the antibody-mediated encephalitis spectrum in neuropediatric care

Am J Psychiatry, 2013

15-year-old girl
NMDAR encephalitis
higher cortical dysfunctions
- imaginary representation
- praxis
- language

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CNS: autoantibodies

other Abs and diseases?

neuromyelitis optica
- anti-AQP4
- anti-MOG
- other?

ADEM
- anti-MOG in children
- not in adults…
- other?

multiple sclerosis
- type II MS (PLEX)
- anti-MOG (low titer)
- anti-MOG in plaques
- complement-dep. dem Abs

neuronal surface antibody syndromes

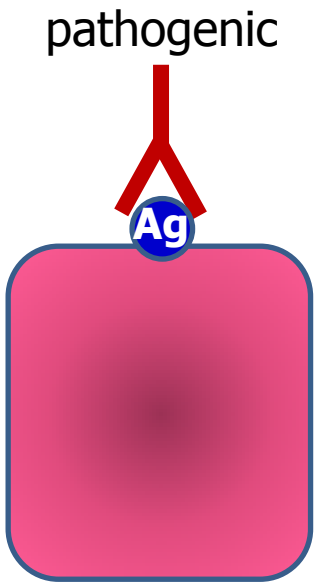
limbic encephalitis

encephalitis

isolated?
(e.g. epilepsy, psychosis, autism, narcolepsy, etc.)

acquired demyelination syndromes
(with anti-MOG, anti-AQP4.)

neuronal surface antibody syndromes (NSAS)



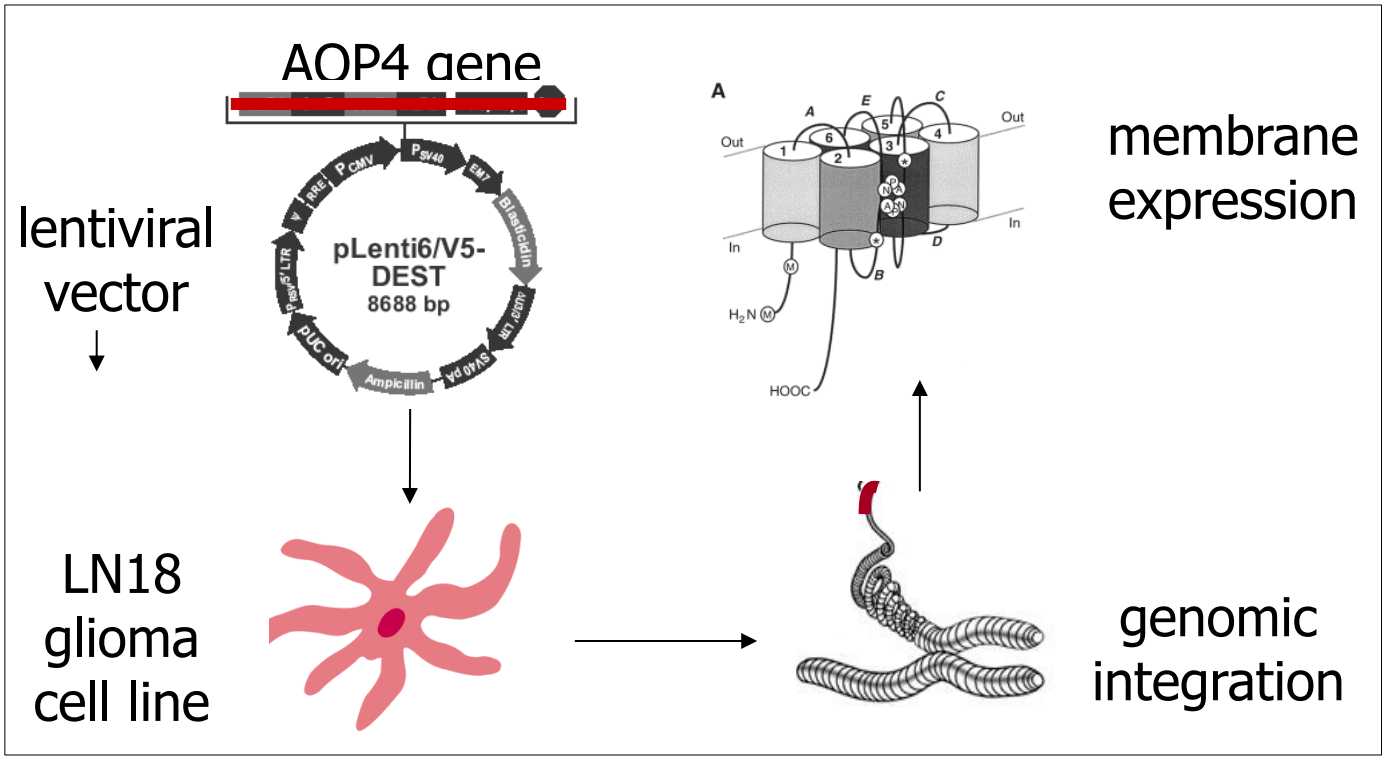
- epitopes are extracellular
- Abs alter function or structure of the Ag
- effects of Abs are often reversible
- clinical picture corresponds to genetic or pharmacologic models
- Ag is often receptor or synaptic protein: transmission, plasticity

