Rheumatologic diseases for neurologists

이 연 아
경희의대 류마티스 내과

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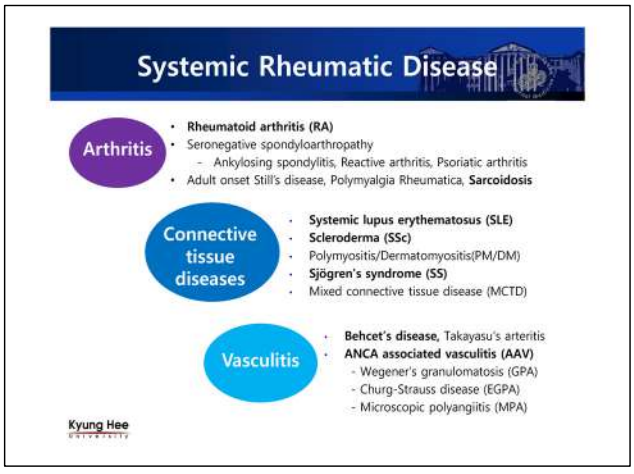
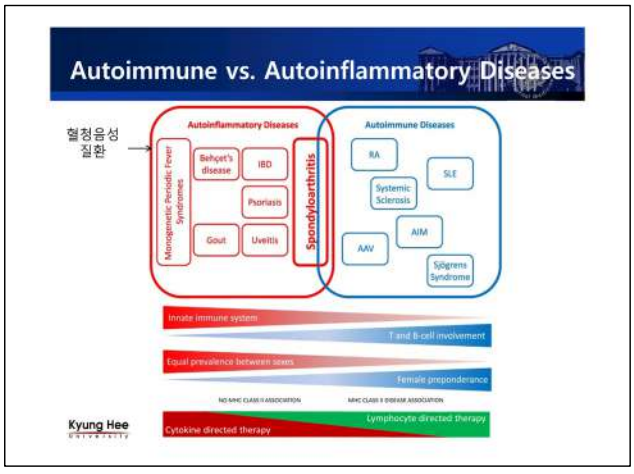
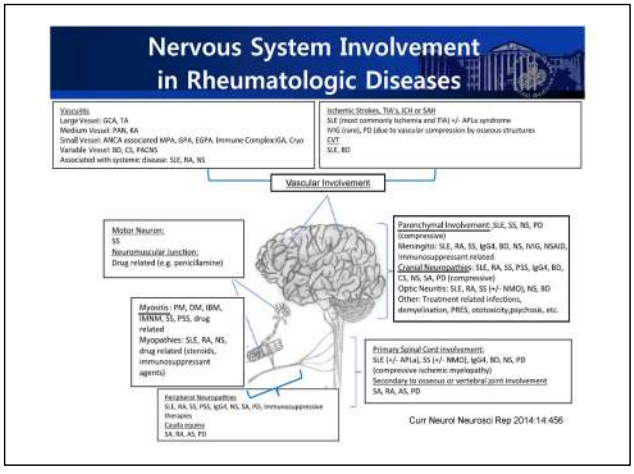
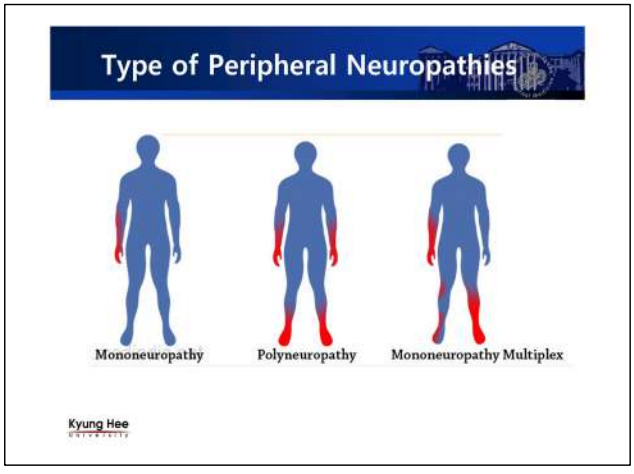
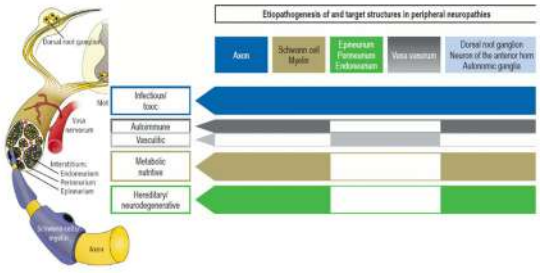








Etiopathogenesis and Target Structures in Peripheral Neuropathies



Case 1.

