5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 9

Antibodies: From autoimmune encephalitis to paraneoplastic myelopathies (Level 2)

Autoimmune encephalitis

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Autoimmune Encephalitis

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Disclosures

Received research funds for serving at the scientific advisory board of MedImmune, LLC, and for consultancy for Guidepoint, Global, LLC

Received an unrestricted research grant from Euroimmun AG, and CSL Behring

Erasmus MC has filed a patent for $GABA_BR$ diagnostics

Will discuss unlabeled use of different immunotherapeutics

ENCEPHALOMYELITIS WITH CARCINOMA

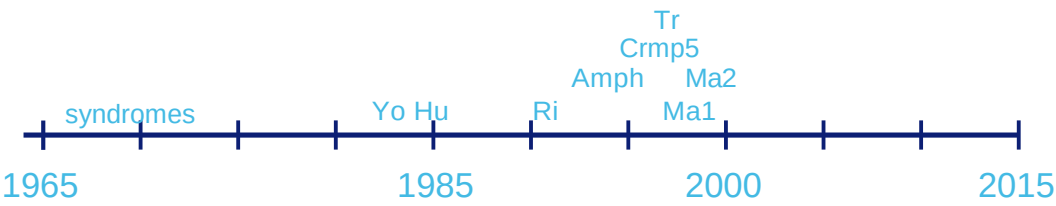
BY

R. A. HENSON, THE LATE H. LOVELL HOFFMAN AND H. URICH

(*From the London Hospital*)

Brain 1965

LE, cerebellar degeneration almost all cancer related, poor response to therapy → Intracellular antigens: Cytotoxic T cells (and antibodies)



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Case 1: H. (65-year old woman)

- 2 months progressive diplopia, vertigo, nausea, fatigue; later dysarthria, tremor face
- Progressive walking difficulties and somnolence; apneas with respiratory insufficiency, and intubation → ICU, transfer
- PMH: glaucoma Medication: none Intoxications: smoking ++
- Alert, snout reflex +, glabella top reflex +, abduction ↓ ODS, opsoclonus ODS. Facial diplegia. Action myoclonus face. Proximal paresis arms/legs MRC 4. Ataxia R > L. Hyperekplexia

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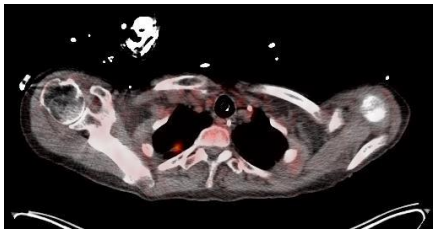
Case 1: H. (65-year old woman)

- LP: OD 14cm H_20, 3 WBC, TP 0.19, glucose 4. IgG index 0.73
- MRI: normal ; EMG: no signs of MG
- Blood: ANA/ANCA-, ACE low, AChR/MuSK-, PNS- (Hu, Ri, Yo, Tr, Ma1/2)
- CT-thorax/abdomen: normal
- CSF: anti-Ri antibodies +
- Plasmapheresis (5x)
- FDG-PET
- Wedge resection: NSCLC
- 3 days ivMP
- Within 3 weeks from admission discharged home



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Case 1: Lessons

- General tests in CSF (WBC, TP) can be normal
- Antibodies can be present only in CSF
- In cases with high suspicion, FDG-PET has additional value
- Tumor treatment is essential
  - Karnofsky PS due to PNS is not a reason to withhold treatment
- In classical PNS prognosis is generally poor, but not always
  - especially Ma2 and Ri

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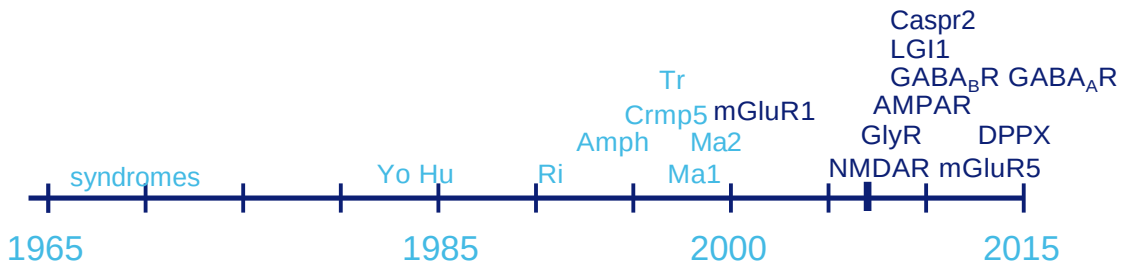
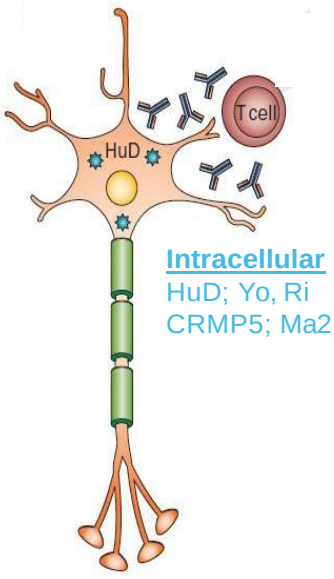
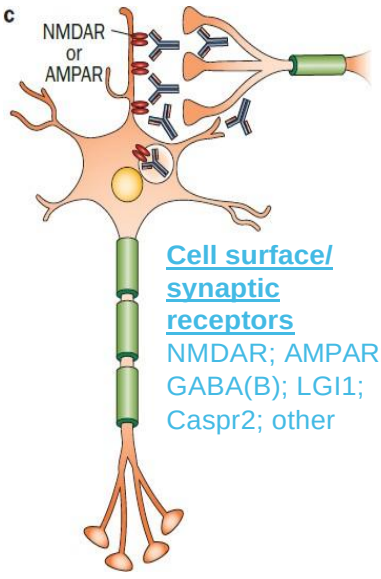




Intracellular
HuD; Yo, Ri
CRMP5; Ma2



Cell surface/ synaptic receptors
NMDAR; AMPAR; GABA(B); LGI1; Caspr2; other

Lancaster and Dalmau, Nat Review Neurol 2012

Case 2: 17-year old girl (1)

Odd behavior, rude on Whatsapp to teachers, paranoid

In days progressive, speaking less; headache → 1st psychosis?