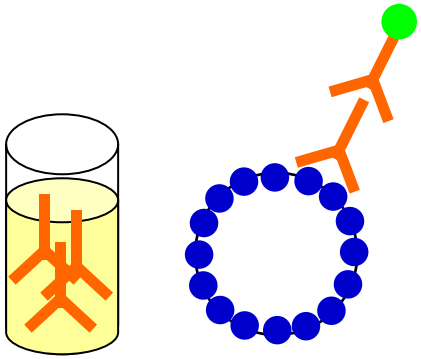
- antibody binding using cells transfected with target Ag

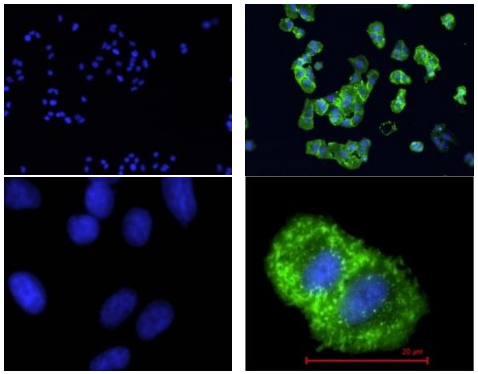
commonly with limbic encephalitis

cell-based assay (CBA)

Arch Neurol, 2010, 67:1201-1208







testing: method and body fluid

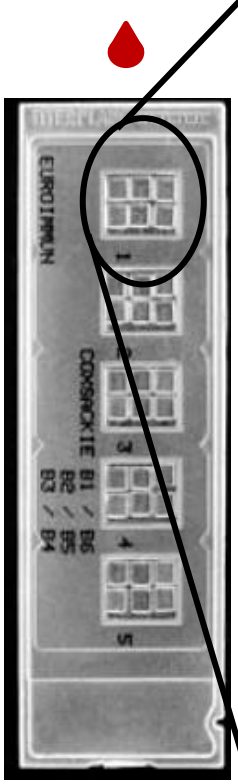
cell-based assay

- CSF: 100% positive with all methods
- serum: 6-13% negative depending methods
- antibody titers are higher in CSF
- **test both serum and CSF**
- if serum is negative CSF may be positive
- if serum positive, CSF negative:
  - test again or use other method (false positive?)

no commercial testing:

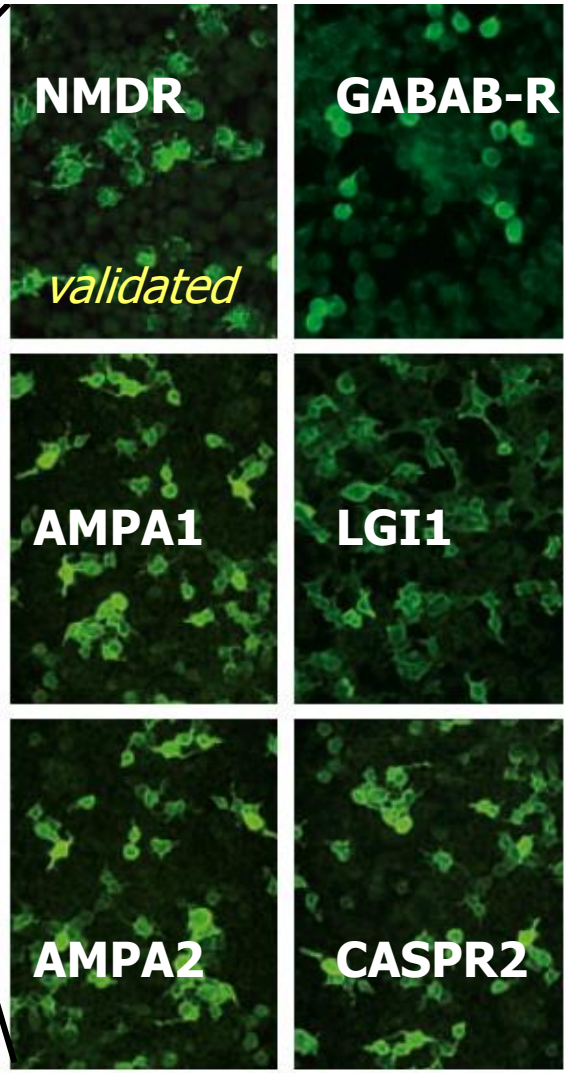
- GlyR
- mGluR5
- D2R
- DPP6 (Kv4.2)
- (anti-MOG)

