Autoimmune Encephalitis

이 순 태
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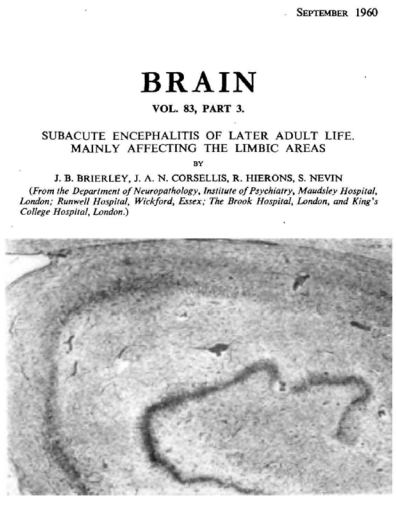
Clinical syndromes of AE

Limbic encephalitis

Brainstem encephalitis

Cerebellar degeneration

Encephalomyelitis


SEPTEMBER 1960

BRAIN

VOL. 83, PART 3.

SUBACUTE ENCEPHALITIS OF LATER ADULT LIFE. MAINLY AFFECTING THE LIMBIC AREAS

BY

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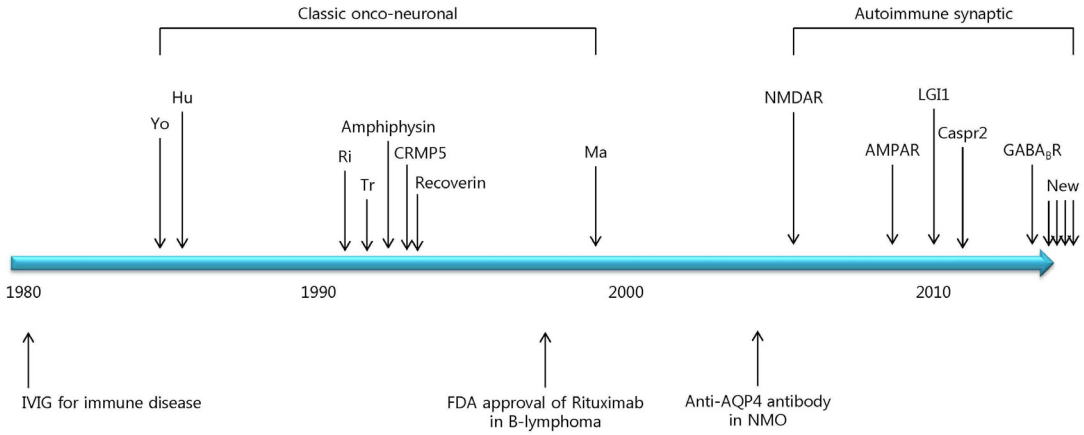
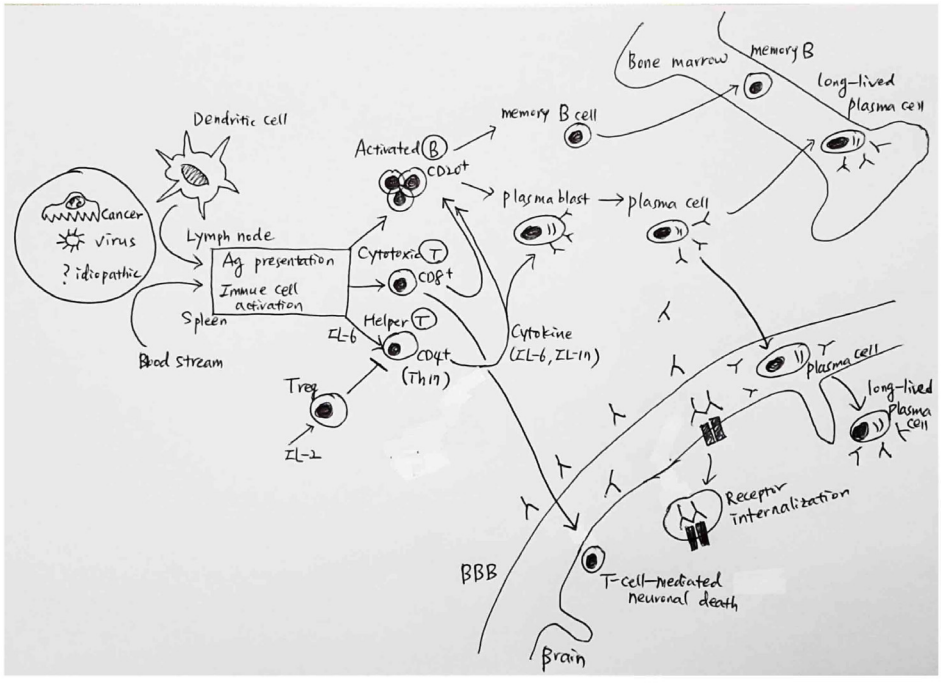
Subacute memory loss, seizure, confusion, and psychiatric symptoms
Pathology: limbic temporal lobe
Frequently with cancer

Discovery of AE auto-antibodies



Immunopathogenesis of autoimmune encephalitis



Paraneoplastic syndromes of the nervous system

Classic Syndromes: Usually Occur with Cancer Association	Nonclassic Syndromes: May Occur with and Without Cancer Association
Encephalomyelitis Limbic encephalitis Cerebellar degeneration (adults) Opsoclonus-myoclonus Subacute sensory neuronopathy Gastrointestinal paresis or pseudo-obstruction Dermatomyositis (adults) Lambert-Eaton myasthenic syndrome Cancer- or melanoma-associated retinopathy	Brainstem encephalitis Stiff-person syndrome Necrotizing myelopathy Motor neuron disease Guillain-Barré syndrome Subacute and chronic mixed sensory-motor neuropathies Neuropathy associated with plasma cell dyscrasias and lymphoma Vasculitis of nerve Pure autonomic neuropathy Acute necrotizing myopathy Polymyositis Vasculitis of muscle Optic neuropathy