Start antipsychotics → EPS

→ Some catatonia

Tonic–clonic seizure

No fever. CT-brain and CSF normal. → Aciclovir

MRI-brain normal

PCR HSV1 negative

EEG: slow, mostly temporal region

Case 2: 17-year old girl (2)

Diagnostic criteria of anti-NMDAR encephalitis

Fulfilled criteria for "probable" anti-NMDAR encephalitis *

Probable*

Rapid onset (<3 months) of at least 4 of the 6 major groups of symptoms:

→ a. Abnormal (psychiatric) behaviour or cognitive dysfunction

→ b. Speech dysfunction (pressured speech, verbal reduction, mutism)

→ c. Seizures

→ d. Movement disorder, dyskinesias, or rigidity/abnormal postures

e. Decreased level of consciousness

f. Autonomic dysfunction or central hypoventilation

and at least 1 of the laboratory studies:

→ a. Abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush)

b. CSF with pleocytosis or oligoclonal bands

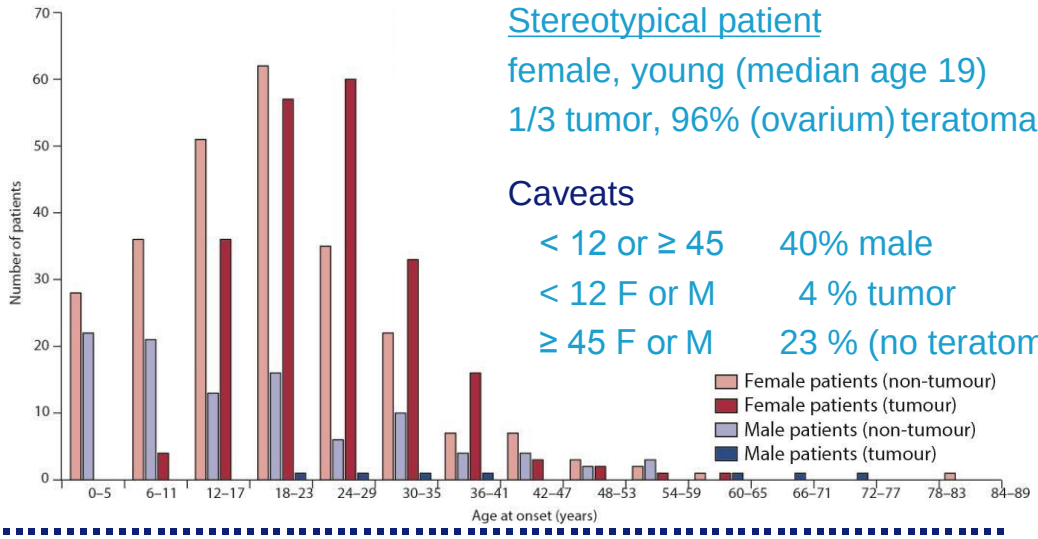
Start immunotherapy

or

Three of the above groups of symptoms and identification of a systemic teratoma

* Graus *et al.* Lancet Neurology 2016

Anti-NMDAR encephalitis: epidemiology



Stereotypical patient

female, young (median age 19)

1/3 tumor, 96% (ovarium) teratoma

Caveats

< 12 or ≥ 45	40% male
< 12 F or M	4 % tumor
≥ 45 F or M	23 % (no teratomas)

Titulaer *et al.* Lancet Neurol 2013

Anti-NMDAR encephalitis: clinical phenotype

Clinical worsening

prodrome

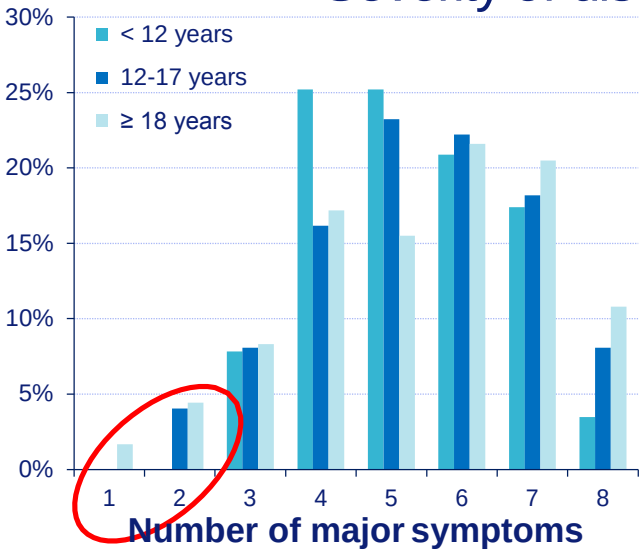
agitation, psychosis, catatonia, memory deficit speech reduction, Abnormal movements +/- seizures

coma, hypoventilation, +/- dysautonomia

Clinical improvement

Dalmau *et al.* Lancet Neurol 2011;Titulaer *et al.* Lancet Neurol 2013

Severity of disease



ICU stay 76%

maximum modified Rankin Scale (mRS) of 5 87%

Titulaer *et al.* Lancet Neurol 2013

Sensitivity and specificity

	serum	CSF
Sensitivity	*~70%*	100%
Specificity	97-99%	100%

0.4 - 3% healthy patients

CBA, without conformational tests

Simple calculation:

Purely psychiatric

- Prior chance ~ 1%

Serum positive:

- Post chance ~ 50%
- CSF confirmation**!**

Gresa, Titulaer *et al.* Lancet Neurol 2014
Viacozz *et al.* Neurology 2014
Hammer *et al.* Mol Psych 2013

When to suspect NMDARE in psychiatry ward?

