying lesion의 빈도가 높은편
  → imaging study 권유



Wrist MRI



1.5 x 0.6 cm-sized suspicious ganglion between pisifom and hamate, adjacent to the ulnar nerve, right.

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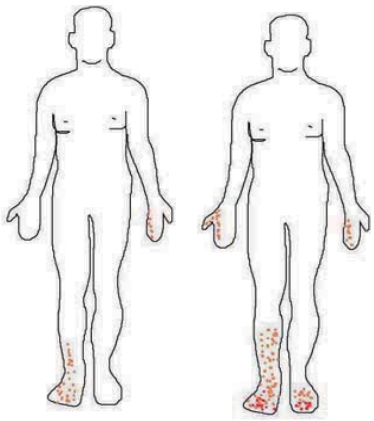
Mononeuropathy

- Carpal tunnel syndrome
- Ulnar neuropathy
- Peroneal neuropathy

1. History
2. Neurologic examination
3. NCS/EMG

- 원인
  - 대부분 compressive lesion
    (Space occupying lesion : ganglion, cyst)
  - Trauma
  - Ischemia
- Evaluation
  - Common site of compression : conservative or surgery
  - Uncommon site of compression : imaging

Multifocal Mononeuropathy



Mononeuritis multiplex

Mononeuritis multiplex (Multiple mononeuropathy)

mononeuritis multiplex is important to recognize
- limited differential diagnosis
- includes several treatable forms of neuropathy

vasculitic neuropathy,
leprosy,
CIDP variants,
multifocal motor neuropathy with conduction block
hereditary neuropathy with liability to pressure palsy

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Causes of Mononeuritis multiplex
Axonal injury
Vasculitis(systemic, nonsystemic)
Diabetes mellitus
Sarcoidosis
Leprosy
Human immunodeficiency virus 1 infection
Demyelinating / conduction block
Multifocal motor neuropathy
Multiful compression neuropathy (hypothyroidisim, diabetes)
Hereditary neuropathy with liability to pressure palsy

Case 2

- 52/F
- C/C : 한달전부터 양쪽 팔다리가 저리고 아파요
- Brief history
  - 한달전 양쪽 다리의 통증발생
  - 이후로 팔다리가 모두 저리고 아프고 힘이 빠짐.
  - progressive course
  - weight loss(+, 2kg)
- PMHx : n-s, medication(-)
- Social history: n-s

N/E

- Motor

shoulder	5/5	hip flexion	5/5
elbow flexion	4-/4+	hip extension	4+/5
elbow extension	4+/4-	knee flexion	4/4
wrist flexion	4/4	knee extension	4+/4+
wrist extension	4/4	ankle dorsiF	3/4-
finger abduction	4-/3	ankle plantarF	4/5
hand grip	4-/3		

- Sensory: painful paresthesia(+)
  position sense : intact

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NCS

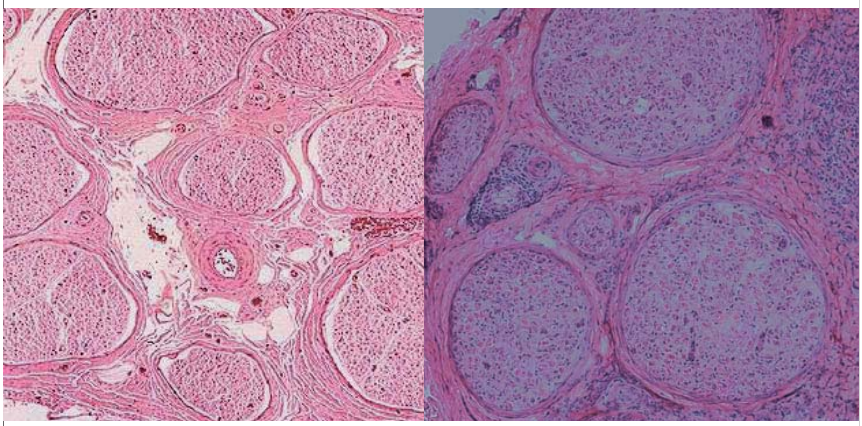
Nerve	Stimulation site	Motor			Sensory	
		TL	CV	Amp	CV	Amp
Median, Lt	Wrist	4.4		2.0	39.7	0.65
	Elbow		44.2	1.1		
	F-latency	NR				
Median, Rt	Wrist	4.10		7.3	40.3	1.9
	Elbow		29.0	6.4		
	F-latency	29.4				
Ulnar, Lt	Wrist	5.55		0.6	36.0	0.92
	Elbow		50.5			
	F-latency					
Ulnar, Rt					37.1	5.1
Peroneal,Lt	Ankle	NR				
	F-latency	NR				
Peroneal,Rt	Ankel	NR				
	F-latency	NR				
Tibial,Lt	Ankle	5.75		0.5		
	Popliteal		34.2			
	F-latency	NR				
	H-reflex	33.05				
Tibial,Lt	Ankle	NR				
	F-latency	NR				
	H-reflex	32.5				
Sural, Lt					4.7	36.4
Sural, Rt					NR	NR