Harrison 19th ed. Table 122-1

Antibodies to intracellular antigens, syndromes, and cancers

Antibody	Associated Neurologic Syndrome(s)	Tumors
Anti-Hu (ANNA1)	Encephalomyelitis, subacute sensory neuronopathy	SCLC
Anti-Yo (PCA1)	Cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA2)	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynecologic, SCLC
Anti-Tr	Cerebellar degeneration	Hodgkin's lymphoma
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral n europathy	SCLC, thymoma, other
Anti-Ma proteins	Limbic, hypothalamic, brainstem encephalitis	Testicular (Ma2), other (Ma)
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Recoverin	Cancer-associated retinopathy (CAR), Melanoma-associated retinopathy (MAR)	SCLC (CAR), melanoma (MAR)
Anti-GAD	Stiff-person, cerebellar syndromes, limbic encephalitis	Infrequent tumor association (thymoma)

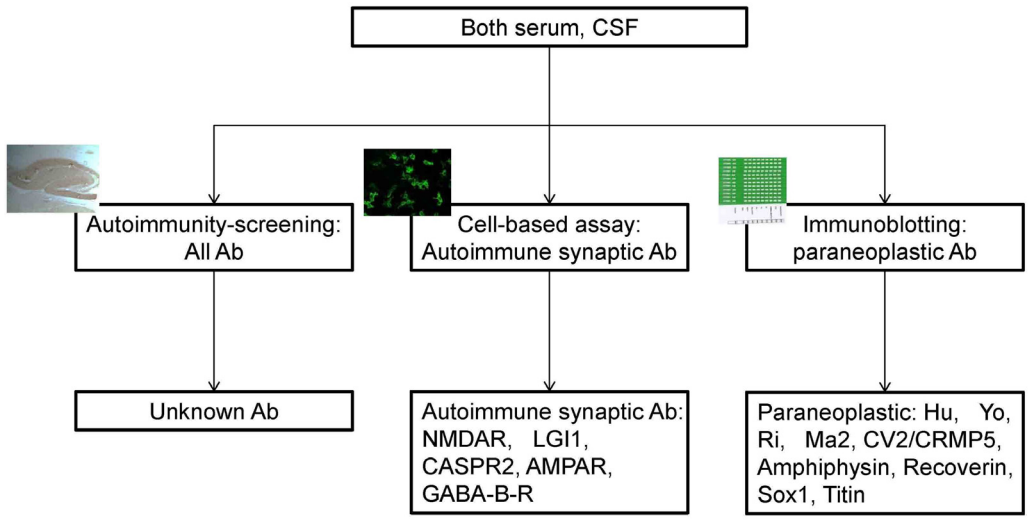
Harrison 19th ed. Table 122-2

Antibodies to cell surface or synaptic antigens, syndromes, and tumors

Antibody	Neurologic Syndrome	Tumor Type When Associated
Anti-AChR (muscle)	Myasthenia gravis	Thymoma
Anti-AChR (neuronal)	Autonomic ganglionopathy	SCLC
Anti-VGCC	LEMS, cerebellar degeneration	SCLC
Anti-NMDAR	Anti-NMDAR encephalitis	Teratoma in young women (children and men rarely have tumors)
Anti-LGI1	Limbic encephalitis, hyponatremia, faciobrachial dystonic seizures	Rarely thymoma
Anti-Caspr2	Morvan's syndrome, neuromyotonia	Thymoma, prostate cancer
Anti-GABA-B R	Limbic encephalitis, seizures	SCLC, neuroendocrine
Anti-GABA-A R	Encephalitis with prominent seizures and status epilepticus; less often opsoclonus and stiff-person syndrome	Rarely thymoma
Anti-AMPAR	Limbic encephalitis with relapses	SCLC, thymoma, breast
Glycine receptor	Encephalomyelitis with rigidity, stiff-person syndrome	Rarely, thymoma, lung cancer
Anti-DPPX	Agitation, myoclonus, tremor, seizures, hyperekplexia, encephalomyelitis with rigidity	No cancer, but frequent diarrhea or cachexia suggesting paraneoplasia