Lancet Neurol, 2013, 13:167



Euroimmun biochip
one serum:
Abs against 5 antigens

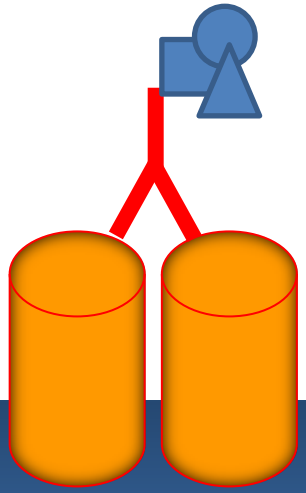
transfected HEK293 cells:
antibodies against



effect of antibodies

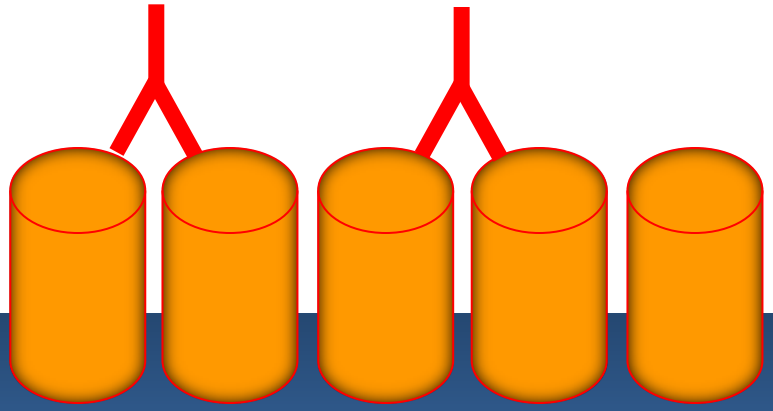
anti-VGKC complex

complement

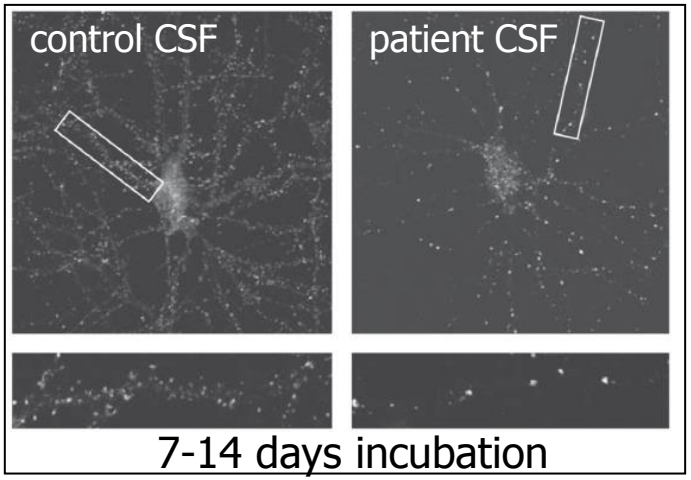


anti-NMDAR and others: along dendrites

anti-$GABA_AR$: selectively at synapses

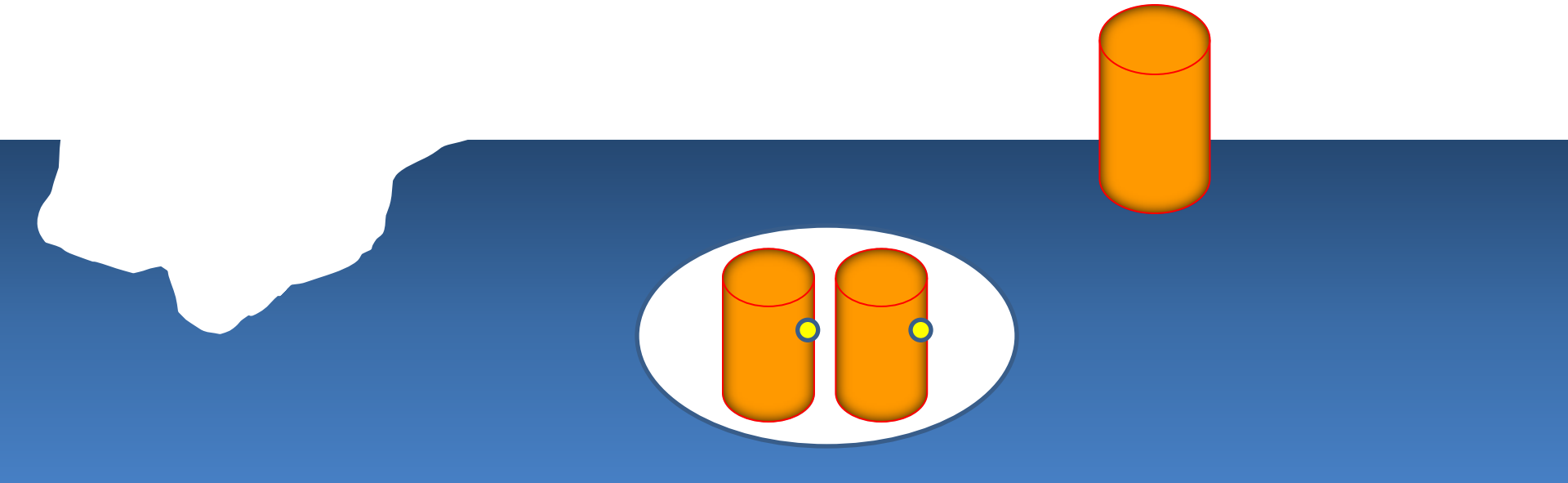


effect of antibodies



reversible!
- immunotherapy (PE, steroid)
  - before intrathecal synthesis
  - before plasmablasts in CNS