- Test in patients with new-onset psychosis, be cautious for (subtle) neurological symptoms; chance of NMDAR-antibodies will decrease sharply without additional symptoms < 4 weeks

Titulaer & Dalmau, Lancet Neur 2013

Red flags:

- Neurological symptoms (seizures, mutism)
- Autonomic disturbances (fever, tachycardia)
- Catatonia
- Extrapyramidal side effects antipsychotics
- Other AID

- Confirm positive serum test in CSF and/or by IHC
- If suspect, test CSF if serum is negative

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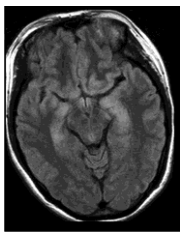
Diagnostics

CSF: 79% abnormal

- Lymphocytic pleocytosis
  WBC 32 (6-511) 75%
- Raised total protein 18%
- Oligoclonal bands 53%

MRI:

33% abnormal

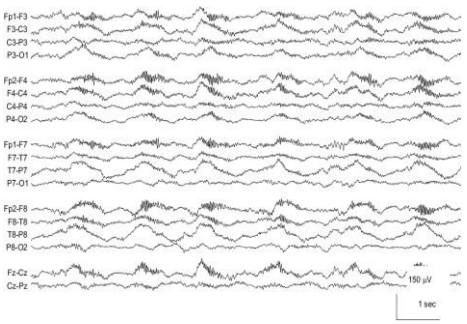


Dalmau *et al.* Lancet Neurol 2008

Titulaer *et al.* Lancet Neurol 2013

EEG: 89% abnormal

- Extreme Delta Brushes ~10%



Schmitt *et al.* Neurology 2012
Armangue *et al.* J Ped 2012
Van Sonderen *et al.* JNNP 2018

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Case 2: 17-year old girl (3)

ivMP → Progression, needed fixation

IVIg → Progression to mute and somnolent

NMDAR-abs in serum and CSF

US/MRI-pelvis: no ovarian teratoma

Two weeks in, and no improvement → what to do?

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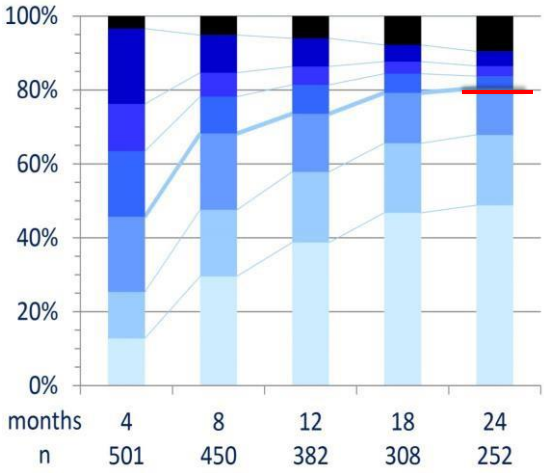
Long-term outcome



Titulaer *et al.* Lancet Neurol 2013

Modified Rankin Scale (mRS)

- 0 No symptoms.
- 1 No significant disability. Able to carry out all usual activities.
- 2 Slight disability. Independent in activities of daily living (ADL).
- 3 Moderate disability. Needs some help, but able to walk unassisted.
- 4 Moderately severe disability. Requires assistance, and unable to walk unassisted.
- 5 Severe disability. Requires constant nursing care and attention, bedridden.
- 6 Dead.

Van Swieten *et al.* Stroke 1988

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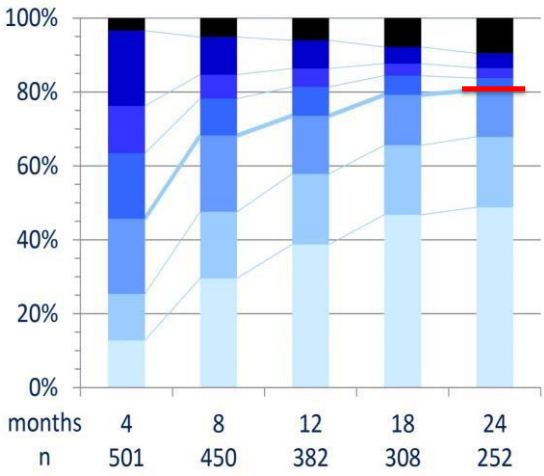
Long-term outcome



Better outcome

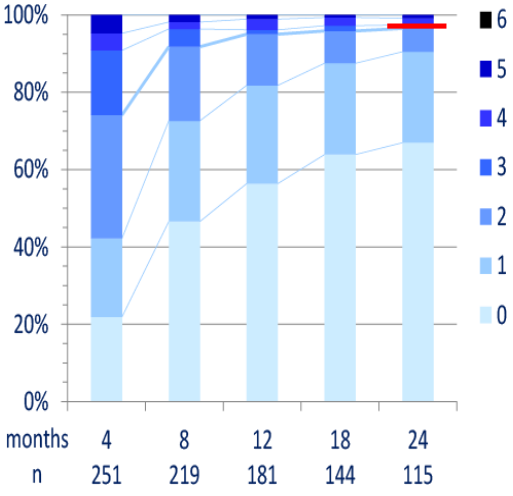
- no ICU stay
- shorter time until treatment
- longer follow-up

(until 18 months)

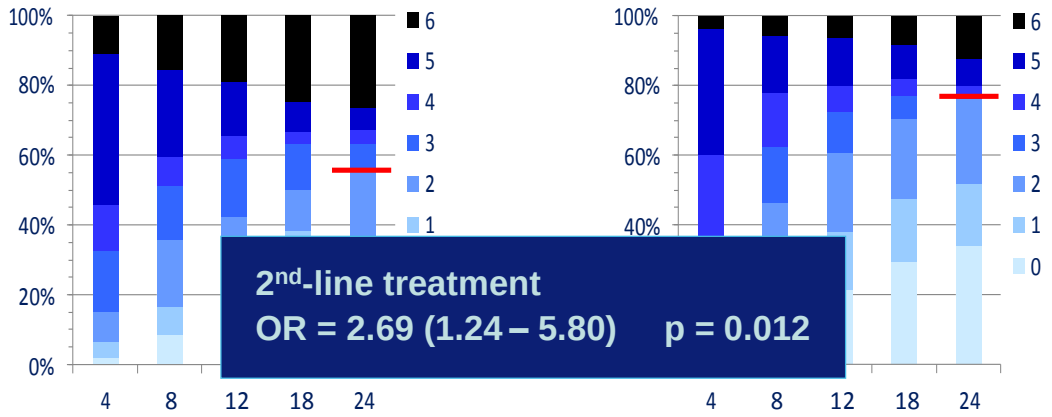
All significant in multivariate analysis