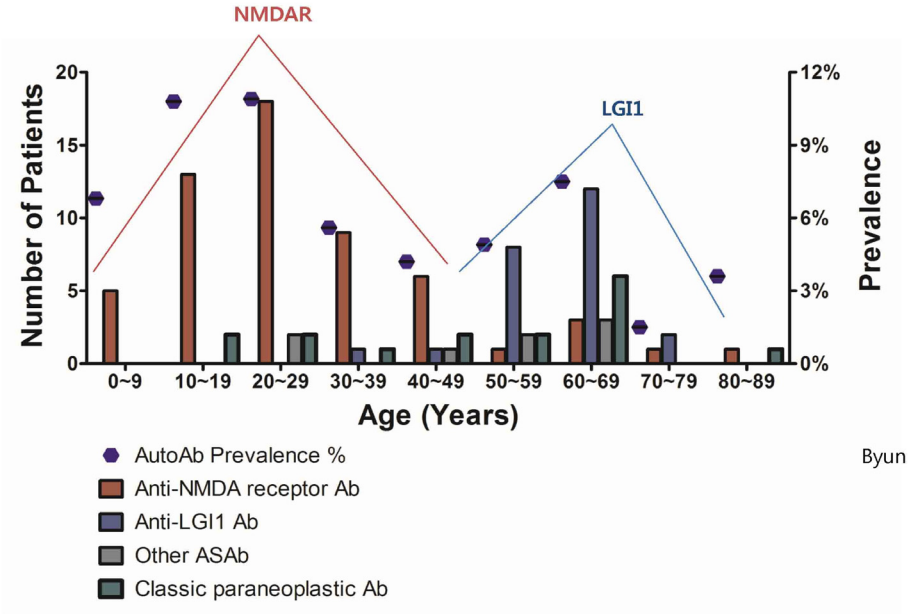
Harrison 19th ed. Table 122-3

Antibody tests algorithm



Antibody tests by www.advancednt.co.kr

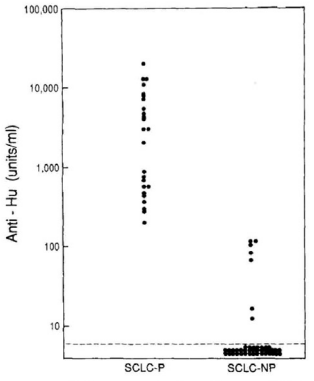
Distribution of AE antibodies in Korea: 6~8% positive



Byun et al., JNI, 2016

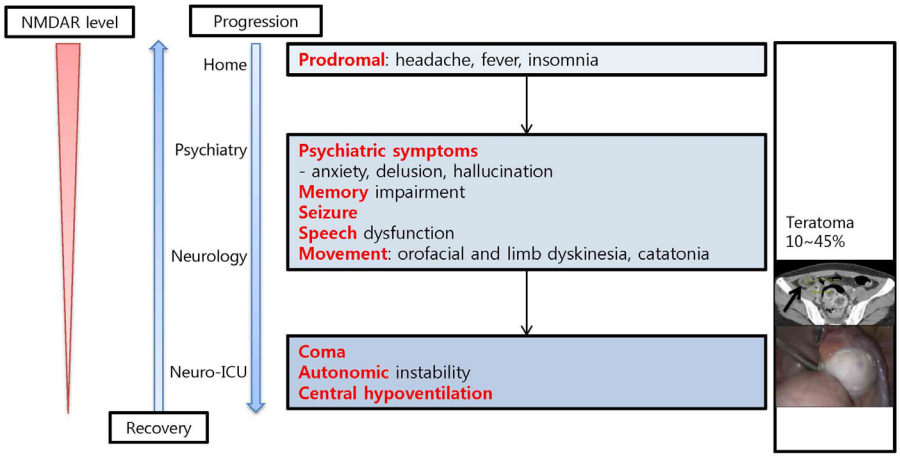
Interpretation of autoantibody

1. **Symptomatic**: Anti-NMDAR, anti-Hu Ab
2. **Asymptomatic**: anti-Hu in SCLC without PNS
3. **Not relevant to the disease**: anti-TPO in Hashimoto
4. **False positive:** low titer of anti-GAD
5. **False negative**
6. **AE with no detectable antibody (AE-noDAB)**



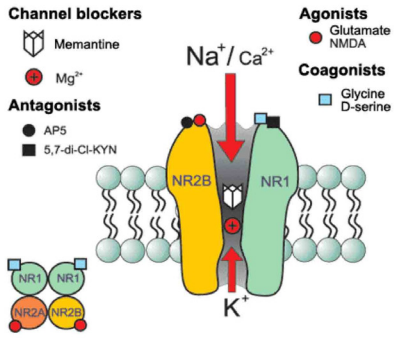
Dalamu et al., Ann Neurol, 1990

Clinical presentation of anti-NMDA receptor encephalitis

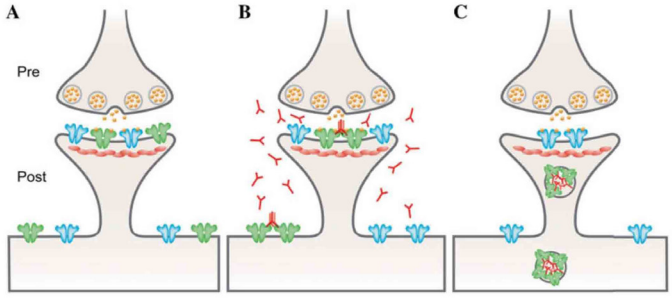


NMDA receptor and pathogenesis

Anti-NR1 antibody

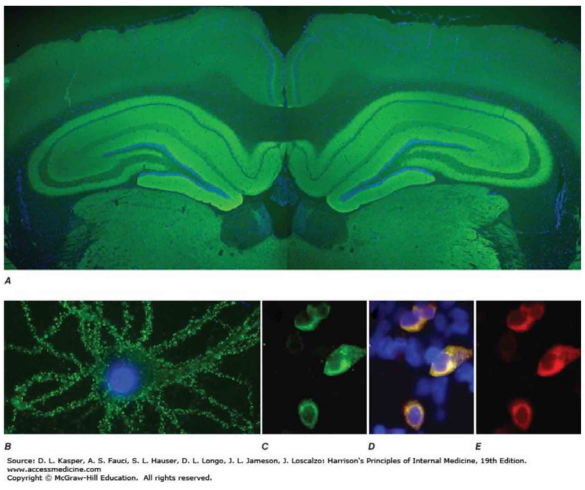


NMDAR internalization by anti-NMDAR antibody

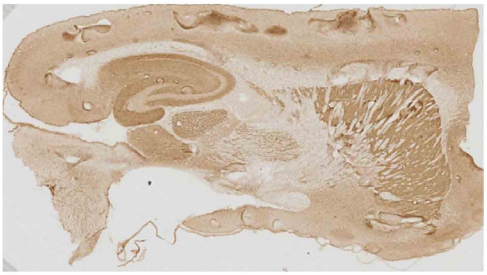


Leypoldt et al., 2015

Antibody staining of anti-NMDAR encephalitis antibody



Rat brain section stained with pt's CSF



Harrison 19th ed. Figure 122-1

CSF antibody in NMDAR encephalitis

Diagnosis

CSF 250/250 (sensitivity 100%)