- endocytosis
- degradation
- brain: Ab, but no complement, no neuron death



consideration in children

	NMDAR	$GABA_AR$	Glycine R	D2R	mGluR5
age	any	<25 cases, any	<10 cases, any	17 cases any	
gender	80% F	equal	more F	equal	equal
manifestation	prodroma behavioral psychosis seizures catatonia MD dysautonomia	rapidly progr enceph.pathy status epil. behavioral	PERM stiff person ADEM/ON epilepsy	dystonia parkinsonism chorea motor tics ocular flutter enceph.pathy psychiatry	psychiatric cognitive memory
CSF abnorm	90%	typical	variable	variable	typical
imaging	up to 50%	all abnormal ext T2/FLAIR	frequently normal	50%, BG enhancing	variable
tumor	ovarian teratoma (>15y)	Hodgkin	no tumor in children	none	Hodgkin
relapse	12-25%	uncommon	relapse rare	25%	unknown
other	-	GAD65 Abs	GAD65 Abs	50% nonCauc	-

adapted from J Clin Neurosci, 2014, 21:722

differential diagnosis of LE

infectious	▪ herpes simplex encephalitis (HSE) ▪ HSV-6 (post-transplant) ▪ neurosyphilis ▪ prion ▪ rabies (NMDAR)	▪ CSF, PCR (relapsing HSE!) ▪ history, CSF ▪ TPA ▪ 14-3-3 in CSF ▪ history
autoimmune	▪ ADEM ▪ primary vasculitis of the CNS ▪ systemic autoimmune (SLE, SS) ▪ Hashimoto encephalopathy	▪ MRI ▪ ANCA, CRP, ESR ▪ ANA, DNS, ENA, ACL/APL ▪ TSH, history
toxic-metabolic	▪ Wernicke-Korsakoff ▪ metabolic ▪ intoxication ▪ alcohol withdrawal	▪ ion ▪ liver, kidney ▪ alcohol, drug ▪ history, liver
epileptic	▪ temporal lobe epilepsies ▪ non-convulsive status	▪ EEG ▪ EEG
vascular	▪ posterior circulation	▪ age, history, risk
tumor	▪ lymphoma, glioma, metastasis	▪ LDH, FACS, MRS
degenerative	▪ AD, LD, FTLD	▪ PET-CT, chronic
tumor	▪ transient global amnesia	▪ duration

response to immunotherapy

	Antibody positive (n=21)	Antibody negative (n=27)
Immunotherapy received	17 (80%)	17 (63%)
Corticosteroids only	6	11
IVIG only	0	2
Corticosteroids+IVIG	11	4
Additional PLEX	4	0
Disease modifying drugs	5	0
Immunotherapy response	16 (94%)	16 (94%)
Probable response	10	13
Definite response	6	3
Modified Rankin scale score (for children) at nadir	4.5+0.60	4.5+0.58
Modified Rankin scale score (for children) at follow-up	1.8+0.75	1.6+0.84
Ongoing problems (further details in figure 3)	15 (71%)	13 (48%)
10/14 (71%) untreated	3/4 (75%)	13 (48%)
18/34 (52%) treated	12/17 (70%)	6/17 (35%)

No significant difference was seen in immunotherapy response and outcome.
Antibody positive patients were more likely to receive PLEX and second line immunotherapy.
IVIG, intravenous immunoglobulins; PLEX, plasma exchange.

JNNP, 2013, 84:748

clues of autoimmune pathogenesis?