Titulaer *et al.* Lancet Neurol 2013

Early responders have good long-term outcome



Efficacy of 2nd-line treatment in non-responders



Follow-up (months)

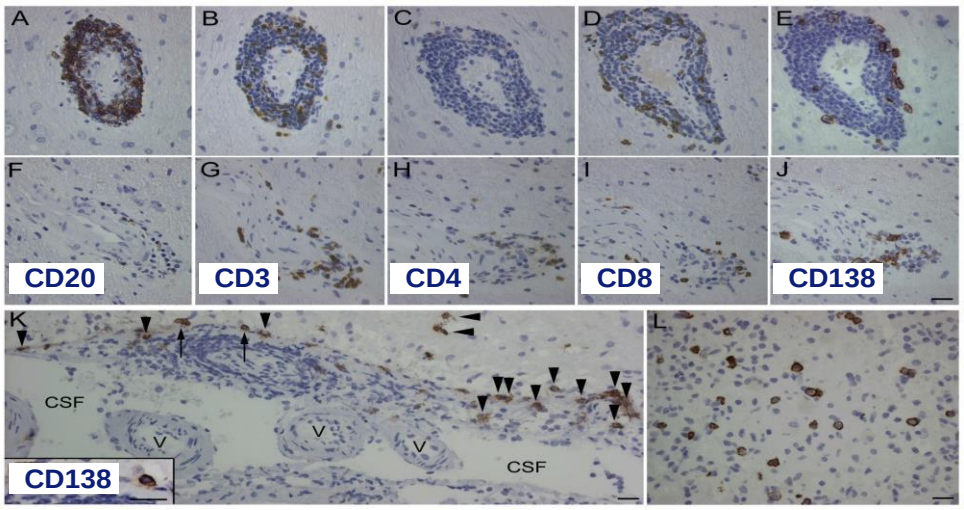
no 2nd-line treatment

Follow-up (months)

rituximab / cyclophosphamide

Titulaer *et al.* Lancet Neurol 2013

Plasma cells in PA brain of patients

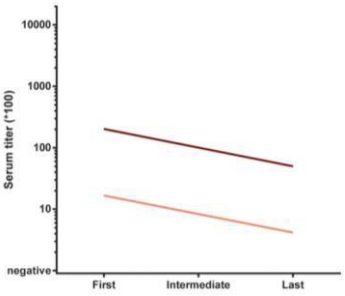


Martinez-Hernandez *et al.* Neurology 2011

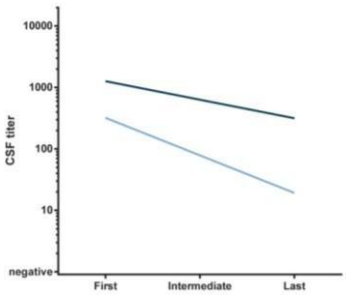
Biomarkers for outcome?

Antibody titers (median decrease)

Serum



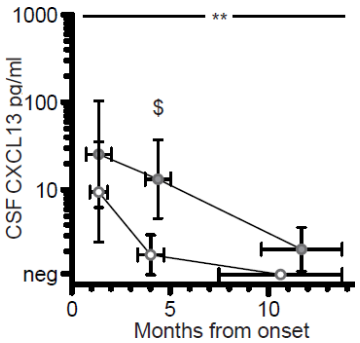
CSF



Gresa, Titulaer *et al.* Lancet Neurol 2014

CXCL13

CSF



Leypoldt, Höftberger *et al. JAMA* Neurol 2014

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Anti-**N**MDAR **E**ncephalitis **O**ne Year Functional **S**tatus score

Item	Odds Ratio	P-value	NEOS
ICU admission	5.89	0.001	1
No treatment effect <4 weeks	12.10	< 0.001	1
No treatment <4 weeks of onset	2.52	0.002	1
Abnormal MRI	2.20	0.009	1
CSF > 20 cells	2.10	0.019	1
NEOS score			**0-5**

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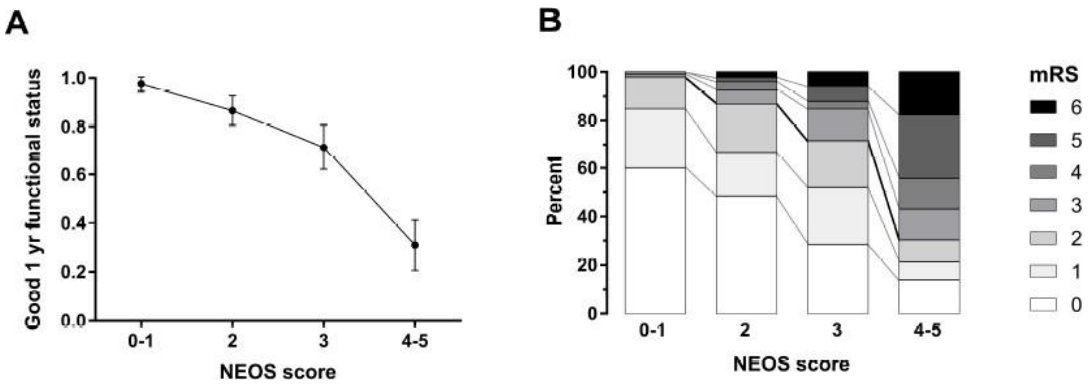
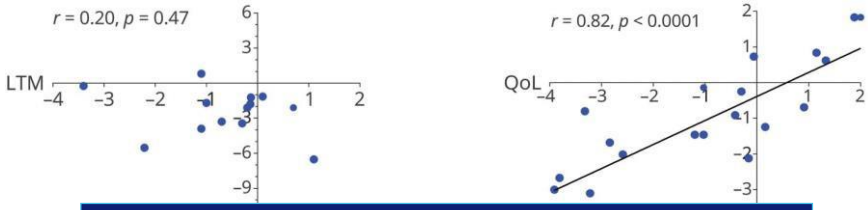
Balu *et al.* Neurology 2018