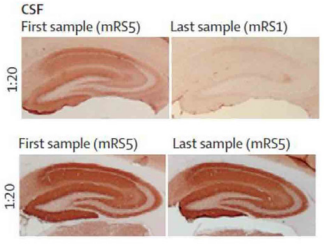
Serum 214/250 (sensitivity 85.6%)

Intrathecal Ab synthesis

Frequent: NMDAR, Hu, Yo, AMPAR, GABA-B

Infrequent: LGI1, Caspr2

Prognosis

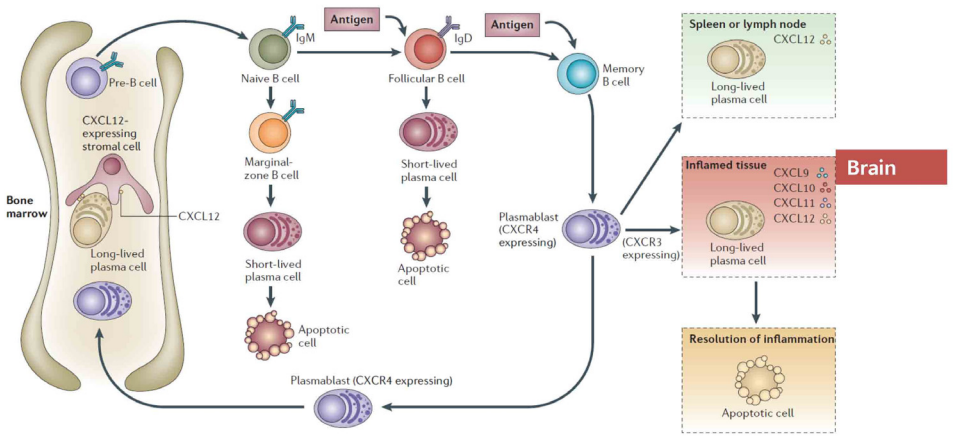


→ **Good outcome**

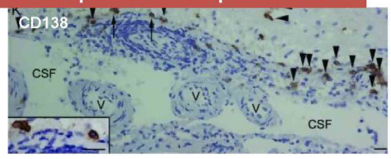
→ **Poor outcome**

Gresa-Arribas et al., Lancet Neurol, 2014

NMDARE: Long recovery time due to long lived plasma cells (6m~ 2yr) in brain



NMDAR encephalitis brain: plasma cell+



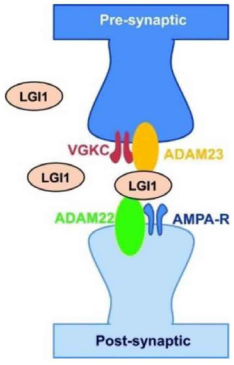
Radbruch et al. Nat Rev Immunology, 2006
Martinez-Hernandez et al, Neurology, 2011

FACT sheet for anti-NMDAR encephalitis

- ❖ 4% of anti-NMDARE → pure psychosis
- ❖ Misdiagnosis: 3.3% of schizophrenia → anti-NMDARE
- ❖ Relapse rate 12~24% (non-rituximab world data)
- ❖ Age > 45 → 20% have cancer (breast, ovary, lung)
- ❖ Mortality by central hypoventilation, rhabdomyolysis, status epilepticus, and hypersalivation/pneumonia/sepsis
- ❖ Movie "Exocist" and "Knut" bear

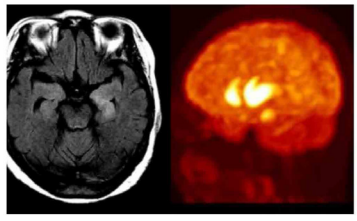
Anti-LGI1 encephalitis

- About ~1% in all encephalitis
- Treatable dementia
- Seizure 100%
- Faciobrachial dystonic seizure (FBDS) ~70%
- Hyponatremia ~60%
- MRI ~70%, PET ~90%
- Tumor (thymus) < 10%
- No intrathecal antibody synthesis

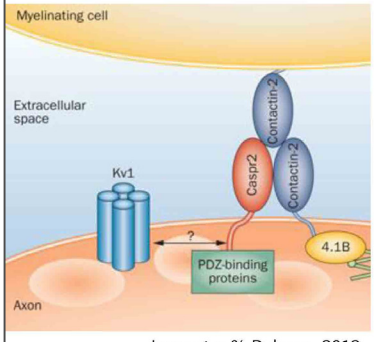


60/M, FBDS by anti-LGI1 antibody

Patient video here



Anti-Caspr2 syndrome



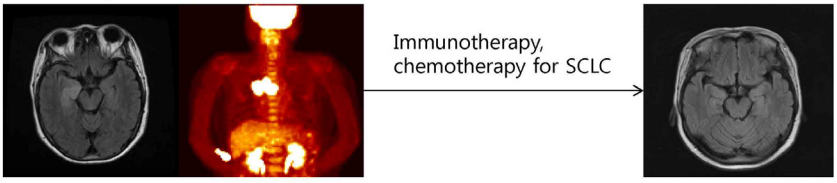
Lancaster % Dalmau, 2012

	Caspr2 (n=5)	LGI1 (n=14)	p-value
Age, median (range)	43.5 (8-65)	60.5 (41-78)	0.057
Male	3 (60%)	8 (57.1%)	1.000
Clinical manifestations			
Seizure	4 (80%)	14 (100%)	0.263
Faciobrachial dystonic seizure (FBDS)	0 (0%)	**10 (71.4%)**	0.011
Confusion or cognitive dysfunction	2 (40%)	12 (85.7%)	0.084
Peripheral nervous hyperexcitability (Morvan)	**2 (40%)**	0 (0%)	0.058
Hyponatremia	0 (0%)	**6 (42.9%)**	0.128
Abnormal EEG	5 (100%)	10 (76.9%)	0.522
Interictal epileptiform discharge	2 (40%)	8 (61.5%)	0.608
Abnormal MRI	2 (40%)	**10 (71.4%)**	0.305
Temporal lobe lesion	1 (20%)	9 (64.3%)	0.141
Abnormal CSF profile	2 (50%)	3 (23.1%)	0.538
Pleocytosis	2 (50%)	1 (7.7%)	0.121
Increased protein level	1 (25%)	3 (23.1%)	1.000