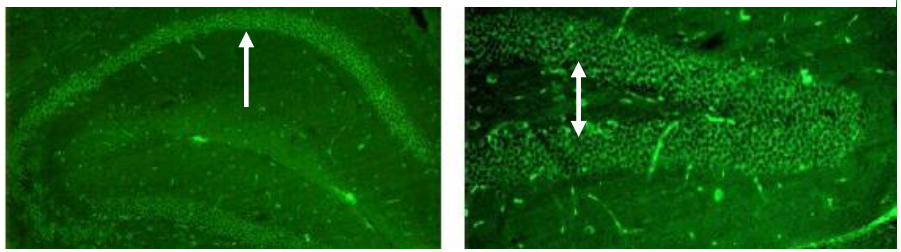
31-year old female

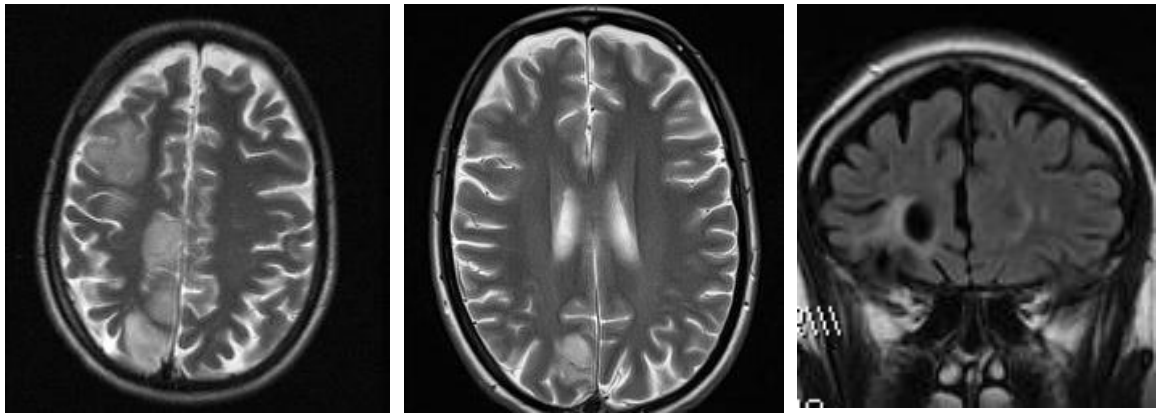
- treatment-resistant epilepsy
- brain MRI: only right hemisphere
- biopsy: Rasmussen encephalitis?
- no tumor for 4 years
- no systemic autoimmunity

- CSF: OCB
- status provoked by infections
- relapse-like clinical picture
- PE: efficient

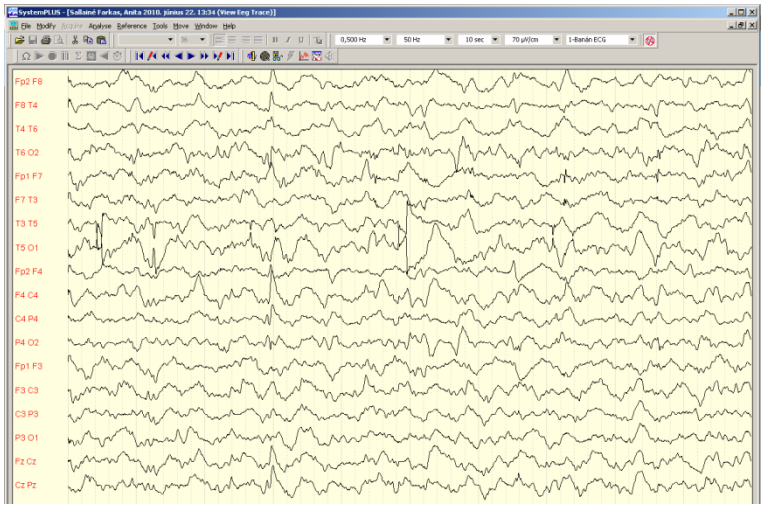
AMPAr neg
NMDAr neg
$GABA_B$r neg
VGKC neg
LGI1 neg
GAD neg
anti-Hu neg
CV2/CRMP5 neg

hippocampus





myoclonus
sharp waves
right central



guideline: diagnosis of autoimmune epilepsy

J Neurol Neurosurg Psychiatry, 2012, 83:638-645; Epilepsia, 2013, 54:1036-1045

suspect autoimmune seizures

- required:
  - acute/subacute presentation (<12 weeks)
  - exclusion of CNS infection, toxic, metabolic, etc.
- supportive *(at least one):*
  - well defined syndrome (e.g. LE, NMDAR)
  - evidence of CNS inflammation (at least one)
    - CSF pleiocytosis *or* neopterin *or* OCB
    - MRI/imaging
    - biopsy
  - other autoimmune disorder

video

NMDA receptor encephalitis

16-year old girl

- fever, headache, nausea

- *a month later:*
  - 4 generalized seizures in the evening
  - complex auditory hallucination
  - agitation, non-adeqauate emotional bursts
  - disturbed memory
- no focal neurological signs then

phase 1: prodrome
- trigger of systemic Ab production?