Prediction: NEOS



Balu *et al.* Neurology 2018

However, we should do better



64% returned to same school level

Domain	Z-score	p-value
Attention	-2.10 (-2.71 – -1.48)	< 0.0001*
Long-term memory	-0.68 (-1.29 – -0.07)	0.031
Fatigue	-0.96 (-1.64 – -0.28)	0.008 *
QoL	-0.86 (-1.84 – -0.08)	0.032

* Significant after multiple correction

De Bruijn *et al.* Neurology 2018

Case 2: 17-year old girl (4)

Just before start Rituximab, started improving

ivMP after 4 and 8 weeks → recovery over months

8 months later: OT identified, and removed

Lessons

- Exclude other diagnoses (a.o. HSV1 encephalitis)
- Start treatment early, if diagnosis is very probable
- Avoid haloperidol for risk of Malignant Neuroleptic Syndrome
- Consider pulse steroids to diminish behavioral side effects
- Do not forget to screen again, even if patient improves

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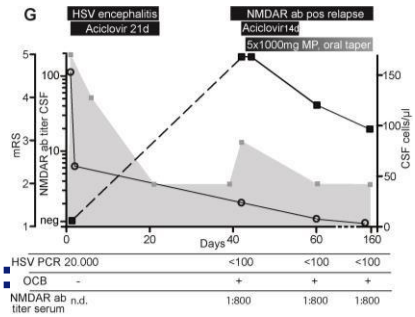
"Choreoathetosis post-HSVE" is anti-NMDAR encephalitis



More patients followed.. up to 25%

Armangué *et al.* J Pediatrics 2012
Leypoldt *et al.* Neurology 2013
Armangue *et al.* Neur 2015

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Case 3: L. (68-year old male)

In one week 5 GTC seizures, start phenytoin

Rapidly progressive memory loss, disinhibition and confusion

Waxing and waning somnolence

PMH: prostate carcinoma (4 years ago, hormonal therapy)

CSF 3 cells, TP **0.67**

MRI: normal

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Case 3: L. (68-year old male)

Serum: **$GABA_BR$**, and also KCTD16 antibodies

Steroids, IVIg

CT-thorax: SCLC → Cisplatin, Etoposide

Very good recovery

Recurrence SCLC 26m later

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Antibodies to the $GABA_B$ receptor in limbic encephalitis with seizures: case series and characterisation of the antigen

Eric Lancaster, Meizan Lai,* Xiaoyu Peng, Ethan Hughes, Radu Constantinescu, Jeffrey Raizer, Daniel Friedman, Mark B Skeen, Wolfgang Grisold, Akio Kimura, Kouichi Ohta, Takahiro Iizuka, Miguel Guzman, Francesc Graus, Stephen J Moss, Rita Balice-Gordon, Josep Dalmau*

Median ~60 years (16-85), male-female ~50-50%

50-60% lung carcinoma (SCLC)

Onset

60% seizures

40% cognition / behavior

Lancaster *et al*. Lancet Neur 2010
Boronat *et al*. Neur 2011
Jeffery *et al*. Neur 2013
Hoftberger *et al*. Neur 2013
Kim *et al.* J Neuroimm 2014

Van Coevorden-Hammeete, De Bruijn *et al*. Brain 2019

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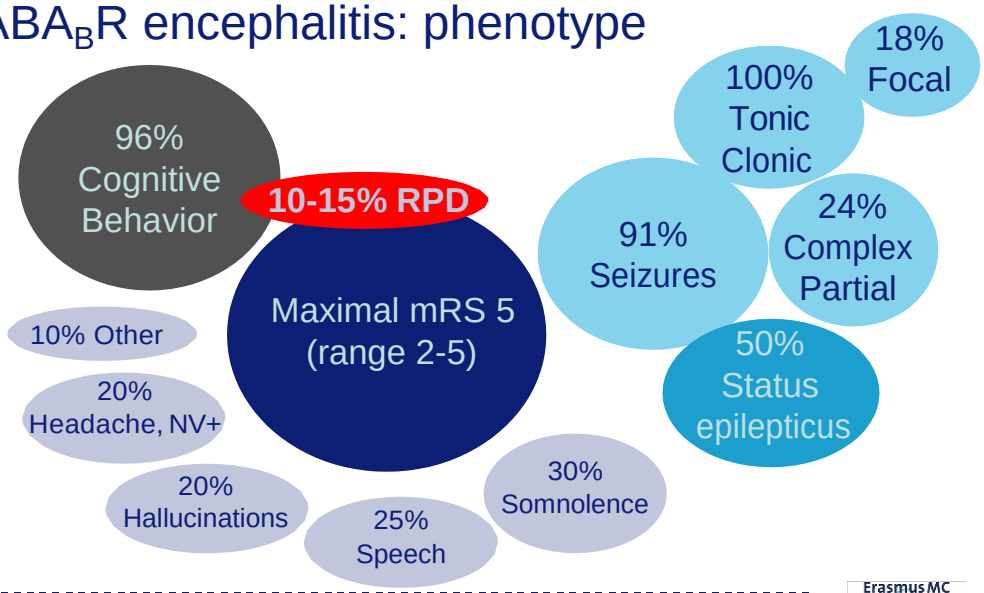
Anti-$GABA_BR$ encephalitis: phenotype



Van Coevorden-Hammeete, De Bruijn *et al*. Brain 2019

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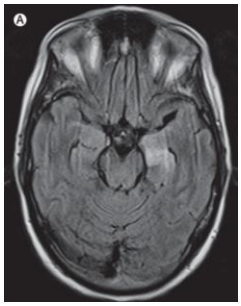
Anti-$GABA_BR$: ancillary testing

MRI: 50-70% temporal FLAIR hyperintensity
30-50% normal or aspec wma

EEG: 85% encephalopathic
30% epileptiform discharges
15% normal

LP 85% pleocytosis (7-192 cells)
30% raised TP
0-12% normal

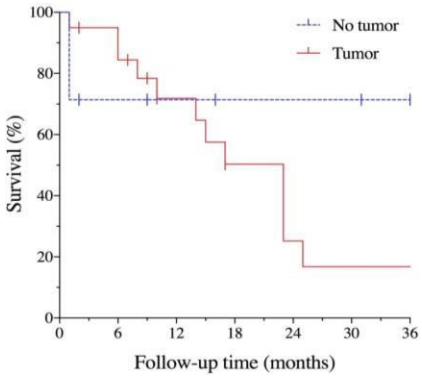
Antibodies in serum and liquor
sensitivity commercial test CSF ~ 80%