Sunwoo et al., 2015

Anti-$GABA_BR$ encephalitis: seizure

71/F, memory loss and seizure



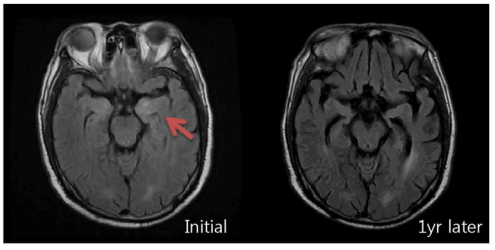
Seoul series

Patient	Presenting symptoms	Tumor	Other antibodies	Immunotherapy	Tumor treatment	Outcome (mRS)	Follow-up (months)
M/62	GTCS, confusion/memory	SCLC	None	IVIg	Chemotherapy (EC #1)	Partial (3→2)	3
F/63	Confusion/memory	SCLC	Anti-Hu	IVIg, prednisolone	Chemotherapy (EP #5) and Definitive radiation (on chest)	Complete (3→0)	3
M/58	GTCS, confusion/memory	SCLC	None	No immunotherapy	Chemotherapy (EP #1) and Definitive radiation (on chest)	Partial (3→2)	At discharge
F/71	GTCS, confusion/memory	SCLC	Anti-Hu	IVIg, prednisolone	Chemotherapy (EC #3)	Partial (3→2)	9
F/64	confusion/memory	-	None	IVIg, prednisolone	No tumor	Complete (2→1)	12

Kim et al., 2014

Anti-Hu: encephalomyelitis (limbic, brainstem, cerebellum, peripheral nerve)

60/M, memory decline, confusion, whole body tingling sense, and gait disturbance, progressing over 2m



Patient video here

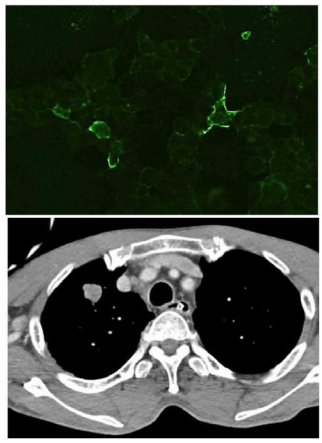
Cancer: Small cell lung cancer, thymic carcinoma

Sx: Sensory polyneuropathy ~ devastating encephalomyelitis (whole CNS)

Anti-AMPAR encephalitis: limbic encephalitis, NMDAR-like

Patient video here

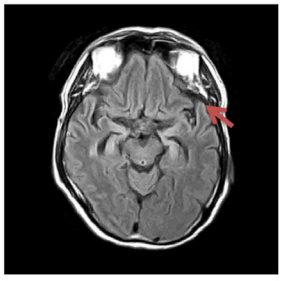
- 66/M
- 2012.1. Memory impairment
- 2012.2 Gait disturbance and abnormal behavior
- 2012.3 Intubated
- 2012.4 Decreased mentality- wax and wane, orofacial-limb dyskinesia, dystonia
- Auto Ab
  - Anti-AMPA2R Ab (+)

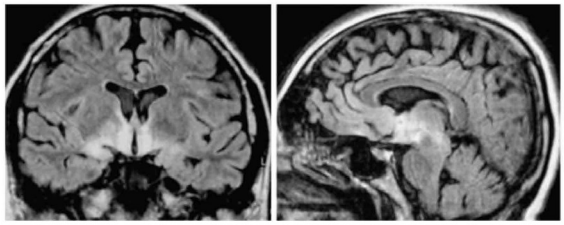


- Lung CT/Bx
  - Small cell lung cancer

Anti-Ma2 encephalitis

76/M, parkinsonism, gaze evoked nystagmus,
memory decline and psychiatric symptoms, over 1m



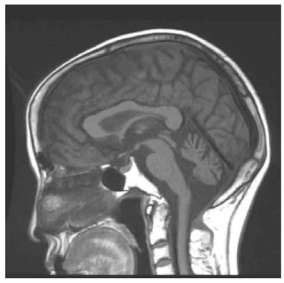


Harrison 19th ed. Figure 122-3

Cancer: Testis, lung, breast, stomach, ...
Sx: brainstem encephalitis (parkinsonism, diplopia, GEN)~ limbic encephalitis

Anti-Yo: cerebellar degeneration

- F/52
- 1년전 2013.6월부터 서서히 진행하는 ataxic gait, dizziness, dysarthria
- 2013.5월 ovarian cancer 로 난소절제 및 항암치료. 치료과정에서 증상 지속 악화

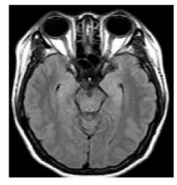


- Anti-Yo=positive

- As> Paraneoplastic cerebellar degeneration
- Cerebellar ataxia: little response to immunotherapy d/t early Purkinje loss

Anti-glycine: PERM (progressive encephalomyelitis with rigidity and myoclonus)