Laboratory findings

- Pleocytosis
- Anemia
- FANA : weakly positive
- ANCA(+) 1:160, p-type
  MPO (+, 662), PR3(+,295),
- ESR >100
- CRP >200
- RF>100
- UA : normal

- Chest CT: N-S
- Abdomen CT : N-S

Sural nerve biopsy



Normal　　Vasculitis

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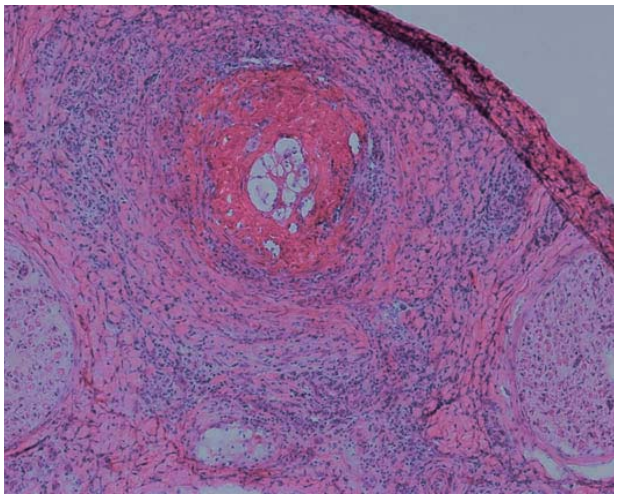
Sural nerve biopsy



ANCA-associated vasculitis

1. Microscopic angitis
2. Wegener's granulomatosis
3. Churg-Strauss syndrome

- Common characteristics
  - Affected vessels are arterioles, capilllaries, and venules **(small vessel vasculitis)**
  - Most common affected organ: **kidney and lung**
  - Common pathogenesis: **ANCA**

- Clinical presentation **typical** for vasculitic neuropathy
  - sensory-motor or sensory
  - asymmetric/multifocal (non-length dependent)
  - lower limb predominant
  - distal predominant
  - painful

Purely motor
Entirely proximal → other disease
Perfectly symmetric

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Suggested algorithmic approach

History, Exam consistent with neuropathy

↓

NCS/EMG

↓

Non-length dependent axon loss, asymmetries, intralimb amplitude disparities

YES ↙ ↘ NO

Screening tests: ESR, CRP, CBC with diff, chemistry panel with glucose, renal and liver function, SPEP, UA, Chest X-ray
Consider: ANCA, Hep B & C Ab, cryoglobulins, ANA, ds DNA, SS-A/B, RF, C3,C4, HIV-Ab, Lyme titer, anti-Hu, if PAN suspected: consider mesenteric angiography
With known CTD or systemic vasculitis, may skip screening tests