Van Coevorden-Hammeete, De Bruijn *et al*. Brain 2019

Anti-$GABA_BR$: outcome

- Tumor treatment essential
- Response to treatment >90%
  - complete or partial
  - cognition and behavior
  - no chronic epilepsy



De Bruijn *et al*. Neurology 2019; Van Coevorden-Hammeete *et al*. Brain 2019

Case 4: V (69-year old male)

PMH: 2014 urothelial cell carcinoma → cystectomy
2018 lymphangitic metastases → Pembrolizumab

After second course: R arm flexing and lifting; also movement mouth; infrequently L side

After 2w also leg movements (3x near falls, 1x fall). Few seconds, no pain. Multiple times per hour. Spouse: slightly amnestic and depressed

Exam: Few episodes observed R-arm/-leg/-mouth, 1-2 seconds; 1x L arm and –mouth

MRI: normal

serum VGKC 361, LGI1 +

LP: 1 WBC, TP 0.43, Pathology normal

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Pembrolizumab (anti-PD1 monoclonal antibody)

- Immune checkpoint inhibitor
- PD1 (Programmed Death-1)
  - Inhibition T-cell response
  - Downregulation immune response
  - Expression tumors 'useful' → escape immune response
- Anti-PD1
  - Anti-tumor effect
  - Activation immune system → autoimmunity
    - 73%, of which 27% severe
    - Skin, gastrointestinal, endocrine, lung

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Pembrolizumab (anti-PD1 monoclonal antibody)

- Neurological autoimmunity
  - Described in 2.9 - 4.2% (increase expected)
  - Polyneuropathy (GBS/CIDP), myasthenia, myositis
  - Encephalitis, cerebellar ataxia

- Treatment
  - Cessation anti-PD1
  - Steroids
  - If necessary consider more aggressive immune therapy

Zimmer *et al*. Eur J Cancer 2016 Kao *et al.* JAMA Neurology 2017

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Anti-VGKC encephalitis is outdated

"VGKC-complex antibodies"

- LGI1 → Limbic encephalitis
- Caspr2 (less frequent) → Limbic encephalitis, Morvan's syndrome, neuromyotonia
- Double negative (30-92%) → No clinical relevance *

Lai, Huijbers *et al.* Lancet Neurol 2010 Irani *et al.* Brain 2010
Lancaster *et al.* Ann Neur 2011 Gadoth *et al.* Ann Neur 2018
* Van Sonderen *et al.* Neurology 2016
* Lang *et al.* JNNP 2017

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Anti-LGI1 encephalitis

- Epidemiology
  - 65% male
  - median age 60 (30-80)
- Tumors 5-10%

  (thymoma, breast carcinoma, renal cellcarcinoma, mesothelioma)
- Serum more sensitive than CSF (especially commercial CBA)

Lai *et al.* Lancet Neur 2010; Irani *et al.* Brain 2010; Van Sonderen *et al.* Neur 2016

Anti-LGI1 encephalitis: seizures

	FBDS
N patients	45%
Duration	< 15 seconds
Seizure Frequency	Median: 40/day Range: 10-100/d
Start compared to cognitive sympt	Before (67%) 3 weeks before
EEG	Undetectable

Courtesy of Dr. de Beer

Van Sonderen *et al.* Neurology 2016

Anti-LGI1 encephalitis: seizures

	FBDS	Focal seizures (no FBDS)
N patients	45%	66%
Duration	< 15 seconds	Median: 25 sec
Seizure Frequency	Median: 40/day Range: 10-100/d	Median: 12/day Range: 1-150/day
Start compared to cognitive sympt	Before (67%) 3 weeks before	Before/ simult (90%); 1.5 week before
EEG	Undetectable	Often detectable

Van Sonderen *et al.* Neurology 2016

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Anti-LGI1 encephalitis: seizures

	FBDS	Focal seizures (no FBDS)	Tonic-clonic seizures
N patients	45%	66%	63%
Duration	< 15 seconds	Median: 25 sec	
Seizure Frequency	Median: 40/day Range: 10-100/d	Median: 12/day Range: 1-150/day	Median: 3 in total Range: 1-100
Start compared to cognitive sympt	Before (67%) 3 weeks before	Before/ simult (90%); 1.5 week before	Simultaneously/ after (78%); 0.5 week later
EEG	Undetectable	Often detectable	Detectable