- 38/Female
- URI Sx 이후 아침에 일어나서 멍한 상태.
- CSF normal, EEG F-T sharp wave → AED에 반응없음.
- 진행하는 의식저하, opisthotonus with rhabdomyolysis, orofacial dystonia, hyperekplexia



Patient video here

Patient video here

IVIG/ Rituximab #4 →

Recently proposed diagnostic criteria for possible AE

***Panel 1:* Diagnostic criteria for possible autoimmune encephalitis**

Diagnosis can be made when all three of the following criteria have been met:

1 Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms

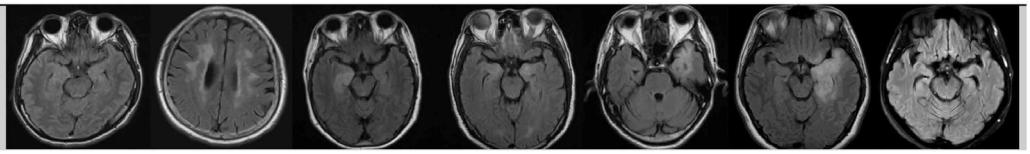
2 At least one of the following:
- New focal CNS findings
- Seizures not explained by a previously known seizure disorder
- CSF pleocytosis (white blood cell count of more than five cells per mm^3)
- MRI features suggestive of encephalitis†

3 Reasonable exclusion of alternative causes (appendix) ← ?

Enable clinical trials
Encourage early immunotherapy.
Limited usefulness for differential diagnosis.

Graus et al., Lancet Neurol, 2016

Tips in differential diagnosis

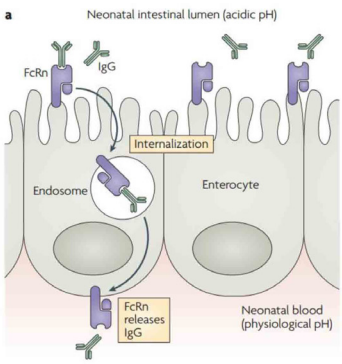
	NMDAR	LGI1	GABAbR	Hu/Ma	Viral (HSV etc)	Glioma	AE-noDAB
							
Fever	Short fever (1~2days)				Prolonged fever (>3 days)		Short fever (1~2days)
Initial MRI	Normal or subtle MRI < Sx	Multifocal MRI =< Sx	Hippocampus MRI < Sx	Hippocampus+ brainstem MRI < Sx	Hemorrhage, swelling, insular+ MRI=Sx	Homogenous, Infiltrative (gray+white), adjacent area+ MRI > Sx	MRI < Sx
F/U MRI	Atrophy (-)	Atrophy (-)	Atrophy (-)	Atrophy (++)	Atrophy ++++ (paper-thining)	No atrophy ~progression	Variable atrophy (-~++)
Course	Progressing >2 weeks	Seizure or months	Seizure	Limbic, brainstem, cerebellum	Progression <2wks	Seizure or months	Progression >2 weeks
Dx	Antibody	Antibody	Antibody	Antibody, cancer	Viral PCR	Resection	Immune response, other auto-Abs

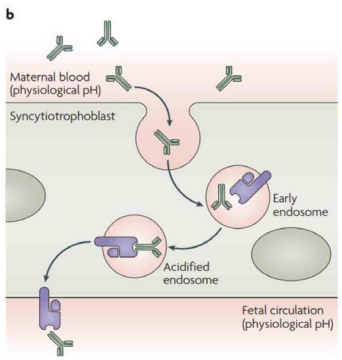
IVIG: mechanism through FcRn

27

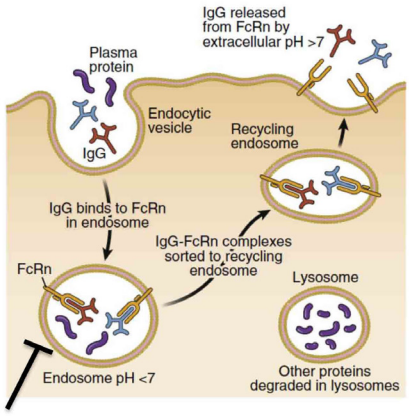
Half life: IgM=5 days, IgG=29 days

Neonatal Fc receptor (FcRn)





IgG degradation



IVIG saturates FcRn

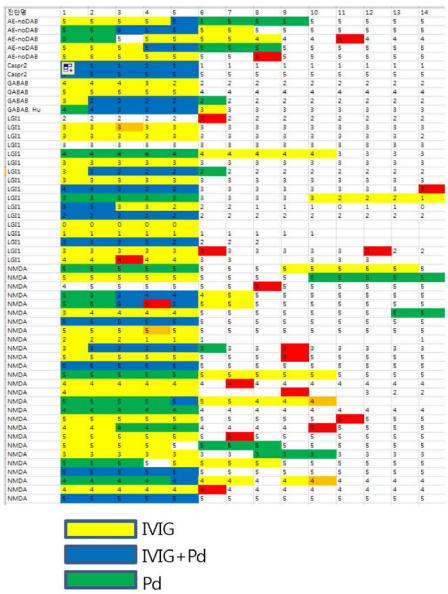
→ Degradation of autoantibody

Roopernian et al., Nat Rev Imm, 2007
Abbas, et al. Basic Immunology 5th edition 2015

Early response to 1st line immunotherapy

AE=55
(NMDA=27, LGI1=17, others 11)