- 76세, 남자
- 2달 전부터 발열, 양 발목 부종으로 신장내과 방문, 단백뇨 및 혈뇨 소견을 보여 검사 위해 입원, ESR상승 및 발목관절 부종으로 의뢰됨

- 병력청취와 신체검사
  - 당뇨병 병력 (-)
  - 양 손발 저림 (+) – stocking & glove pattern
  - 피부발진 (-), 구강궤양 (-)
  - 양 발목 관절에 압통 및 부종
- 검사 소견
  - ESR 110mm/hr, CRP 4.43mg/dL
  - RF (-), anti-CCP (-)
  - ANA 양성 (speckled, 1:40)
  - P-ANCA 4+

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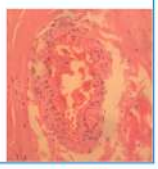
Case 1. Work up result

- Inflammatory arthritis, maxillary sinusitis
- 24 시간 단백뇨: 1330 mg/day, 현미경적 혈뇨
  (신조직 검사는 양측 신장이 cystic 하여 시행 못 함)
- NCS : sensorimotor polyneuropathy (axonal)
  → Sural nerve biopsy : leukocytoclastic vasculitis
- 검사 소견:
  - MPO-ANCA (+) 5.2, PR3-ANCA (-) 3.8
- HRCT: early stage of ILD, both lower lobes



→ Microscopic polyangiitis (MPA)

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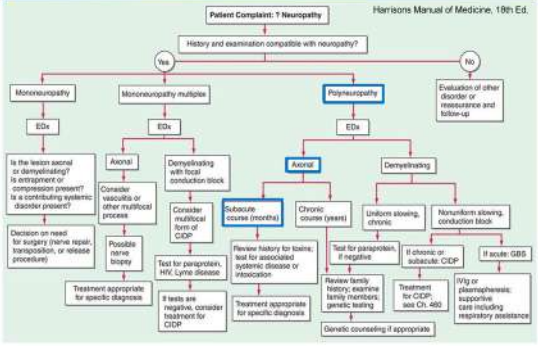
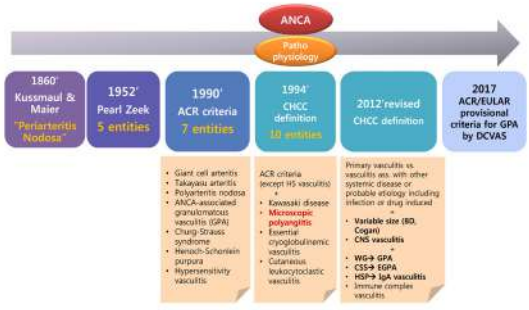
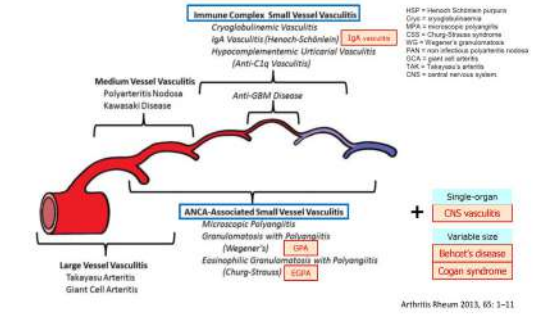
Approach of Peripheral Neuropathies



History and Evolution of Vasculitis Classification Systems



2012 Revised International CHCC Nomenclature of Vasculitis



2012 Revised International CHCC Nomenclature of Vasculitis

- Large vessel vasculitis (LVV)
  - Takayasu arteritis (TAK)
  - Giant cell arteritis (GCA)
- Medium vessel vasculitis (MVV)
  - Polyarteritis nodosa (PAN)
  - Kawasaki disease (KD)
- Small vessel vasculitis (SVV)
  - Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
    - Microscopic polyangiitis (MPA)
    - Granulomatosis with polyangiitis (Wegener's) (GPA)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
  - Immune complex SVV
    - Anti–glomerular basement membrane (anti-GBM) disease
    - Cryoglobulinemic vasculitis (CV)
    - IgA vasculitis (Henoch-Schönlein) (IgAV)
    - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
- Variable vessel vasculitis (VVV)
  - Behçet's disease (BD)
  - Cogan's syndrome (CS)
- Single-organ vasculitis (SOV)
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- Vasculitis associated with systemic disease
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- Vasculitis associated with probable etiology
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

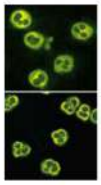
✓ 28 participants from 12 countries

✓ nephrology, otolaryngology, pathology, pulmonology, rheumatology, pediatrics

Arthritis Rheum 2013, 65: 1–11

ANCA (Antineutrophil cytoplasmic antibody)