Routinge PN work-up; if CTD or systemic vasculitis

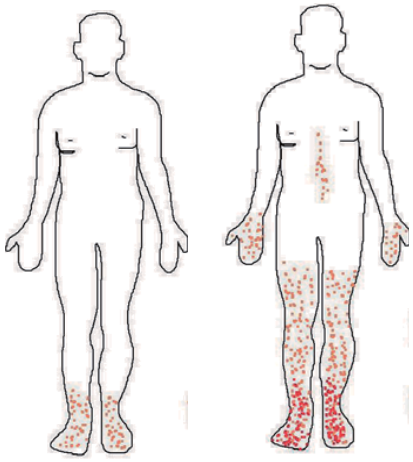
↓

Nerve/Muscle biopsy

Polyneuropathy

Length dependent neuropathy

Glove & stoking pattern



Etiology of polyneuropathy

Acquired	Toxins or drugs
Dysmetabolic	Heavy metals and industrial toxins
Diabetes mellitus	Chemotherapy induced
Renal disease	Deficiency state
Primary amyloidosis	Alcoholism (Vitamin B1 deficiency)
Hypothyroidism	Vitamin B12 deficiency
Immune-mediated	
CIDP	**Hereditary**
Vasculitis	Neuropathies in which the neuropathy is the sole or primary part of the disorder
Connective tissue disease	Hereditary motor and sensory neuropathy
Paraproteinemia	Hereditary sensory and autonomic neuropathy
Infectious	Distal hereditary motor neuropathy
Leprosy, Sarcoidosis	Neuropathies in which the neuropathy is part of a more widespread neurological or multisystem disorder
Lyme, HIV	
Cancer related	
Lymphoma, myeloma	
Paraneoplastic	

Common causes : diabetes, alcohol abuse, poor nutrition, and genetics

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Screening laboratory tests

Hematology	Complete blood count, erythrocyte sedimentation rate or C-reactive portein, Vitamin B 12, folate. (Methylmalonic acid with or without homocysteine for low normal vitamin B12 levels)
Biochemical and endocrine	Fasting glucose, renal function, liver function, thyroid function tests, serum protein immunofixation electrophoresis. (Glucose tolerance test if indicated to look for impaired glucose tolerance)
Urine	Urine protein electrophoresis with immunofixation
Drugs and toxins	Inquire about drugs and toxins

Categorization

I. Pattern of involvement
II. Fiber type is involved
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NCS/EMG

		Axonal degeneration	*demyelination*
NCS	Latency	Normal	Increased
	Amplitude	Decreased	Normal
	Velocity	Normal	Decreased
	F-latency	Normal	Increased
EMG	Acute denervation	Present	Absent
	MUP amplitude	Increased	Normal
	Recruitment	Decreased	Normal

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Demyelinating polyneuropathy

inherited	acquired
Charcot-Marie-Tooth(CMT) disease CMT1, CMT3 CMT4, CMT X HNPP Refsum's disease Leukodystrophy adrenoleukodystrophy /adrenomyeloneuropathy Metachromatic leukodystrophy Krabbe's disease Cockayne's syndrome Pelizaeus-Merzbacher disease	Guillain-Barre syndrome CIDP Monoclonal gammopathy Multifocal motor neuropathy with conduction block Diphtheria Drug amiodarone perhexiline cytosine arabinoside

Family history

- Acquired or inherited ?
- Inheritance pattern ?

- Idiopathic neuropathy : inherited neuropathy comprise the largest group
- 42% of patients with undiagnosed neuropathy : inherited neuropathy

Hereditary polyneuropathy

- An important subtype of polyneuropathy
- Prevalence : 1/2500

- Clinical phenotype is extremely variable
- De novo mutation
- Genetic heterogeneity
- Phenotype heterogeneity

→ genetic test is necessary

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Which patients with polyneuropathy should be screened for hereditary neuropathies?