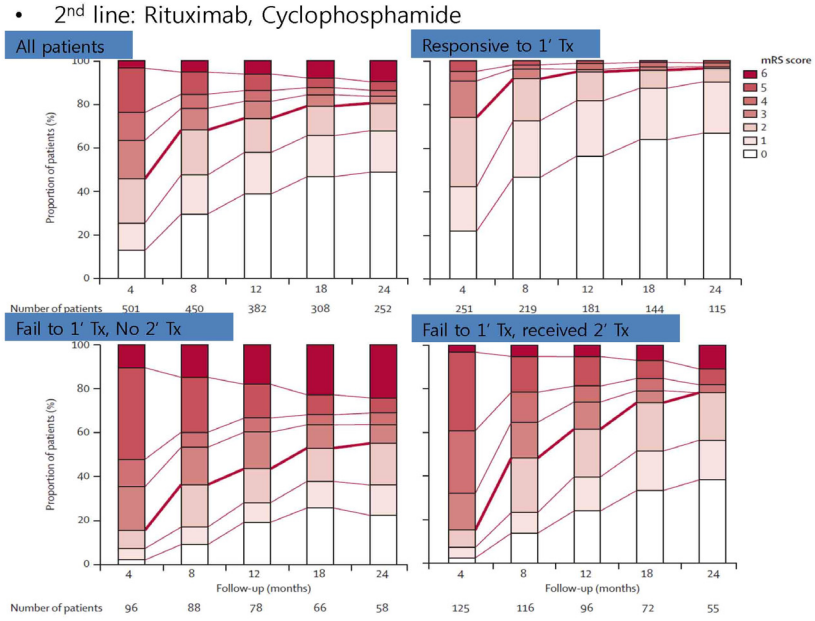
- IVIG (n=9/45): RR=20%
- Pd pulse (n=4/31): RR=12.9%
- IVIG+Pd (n=9/24): RR=37.5%



Jun et al., manuscript in preparation

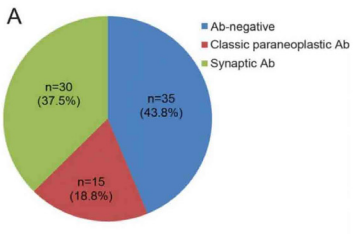
Treatment response of anti-NMDAR encephalitis

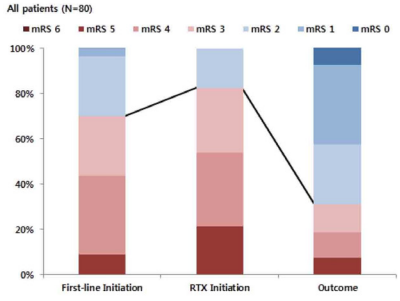
- 1st line: IVIg, Steroid
- 2nd line: Rituximab, Cyclophosphamide

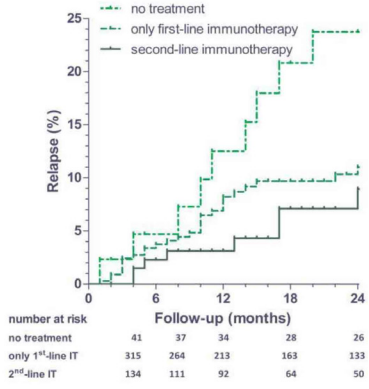


Titulaer et al., Lancet Neurol, 2013

Rituximab in AE: effective % reduction in recurrence



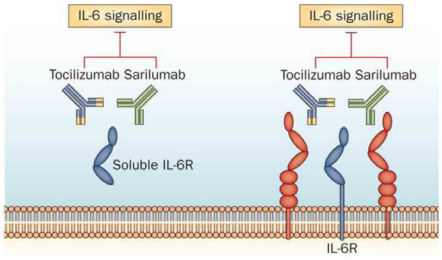


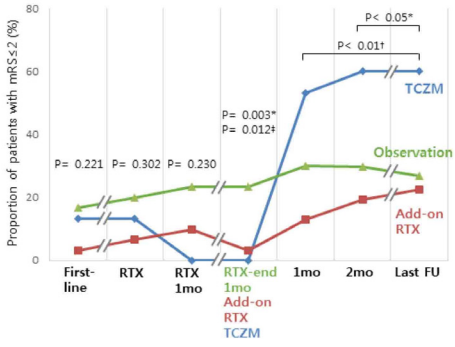


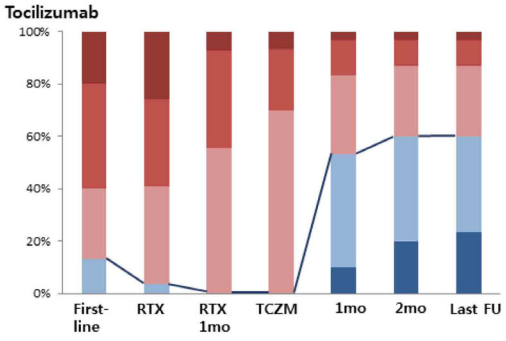
Lee et al., Neurology, 2016

Titulaer et al., Lancer Neurol, 2013

Tocilizumab treatment in AE







Lee et al., Neurotherapeutics, 2016

Detailed regimens

- IVIG
  - 0.4g/kg/day X 5 days → monthly boosting (half dose)
- Steroid pulse
  - mPd pulse for 5 days: no oral Pd maintenance in synaptic AE
- Rituximab
  - 375mg/m2 weekly X 4 weeks → monthly till sufficient improvement
  - Premedication
- Tocilizumab
  - 4mg/kg at week1 → 4mg/kg at week2→ 8mg/kg monthly
  - low dose maintenance (4mg/kg q4w or 8mg/kg q8w), subcutaneous injection
- Cyclophosphamide
  - 750mg/m2 monthly → 500mg/m2 if neutropenia
  - Premedi: hydration, monthly decapeptyl to prevent infertility

Examples of combinations

- IVIG
- IVIG + Steroid pulse
- IVIG + Steroid pulse → Rituximab (+ IVIG)
- IVIG + Steroid pulse → Rituximab + Tocilizumab (+ IVIG)
- IVIG + Steroid pulse → Rituximab + Cyclophosphamide + IVIG