- **Definition:** Ab directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes
- **c-ANCA**
  - major target antigen : **Proteinase-3**, a 29-kDa neutral serine proteinase
  - positive in more than 90% of patients with typical active GPA
- **p-ANCA**
  - major target : **myeloperoxidase**
  - other targets : elastase, cathepsin G, lactoferrin, lysozyme…
  - Only MPO-ANCA is associated with vasculitis (MPA, CSS)
  - positive in patients with MPA : 70-80% ; CSS : 30-40%
  - Other ANCA
    : in IBD, certain drugs, endocarditis, bacterial infections in patients with cystic fibrosis
- **Two major diagnostic pitfalls:**
  - Cocaine/levamisole induced pathology, Bacterial endocarditis



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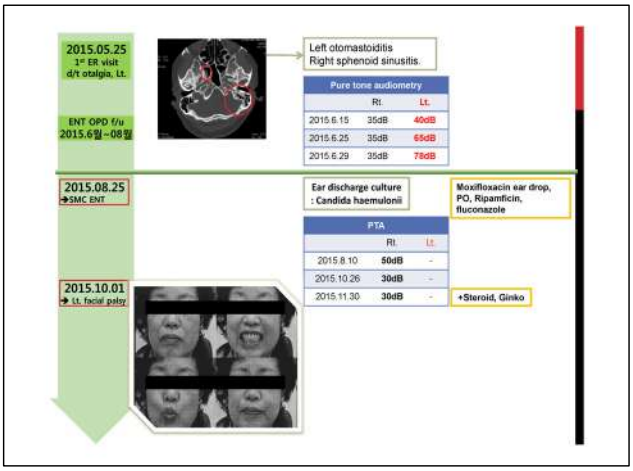
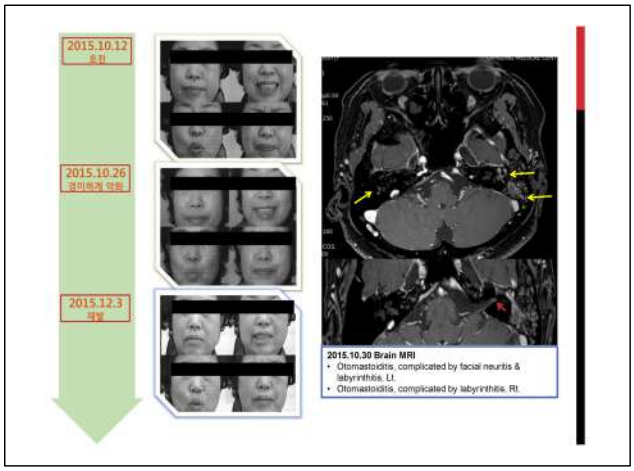
Comparison of clinical manifestations of AAV

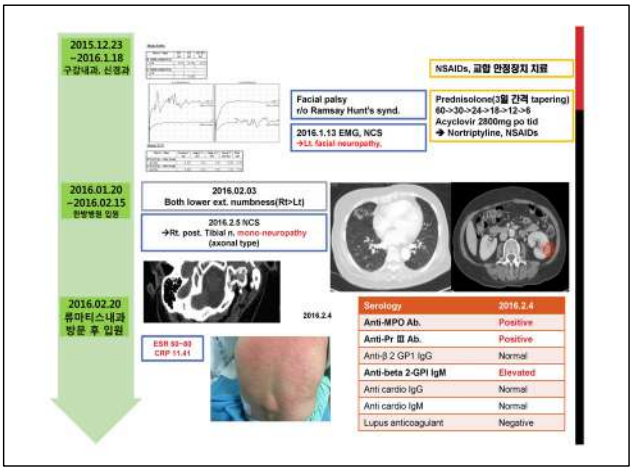
	GPA	MPA	EGPA
ANCA-positive (%)	90	90	50
Typical ANCA result	C-ANCA/PR3-ANCA	P-ANCA/MPO-ANCA	P-ANCA/MPO-ANCA
Granuloma	Present	Absent	Present with abundant eosinophil
Upper respiratory tract	90% Nasal septal perforation Saddle-nose deformity Subglottic stenosis	Usually absent or mild	Nasal polyps Allergic rhinitis Sinusitis
Lung	85–90% Nodules, infiltrates or cavitary lesion	Alveolar hemorrhage (10-20%)	Asthma Migratory infiltrates Alveolar hemorrhage
Kidney	40-80% NCGN, occasional granulomatous feature	80% NCGN	25-58% NCGN
Peripheral neuropathy	20%	58%	66-78%
Distinguishing feature	Destructive upper airway disease		Asthma, allergy, Eosinophilia

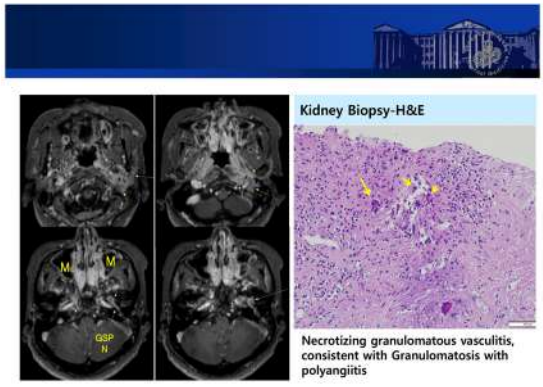
Case 2.