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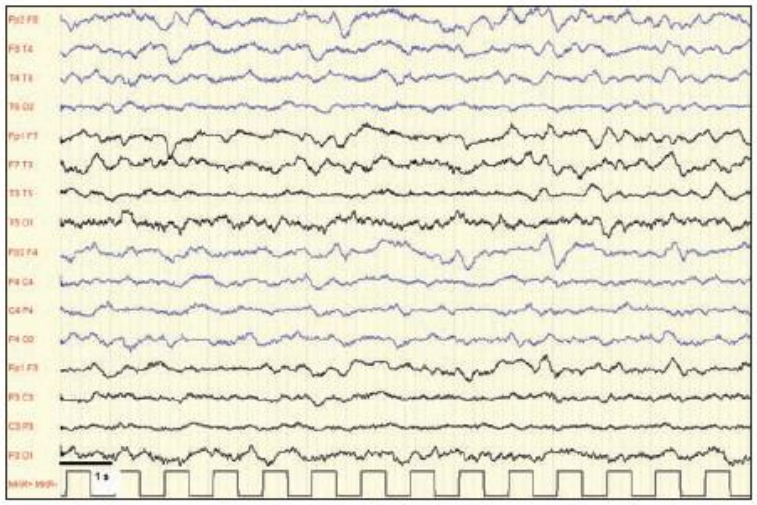
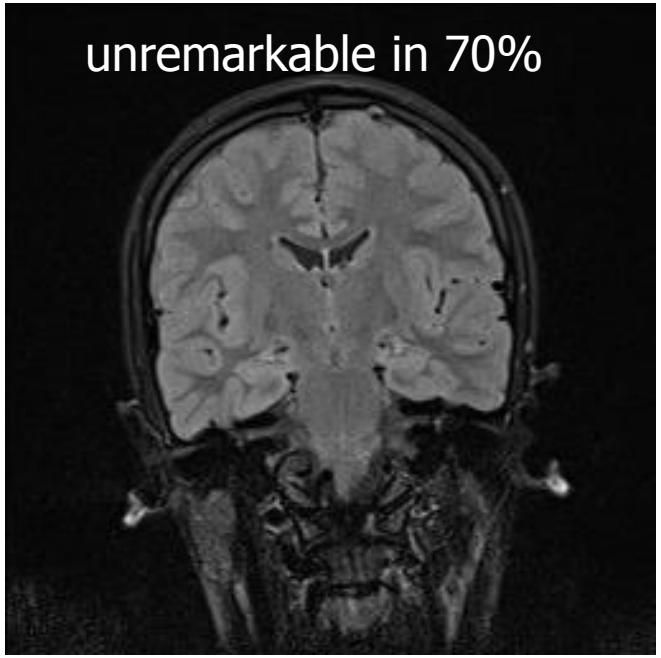
phase 2: psychotic/seizure
- cortical dysfunction?
- internalization of receptors?





OCB
in CSF

NMDA receptor encephalitis

- steroid pulse for 3 days: no response
- start PE within 3 days

↓

- serum *and* CSF:
  - anti-NMDAR seropositive

↓

- perioral myoclonus, lip-smacking, jaw movements, grimacing
- catatonia, inapropriate smiling
- progressive loss of consciousness
- autonomic instability
  - hypertonia, fever, tachycardia

phase 3: neurological
- subcortical dysfunction?
- intrathecal Ab production

NMDA receptor encephalitis

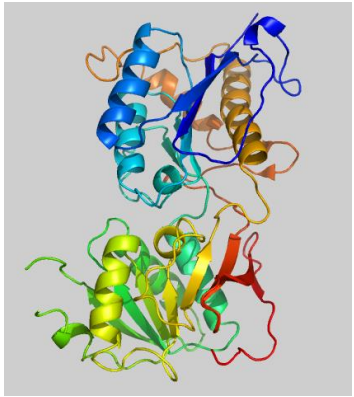
- improvement in 2 weeks
- complete recovery in 3 months
- cognitive recovery slower, later

questions:

- long-term treatment necessary?
- ovarium teratoma, screening:
  - female
  - >12-year-old
  - abdominal/pelvis MRI every 6 months (transvaginal ultrasound?)
  - for 4 years

NMDA receptor encephalitis

- discovery in 2007
- over 500 patients worldwide
- more common than viral encephalitis in young
- 1% of all young patients' admission to the ICU
- 48% are children
- incidence in children 0.85/mill/year (UK)
- 78% of pediatric cases in April-September (seasonal)
- may develop concurrent or separate demyelinating episodes and after HSE
- patients with NMO with atypical symptoms can have NMDAR Abs



- tumor (teratoma)
- in the largest series of children only 25%
- inversely related to age:
  - 31% under the age of 18
  - 9% under the age of 14
  - nonexistent in the first decade