Refractory

- Experimental drugs: IL-2, Bortezomib

Other symptomatic care of AE

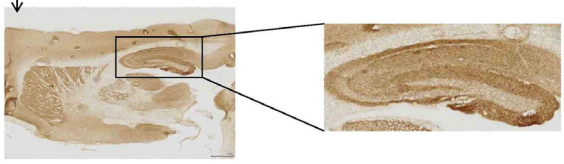
- Anti-NMDAR encephalitis
  - Hypersalivation: botulism toxin injection to salivary gland
  - Autonomic dysfunction (ileus, low BP): pyridostigmine 0.5mg q8hr
  - Loss of circadian rhythm: high dose melatonin
- Anti-LGI1 encephalitis
  - FBDS (faciobrachial dystonic seizure): immunotherapy (AED-refractory)
  - Hyponatremia (70%): avoid oxcarbazepin
  - Psychiatric symptom: avoid levetiracetam

Case #1

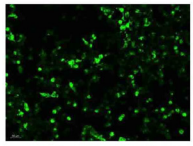
F/28
Visual hallucination, psychiatric symptom, altered mentality, catatonia, seizure, speech dysfunction
Progressing over 3 weeks
EEG: slowing, CSF: normal, MRI: normal
Job: office worker, engaged to be married.
Reasonably excluded other causes

↓

Probable anti-NMDAR encephalitis



Positive immunohistochemistry to rat brain



Positive anti-NMDAR encephalitis

↓

Definite anti-NMDAR encephalitis

Steroid, IVIG, Rituximab weekly#4, Tocilizumab #1

↓

After 4 months, mRS=0, Married

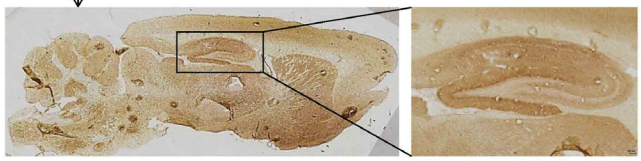
Antibody tests by www.advancednt.co.kr

Case #2

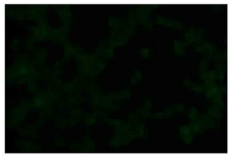
F/23
Left arm dystonic seizure since age 10
A few attacks per 2-3 year (on AED). Admitted via ER for seizure
Mild obsession, normal memory. No psychiatric symptom
Job: university student
MRI, CSF: normal

↓

Not possible AE by the diagnostic criteria



Positive immunohistochemistry to rat brain



Negative cell-based assay for known Ab

↓

AE with unknown antibody

Steroid, Rituximab weekly#4, monthly #2

↓

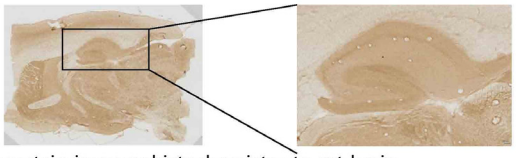
Seizure free. mRS=1

Antibody tests by www.advancednt.co.kr

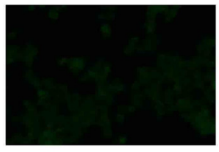
Case #3

M/69
Cognitive dysfunction, psychiatric symptoms, memory decline, hallucination, catatonia/rigidity, parkinsonism, both Babinski sign+ (mRS=5): progressing over 2 month
Known idiopathic Parkinson disease (IPD) on L-dopa for 7years
Job: CEO
MRI: normal, CSF: mild protein elevation only
Reasonably excluded other causes, except aggravation of IPD and L-dopa psychosis

↓ **Possible AE / Brainstem-limbic encephalitis**



Uncertain immunohistochemistry to rat brain



Negative cell-based assay for known Ab

↓ **Not matching to Ab-negative probable AE (MRI/CSF/Biopsy)**
Clinical suspicion of AE-noDAB (AE with no detectable ab)

↓ Steroid, IVIG, Rituximab weekly#4, Tocilizumab #1, Rituximab monthly #3

↓ Normal cognitive function, mRS=1

Antibody tests by www.advancednt.co.kr

Key AEs with high clinical significance

Antigens	Syndrome	Tumor
NMDAR	Psychiatric, seizures, amnesia, aphasia, movement disorder, autonomic instability, coma	10~45% ovarian teratoma (age-dependent), carcinoma
LGI1	Limbic encephalitis, 60% hyponatremia, 70% faciobrachial dystonic seizure	<10% thymoma
Caspr2	Limbic/brainstem encephalitis, 40% Neuromyotonia (Morvan syndrome)	~25% thymoma
GABAbR	Limbic encephalitis (seizure)	~70% SCLC
AMPAR	Limbic encephalitis, movement disorder, psychiatric symptoms	~70% Lung cancer
Hu	Limbic/brainstem encephalitis, sensory polyneuropathy	>95% SCLC, neuroendocrine tumor
Ma	Brainstem encephalitis	>95% Testicular, lung, breast, other
Yo	Paraneoplastic cerebellar degeneration	> 95% Breast, Ovary

Key clinical principles in diagnosis of AE

Go to the bedside, listen, examine, and decide.

- Determine the duration and mode of progression.

- Do not stick to brain MRIs. Most misdiagnoses come from brain MRI

Do rapid antibody tests and full brain autoimmune screening

- Do not delay immunotherapy to wait antibody test results

- Do not treat the antibodies, but treat the patients.

Consider IVIG first, if viral is not excluded

- Explain the patient and family about the concept of empirical immunotherapy

- Consider side effects of immunotherapy (disseminated infection)

Biopsy sometimes helpful: i.e. brain biopsy- CD3 >CD20 infiltration, viral

After empirical treatments, continue the differential diagnosis