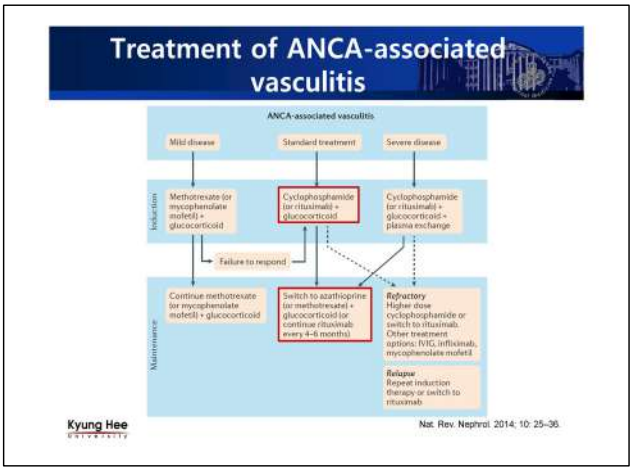
- 60세, 여자
- **주소:** 양측 중이염, 반복적 안면마비
- **병력:**
  - 2015년 4월 both ear discharge, tinnnius 로 이비인후과 진료, 호전되지 않아
  → 타병원 이비인후과 진료 중 좌측 안면마비 발생
  → 스테로이드 복용 후 호전되었다가 2015.12 재발, 한방 입원 중에 양하지 저림, 염증수치 상승으로 의뢰됨.






2015.12.23
~2016.1.18
구강내과, 신경과
NSAIDs, 교합 안정장치 지료
Facial palsy
r/o Ramsay Hunt's synd.
Prednisolone(3월 간격 tapering)
60->30->24->18->12->6
Acyclovir 2800mg po tid
→ Nortriptyline, NSAIDs
2016.1.13 EMG, NCS
→Lt. facial neuropathy.
2016.01.20
~2016.02.15
2016.02.03
Both lower ext. numbness(Rt>Lt)
2016.2.5 NCS
→Rt. post. Tibial n. mono-neuropathy
(axonal type)
2016.02.20
2016.2.4
ESR 93~90
CRP 11.41
Serology 2016.2.4
Anti-MPO Ab. Positive
Anti-Pr III Ab. Positive
Anti-β2 GP1 IgG Normal
Anti-beta 2-GPI IgM Elevated
Anti cardio IgG Normal
Anti cardio IgM Normal
Lupus anticoagulant Negative


Kidney Biopsy-H&E
Necrotizing granulomatous vasculitis, consistent with Granulomatosis with polyangiitis


Treatment of ANCA-associated vasculitis
ANCA-associated vasculitis
Mild disease
Standard treatment
Severe disease
Induction
Methotrexate (or mycophenolate mofetil) + glucocorticoid
Cyclophosphamide (or rituximab) + glucocorticoid
Cyclophosphamide (or rituximab) + glucocorticoid + plasma exchange
Failure to respond
Maintenance
Continue methotrexate (or mycophenolate mofetil) + glucocorticoid
Switch to azathioprine (or methotrexate) + glucocorticoid (or continue rituximab every 4–6 months)
Refractory
Higher dose cyclophosphamide or switch to rituximab. Other treatment options: IVIG, infliximab, mycophenolate mofetil
Relapse
Repeat induction therapy or switch to rituximab
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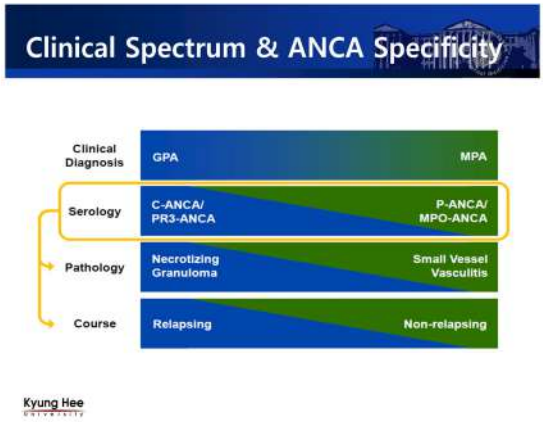
Nat. Rev. Nephrol. 2014; 10: 25–36.