Van Sonderen *et al.* Neurology 2016

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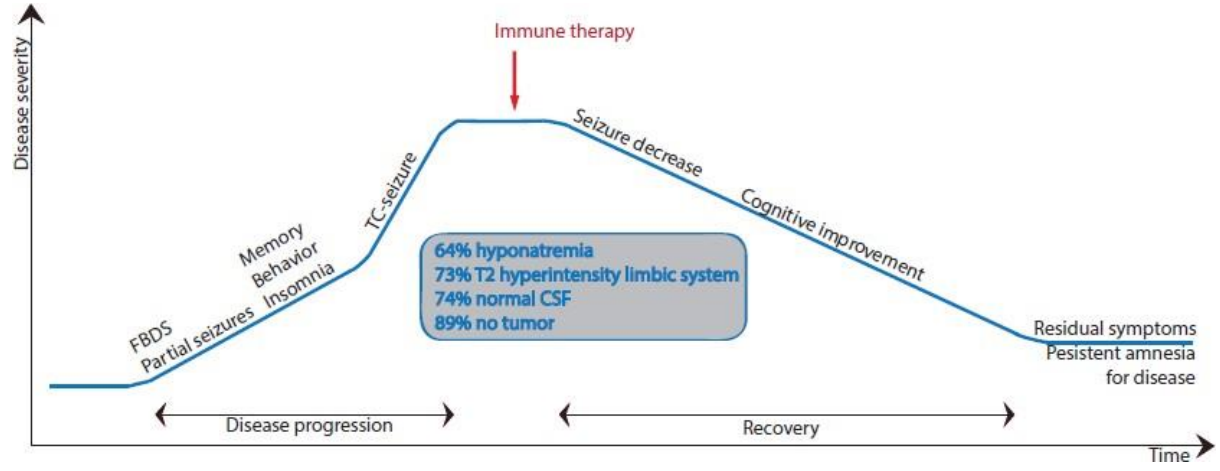
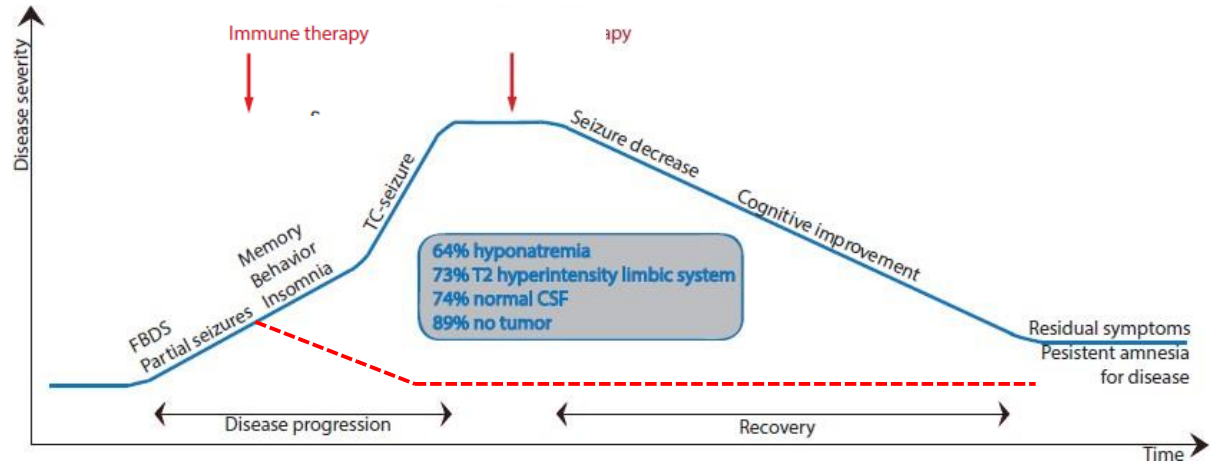
Anti-LGI1 encephalitis: course



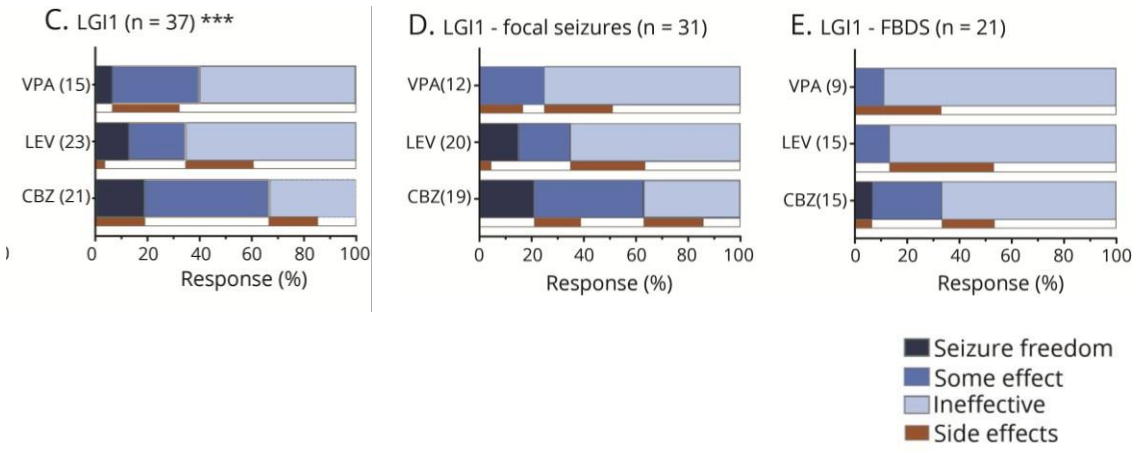
Van Sonderen *et al.* Neurology 2016

Anti-LGI1 encephalitis: course



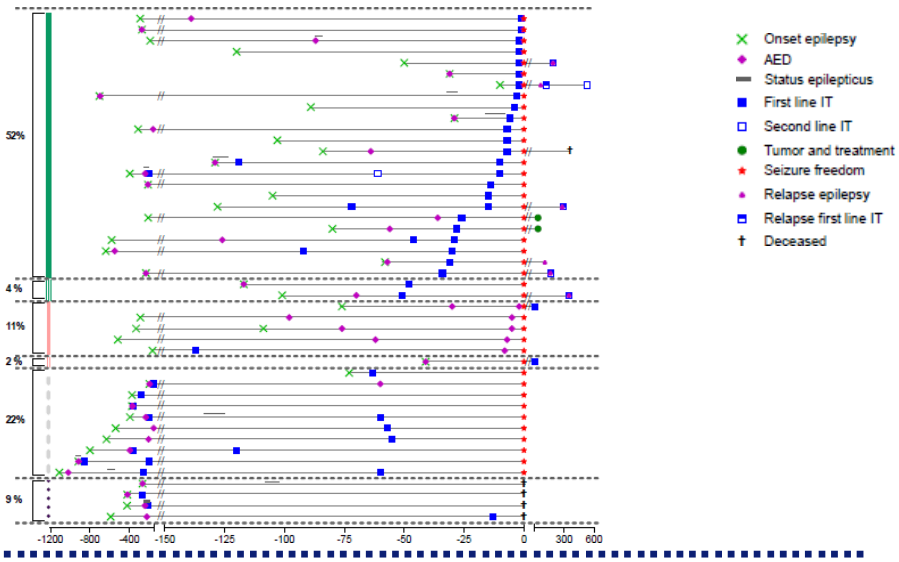
Van Sonderen *et al.* Neurology 2016

Treatment: what anti-epileptic drug to use?