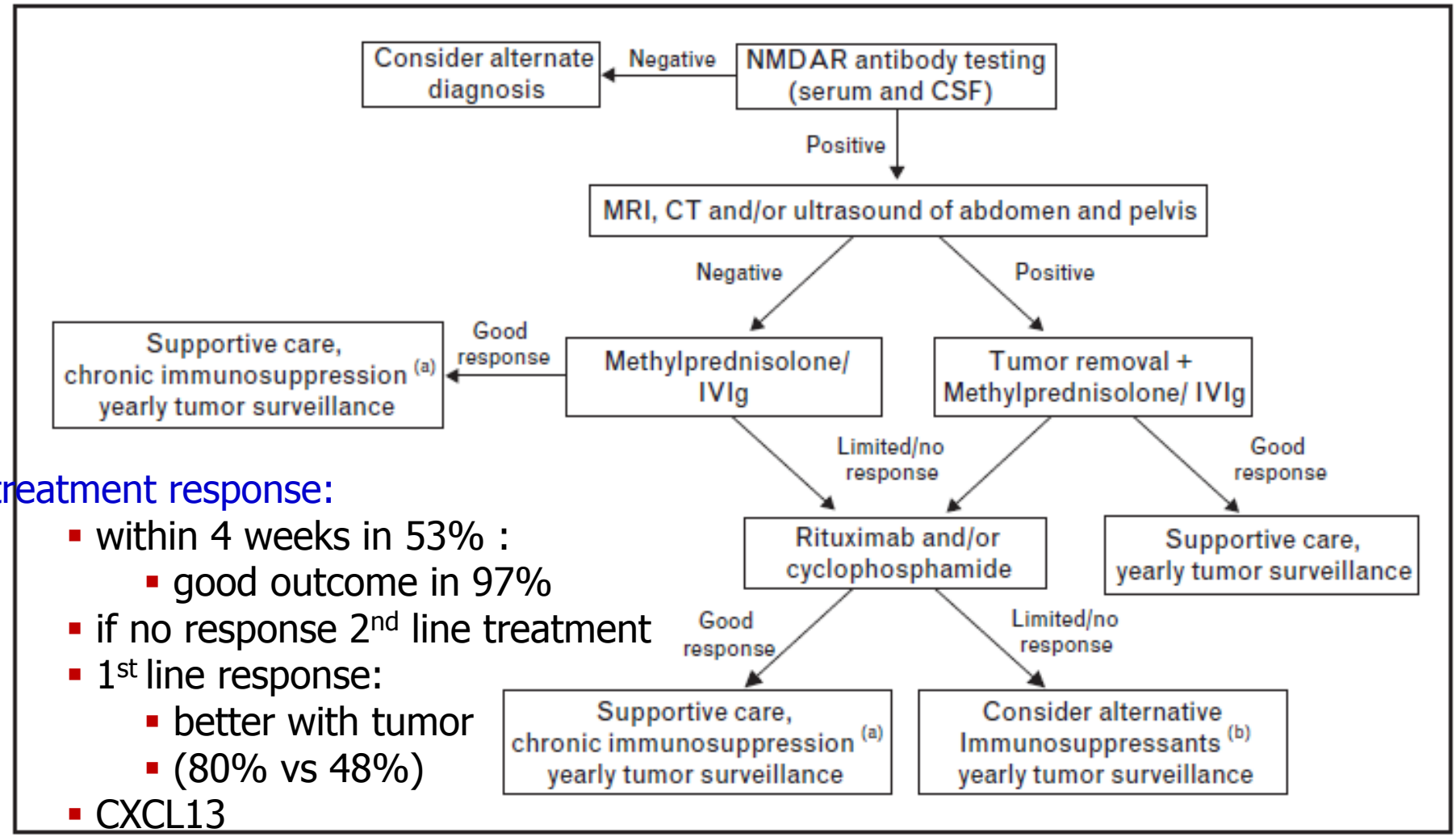
- synaptic plasticity
- learning
- memory

pathogenic role

- neuronal culture: decreases the level of NMDAR and synaptic currents
  - reversible
- infusion into rat brain: decrease of NMDAR, increase of corticomotor excitability

treatment in children

Florance-Ryan and Dalmau, Curr opin Pediatr, 2010, 22:739



treatment response:

- within 4 weeks in 53% :
  - good outcome in 97%
- if no response 2nd line treatment
- 1st line response:
  - better with tumor
  - (80% vs 48%)
- CXCL13
  - biomarker of treatment response?

treatment and outcome in children

- majority require extended hospital admission: 2-14 months
- recovery may take 3 years or longer

prompt aggressive treatment:

- 75% complete or near complete recovery
- full recovery in 89% with PLEX *vs* 47% with IVIG and steroids only (p=0.05, UK)

relapse:

- 20-25% of patients within 3 months – 9 years
- multiple relapses may occur, usually milder
- more common
  - in patients not treated or not propely treated
  - no tumor

maintenance treatment:

- 1 year of mycophenolate mofetil or azathioprine (Dalmau et al, 2011)
- case-by-case evaluation:
  - comorbidities, severity, response to therapy