Clinical Spectrum & ANCA Specificity
Clinical Diagnosis
GPA
MPA
Serology
C-ANCA/ PR3-ANCA
P-ANCA/ MPO-ANCA
Pathology
Necrotizing Granuloma
Small Vessel Vasculitis
Course
Relapsing
Non-relapsing
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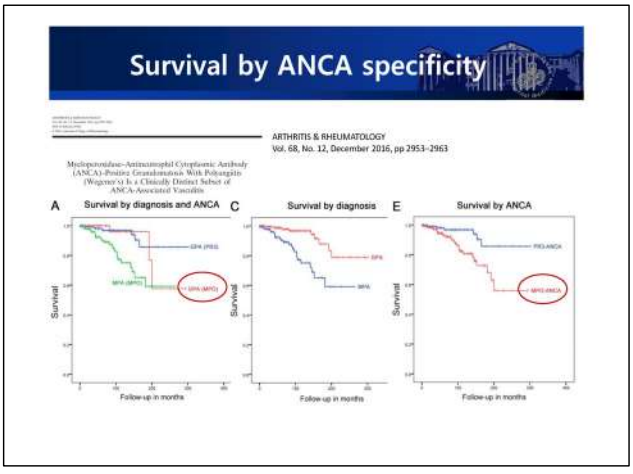
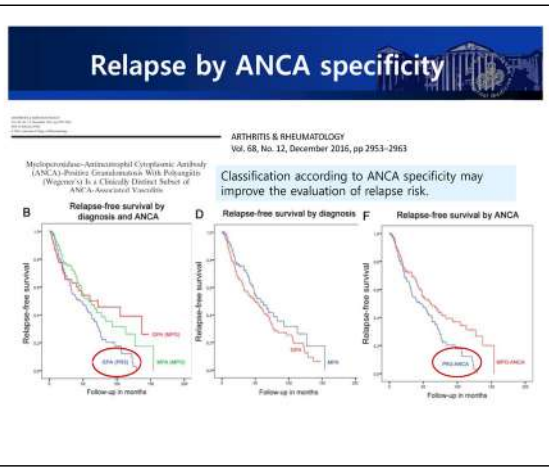

Survival by ANCA specificity
ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 12, December 2016, pp 2953–2963
A Survival by diagnosis and ANCA
C Survival by diagnosis
E Survival by ANCA
Survival
Follow-up in months


Relapse by ANCA specificity
ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 12, December 2016, pp 2953–2963
Classification according to ANCA specificity may improve the evaluation of relapse risk.
B Relapse-free survival by diagnosis and ANCA
D Relapse-free survival by diagnosis
F Relapse-free survival by ANCA
Relapse-free survival
Follow-up in months

Differences between PR3-ANCA vasculitis and MPO-ANCA vasculitis

Feature	PR3-ANCA vasculitis	MPO-ANCA vasculitis
Epidemiology	• Frequent in Northern European and American countries and Australia	• Frequent in Southern Europe and Asia
Usual age at diagnosis	• 45–55 years	• 60–65 years
Genetic associations	• *HLA-DP* • *SERPINA1* (encoding α1-antitrypsin) • *PRTN3* (encoding PR3)	• *HLA-DQ*
Pathology	• Granuloma and vasculitis	• Vasculitis and fibrosis
Organ involvement	• Frequent upper airway involvement and lung nodules • High number of organs involved	• Frequent renal involvement and pulmonary fibrosis
Prognosis	• Increased risk of relapse	• Increased rate of initial treatment failure • Increased long-term risk of end-stage renal disease
Response to therapy	• Rituximab superior to cyclophosphamide for remission induction • PR3-ANCA titre might guide therapy after rituximab	• Similar response to rituximab and cyclophosphamide

ANCA, Anti-neutrophil cytoplasmic antibody; PR3, leukocyte proteinase 3; MPO, myeloperoxidase.

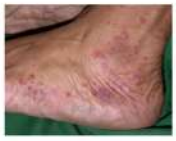
Nature Reviews Rheumatology 2016; 12: 570–579

ANCA test는 언제 하나?

- **Clinical suspicion이 가장 중요!**

→ **Unexplained multi-systemic disease시 의심될 때 시행**

- Pulmonary: hemorrhage, interstitial infiltrate
- GN을 시사하는 U/A 소견: esp. microscopic hematuria
- Chronic inflammatory sinusitis
- Unexplained ischemic events
- Palpable purpura
- Peripheral neuropathy : ex) mononeuritis multiplex



- **Confirm diagnosis**
  - Necessary of Histologic verification of vasculitis

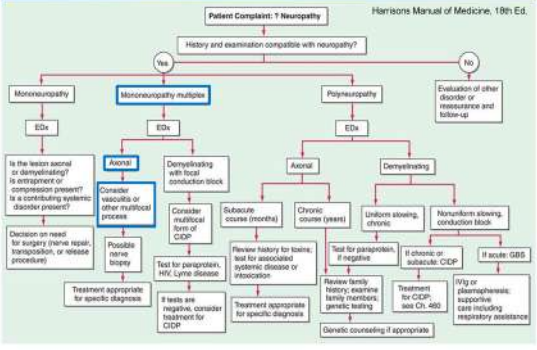
Case 3.