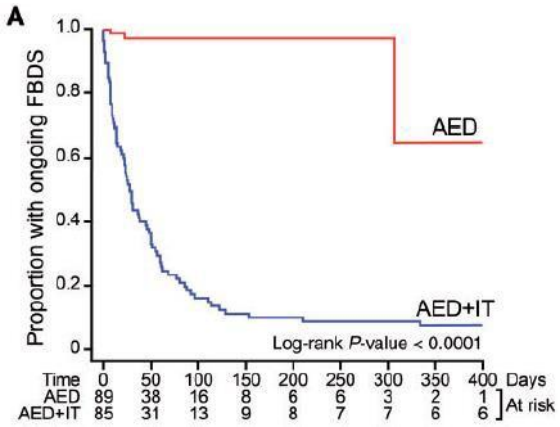
De Bruijn *et al*, Neurology 2019

Immunotherapy works better than anti-epileptic drugs



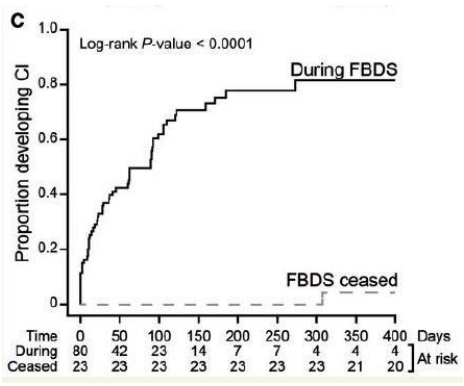
De Bruijn *et al*, Neurology 2019

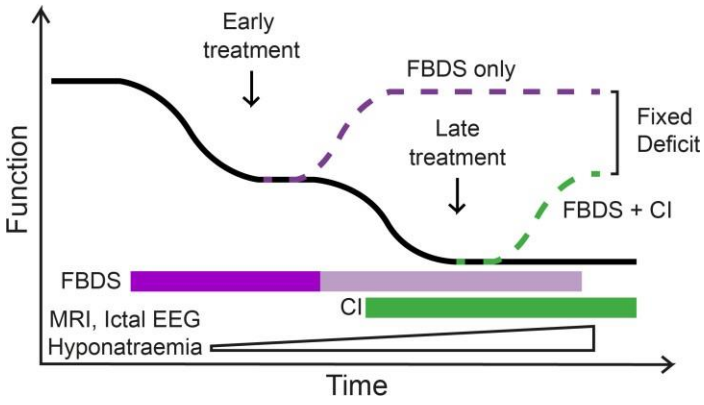
Immunotherapy works better than anti-epileptic drugs



Thompson *et al.* Brain 2018

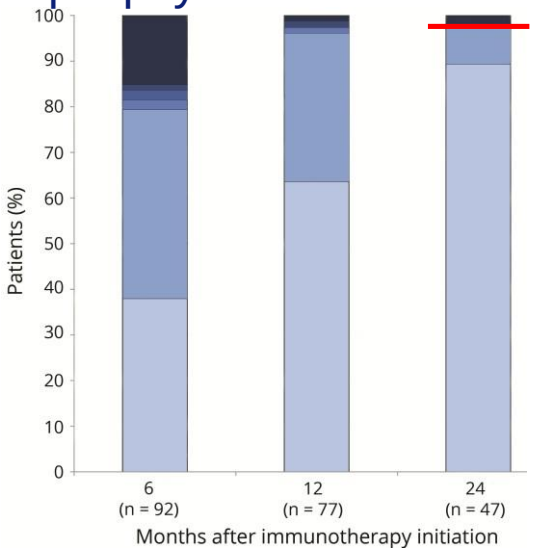
Treating early prevents cognitive deficits





Thompson *et al.* Brain 2018

Epilepsy after resolved encephalitis is rare



Not seizure-free
- AEDs
- Due to relapse
- No AEDs

Seizure-free
- < 3 months after relapse
- AEDs
- no AEDs

Anti-LGI1

Anti-NMDAR

Anti-$GABA_BR$

De Bruijn *et al*, Neurology 2019

Case 4: V (69-year old male)

Pembrolizumab discontinued,

Steroids and IVIg

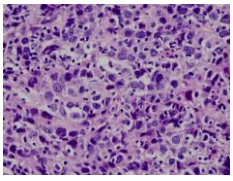
<u>Eight months later</u>:

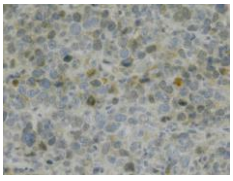
Recurrence tumor

Pembrolizumab restarted

Also prednisone 15mg

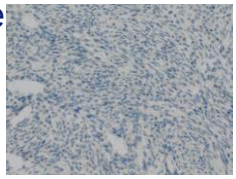
HE tumor

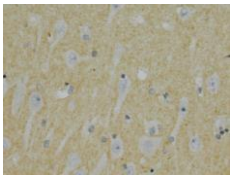




Lgi1 tumor

negative control ovary





positive control brain

Antigen	Syndrome and main features
NMDAR	Anti-NMDAR encephalitis
LGI1	Limbic encephalitis, myoclonus, hyponatremia
Caspr2	Encephalitis and/or neuromyotonia, Morvan's
$GABA_BR$	Limbic encephalitis with prominent seizures, status epilepticus
$GABA_AR$	Limbic encephalitis with prominent seizures, status epilepticus
AMPAR	Limbic encephalitis, psychosis
DPPX (Kv4.2)	Hallucinations, agitation, myoclonus, tremor, diarrhea, weight loss
GlyR	Stiff-person syndrome, hyperekplexia, PERM
IgLON5	Abnormal sleep and behavior, dysphagia, ataxia, chorea
mGluR1	Cerebellitis (+/- Hodgkin's Disease)
mGluR5	Ophelia syndrome

Graus *et al.* Lancet Neur 2016 Leypoldt *et al.* Ann NY Acad Sci 2015

Erasmus MC

Take home messages

- ✓ Autoimmune encephalitis are treatable diseases
- ✓ AIE occur at all ages, *-itis* can be less specific
  - ✓ Know the phenotypes
- ✓ Tumor treatment essential
- ✓ New treatments pose new risks
- ✓ Every patient deserves a chance
- ✓ Treatment can be difficult, but is often rewarding

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