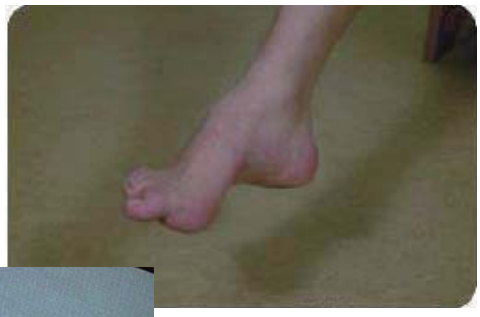
- Patients with the classic CMT phenotype with and without a family history of polyneuropathy
- Usefulness of routine genetic screening in cryptogenic polyneuropathy without classical CMT phenotype : uncertain

Classic CMT phenotype

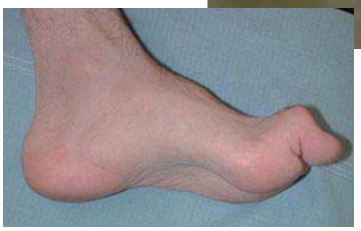
- Lower limb motor symptom (difficulty in walking)
- Beginning in the first two dacades
- distal weakness, atrophy, sensory loss
- Hyporeflexia
- Foot deformity (pes cavus)

Foot deformity

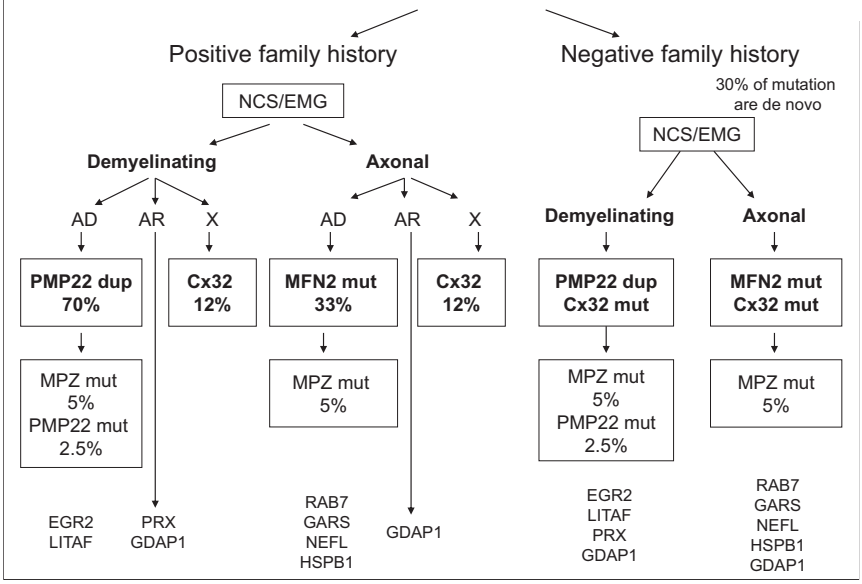
- Pes cavus



- Hammer toe



Suspected hereditary neuropathies



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Polyneuropathy associated with chronic alcoholism

- Common polyneuropathy
  - 12.5-48.6% of chronic alcoholics
- Pathogenesis
  - direct neurotoxic effect of ethanol or its metabloites
  - thiamine deficiency
  - malnutrition related to dietary imbalance
- pathogenesis and clinical features are incompletely understood

Excessive alcohol use?

- More than 100g of daily ethanol consumption for at least 10 years prior to the onset of neuropathic symptoms

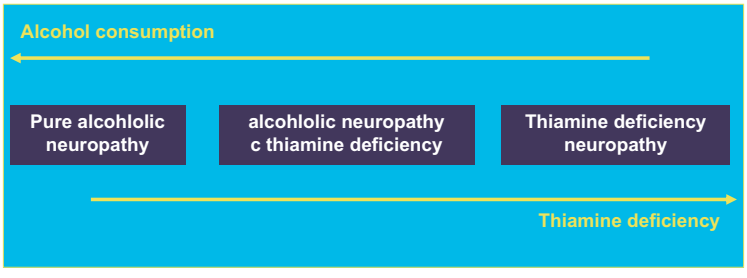
Ethanol 100g

25° 소주 500ml (한병 300ml)

5° 맥주 2500ml

Alcoholic neuropathy

- Pure alcoholic neuropathy : slowly progressive, sensori-dominant symptom, painful paresthesia
- Thiamine deficiency neuropathy : acutely progressive, motor-dominant pattern, loss of ambulation
- Usual alcoholic neuropathy : a spectrum raging from a pictures of pure alcoholic neuropathy to that of thiamine deficiency neuropathy



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