- 66세, 여자
- 주소 : 오른손 엄지, 검지 및 진행성 양 발 저림 및 감각저하
- 내원 1년 전 부터 오른손 엄지와 검지, 이후 양 엄지 손가락의 tingling sense→ 2달 전 CTS로 진단받고 수술 받은 이후에도 증상 지속→ 양 발 뒤꿈치에서 하지 전체로 감각저하 진행 되어 2016. 04. 29 신경과 방문. NCS소견에서 mononeuritis multiplex로 진단받은 뒤 MethylPD pulse Tx (1g/day*5days, 2016.05.13-17) 후 ANA 양성 소견으로 류마티스내과로 의뢰됨

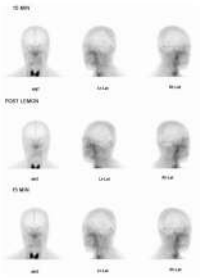
Case 3.

- **병력청취와 진찰소견** :
  - 레이노 증상 (+): 1년 전부터, Dry mouth (+), 구강궤양(-)
  - both ankle swelling Hx (+), 광과민성 (+), 발진 (-)
- **검사실 소견**:
  - ESR 46 mm/hr, RF (+)-high titer, ANA 양성 (1:160)
  - anti-Ro/La (+/+), aCL IgM (+), C4 감소
  - 손톱모세혈관 검사:

Approach of Peripheral Neuropathies



Salivary scan, Schirmer test & Salivary gland Bx



Salivary scan
: both parotid & submandibular gl. 섭취 보이지 않음

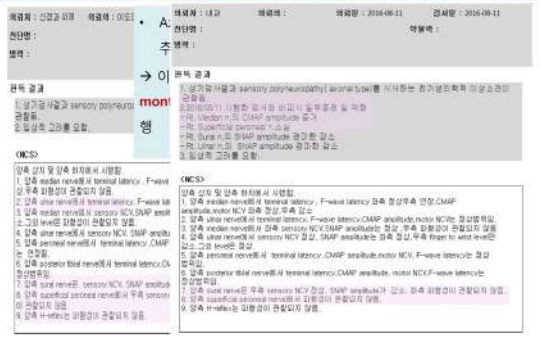
Schirmer test (+/+) <5mm/5min

- **Schirmer** <5 mm/5min at least one eye - 1점
- **Unstimulated whole saliva flow** ≤0.1/min - 1점
- **Salivary gland Bx: focus score** ≥1 - 3점
- **Anti-Ro positive** - 3점

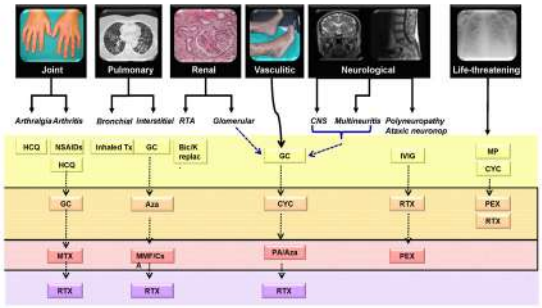
→ Total score 8 ≥4

→ **Primary Sjogren Syndrome**

Clinical Course



Extraglandular Involvement of Primary Sjogren Syndrome



Case 4.

- 73세, 여자
- 주소: 반복적 복시, 우측 안면마비

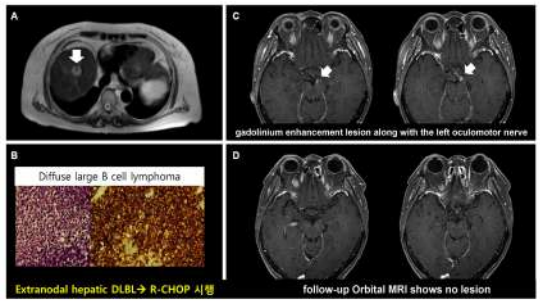
- 2011년 류마티스관절염 진단
- 2013.11 복시 발생 (right abducens nerve palsy)
- 2014.11 복시 재발 (left oculomotor palsy), 우측 facial palsy

→ RA동반된 multiple cranial neuropathy 진단, 고용량 스테로이드 사용 후

→ 2015년부터 Azathioprine 추가 사용에도 수개월 간격으로 복시, 우측 안면마비 반복되어 2016년 3월 부터 cyclophosphamide monthly pulse Tx 시작

→ Cyclophosphamide Tx 3차 시행 당시 2016. 9 간수치 상승으로 Liver image 시행

Recurrent multiple CN - DLBL related ? or RA related ?



Lymphoma and Oculomotor Nerve Palsy

- Lymphoma as a cause of isolated oculomotor nerve palsy

Hiromasa Sato [a], Takao Hashimoto [a,*], Suguru Yoneda [b], Kazuko Hirabayashi [b], Kazuhiro Oguchi [c], Kayoko Higuchi [d]

Journal of Clinical Neuroscience 18 (2011) 1256–1258

- 12 detailed case reports of patients with central nervous system (CNS) lymphoma who manifested isolated oculomotor nerve palsy
  - 4 patients : DLBCL
  - 1 patient : NK-cell lymphoma
  - 1 patient : Burkitt's lymphoma

- **Isolated Oculomotor Nerve Palsy due to Non-Hodgkin's Lymphoma Demonstrated by Serial MRI**

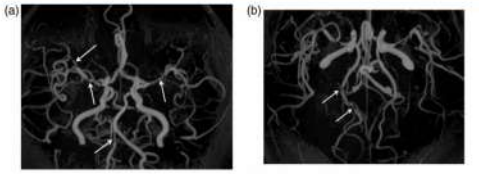
Seong-Min Choi*, Joon-Tae Kim, Seung-Han Lee, Man-Seok Park, Byeong-Chae Kim, Myeong-Kyu Kim and Ki-Hyun Cho

Department of Neurology, Chonnam National University Medical School, Gwangju, Korea

We present a 34-yr-old lymphoma patient who developed isolated oculomotor nerve palsy. Initial brain MRI and cerebrospinal fluid (CSF) findings were negative, but follow-up brain MRI showed a mass lesion in the cavernous sinus which encroached on the oculomotor nerve. This case suggest that, when isolated oculomotor nerve palsy develops in a patient with lymphoma, cavernous sinus involvement should be considered. Although initial brain imaging and CSF findings were negative, the follow-up imaging should be performed to detect the cause of the neurologic sign.

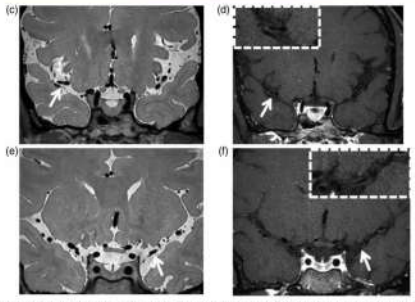
Case 5.

- 35세, 여자
- 안면발진, 다발성 관절통, 레이노 현상, 근육통 등으로 방문하여 검사 후 SLE 진단 받음. 발열을 동반한 lupus flare 로 고용량 스테로이드 pulse Tx 이후 taper 중 어지럽고 깨질듯한 두통 발생.



Magnetic resonance angiogram of brain shows multifocal stenosis (long white arrows) of M1 segment and distal branches of bilateral middle cerebral artery (MCA), right posterior cerebral artery and right vertebral artery

Case 5.



Magnetic resonance vessel wall imaging of brain shows insignificant enhancement of MCA

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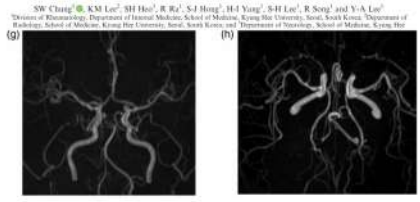
Case 5.

CASE REPORT

A systemic lupus erythematosus patient with thunderclap headache: reversible cerebral vasoconstriction syndrome



resolution of the previous multifocal stenosis with reversibility

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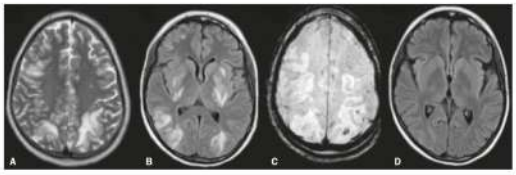
SLE with Reversible Posterior Encephalopathy



A,B: Axial T2-weighted and FLAIR images, respectively, showing bilateral cortical-subcortical areas of hyperintense signals in the occipital, parietal, and frontal lobes, with a slight expansile effect, including the basal ganglia. C: Susceptibility-weighted imaging sequence identifying a subcortical focus with a hypointense signal in the left parietal lobe (petechial hemorrhage). D: Follow-up image obtained after the acute stage, showing reduction of the previously demonstrated lesions.

2019 EULAR/ACR for SLE Classification Criteria

- Entry criterion : positive ANA at ≥ 1:80 on Hep-2 cell or an equivalent positive test (ever)
- Additive criteria were chosen from 7 clinical and 3 immunologic categories
- Weight based scoring rules: weighted from 2 to 10
- Patients with ≥10 points are classified as having SLE

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL or anti-β2GP1 IgG > 40 units or lupus anticoagulant	2
Complement proteins domain	
Low C3 or low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

Additive Criteria

- ✓ Classification criteria are not diagnosis criteria
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ Patients must have ≥ 10 points to be classified as SLE
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

Neuropsychiatric Syndromes in SLE

- **12 Central nervous system**
  - Aseptic meningitis
  - Cerebrovascular disease
  - Demyelinating syndrome
  - Headache
  - Movement disorder
  - Myelopathy
  - Seizure disorders
  - Acute confusional state
  - Anxiety disorder
  - Cognitive dysfunction
  - Mood disorder
  - Psychosis
- **7 Peripheral nervous system**
  - Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)
  - Autonomic neuropathy
  - Mononeuropathy
  - Myasthenia gravis
  - Cranial neuropathy
  - Plexopathy
  - Polyneuropathy

Arthritis Rheum. 1999;42:599–608

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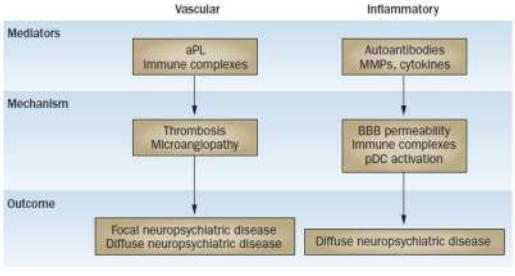
Autoimmune Pathogenesis of NPSLE



Nat Rev Rheumatol. 2014;10:338–47

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NPSLE

- Neuropsychiatric events are common in patients with SLE but only 1/3 are attributed directly to SLE.
- Pathogenetic mechanisms for NPSLE
  : autoimmune-mediated inflammatory injury and vascular injury
- Diagnosis of NPSLE : determined primarily by clinical assessment
- Investigations in support of the clinical diagnosis
  - measurement of autoAbs: antineuronal, antiribosomal P and aPL antibodies
  - analysis of CSF: to exclude infection, assess the BBB, and measure autoAb inflammatory mediators and degradation proteins
  - electrophysiological studies
  - neuropsychological assessment
  - neuroimaging (CT, MRI, MTI, DWI, DTI/ PET, SPECT, MRA, MRS, fMRI)
- Treatment options: symptomatic therapies, immunosuppression and anticoagulation

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Peripheral Neuropathies in SLE

-25-year study of 2,097 SLE patients in the Hopkins Lupus Cohort-

- **Small-fiber neuropathies in SLE pts**
  - more frequent than ACR NPSLE case definitions (i.e.,Guillain-Barre´ syndrome, plexopathies) or mononeuritis multiplex
- **Most common peripheral neuropathy** : axonal neuropathy (56.1%)

Type of peripheral neuropathy	No. (%) of patients
Axonal neuropathies	46 (56.1)
Sensory axonal polyneuropathy	19 (23.2)
Sensorimotor axonal polyneuropathy	21 (25.6)
Mononeuritis multiplex	6 (7.3)
Small-fiber neuropathies	14 (17.1)
Non–length-dependent small-fiber neuropathy	9 (11.0)
Length-dependent small-fiber neuropathy	5 (6.1)
Demyelinating polyneuropathies	
Acute inflammatory demyelinating polyneuropathy	1 (1.2)
Sensory demyelinating polyneuropathy	1 (1.2)
Mixed axonal–demyelinating sensorimotor polyneuropathy	3 (3.6)
Plexopathy	1 (1.2)
Neuropathy characterized by clinical criteria	16 (19.5)

Arthritis Rheumatol. 2014;66(4):1000-9

Peripheral Neuropathies in SLE

-18-year study of 4,924 Chinese patients with SLE-

	Cases of SLE-PN*
Polyneuropathy, n (%)	47 (59.5%)
Mononeuropathy, n (%)	11 (13.9%),
Cranial neuropathy, n (%)	10 (12.7%)
Myasthenia gravis, n (%)	8 (10.1%)
Autonomic neuropathy, n (%)	2 (2.5%)
Acute inflammatory demyelinating polyradiculoneuropathy	1 (1.3%)
Plexopathy, n (%)	0

PN = peripheral neuropathy, SLE = systemic lupus erythematosus.
* 79 cases of PN occurred in 73 patients.

Medicine (Baltimore). 2015 Mar; 94(11): e625.

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Conclusion

- Neurological involvement in rheumatic disease is associated with high morbidity and in some cases can be life-threatening.
- Be a CTD detective…Screening for CTD in patients with neurological manifestations
  - may present in patients with preexisting rheumatologic diagnoses, occur concurrently with systemic signs and symptoms, or precede systemic manifestations by months to years.
- Immunosuppressive therapy warranted in vasculitic neuropathies
- Multidisciplinary approach is vital for early detection and better outcome

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