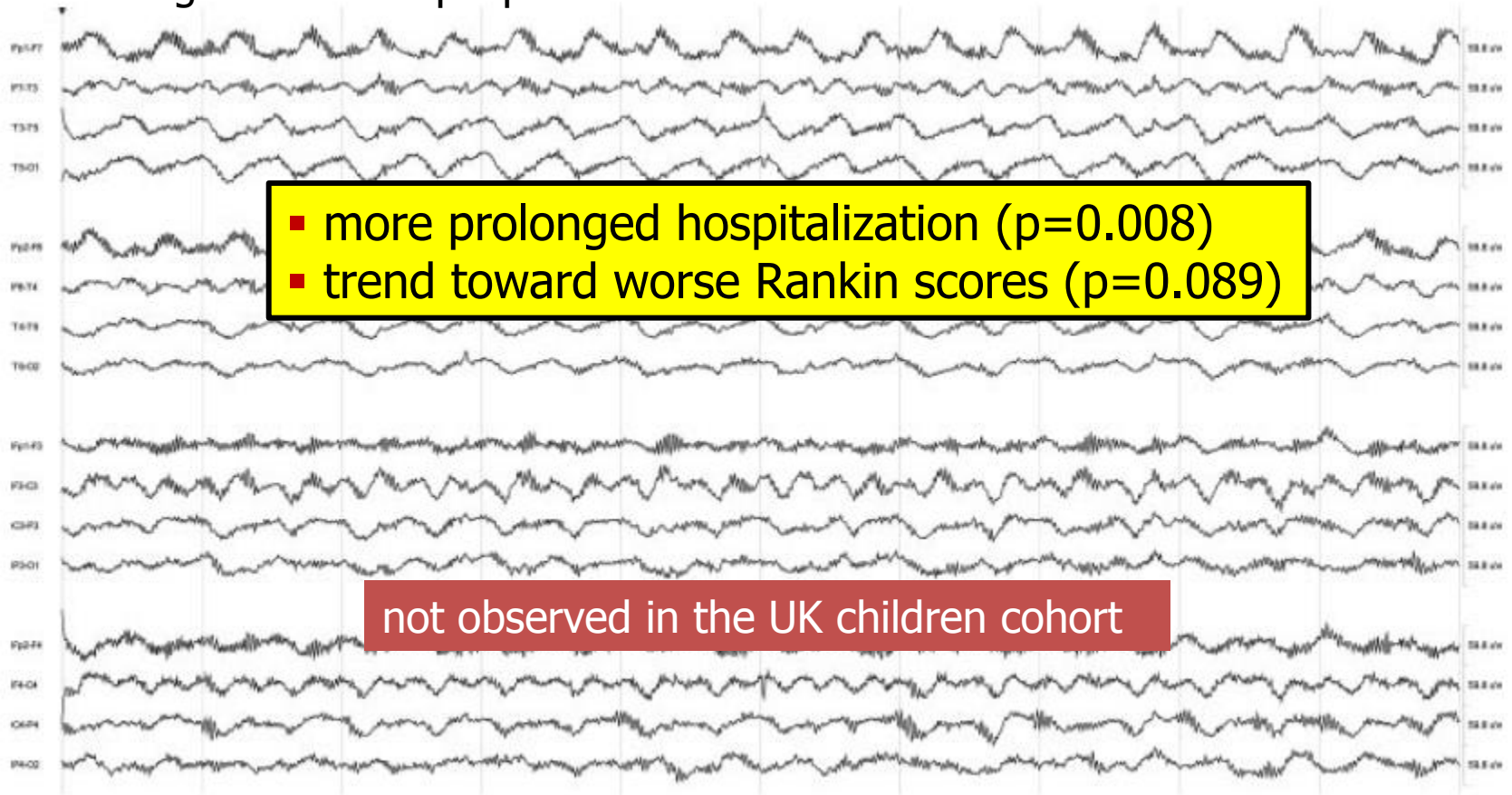
NMDAR encephalitis: unique EEG pattern?

Neurology, 2012, 79:1094-1100

23 patients: EEG monitoring for a median of 7 days

- unique pattern in 30%: „extreme delta brush"

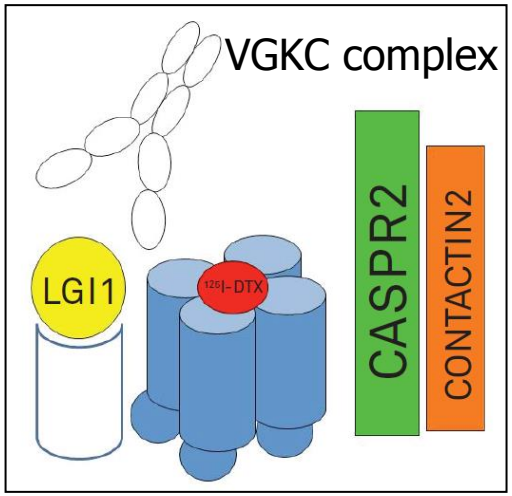
generalized rhythmic delta activity at 1-3 Hz
superimposed bursts of rhythmic 20-30 Hz beta riding on each delta waves
no change to IV antiepileptics

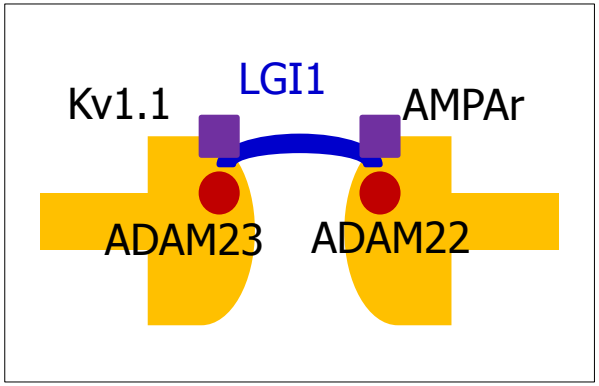


- more prolonged hospitalization (p=0.008)
- trend toward worse Rankin scores (p=0.089)

not observed in the UK children cohort

VGKC complex and LGI1

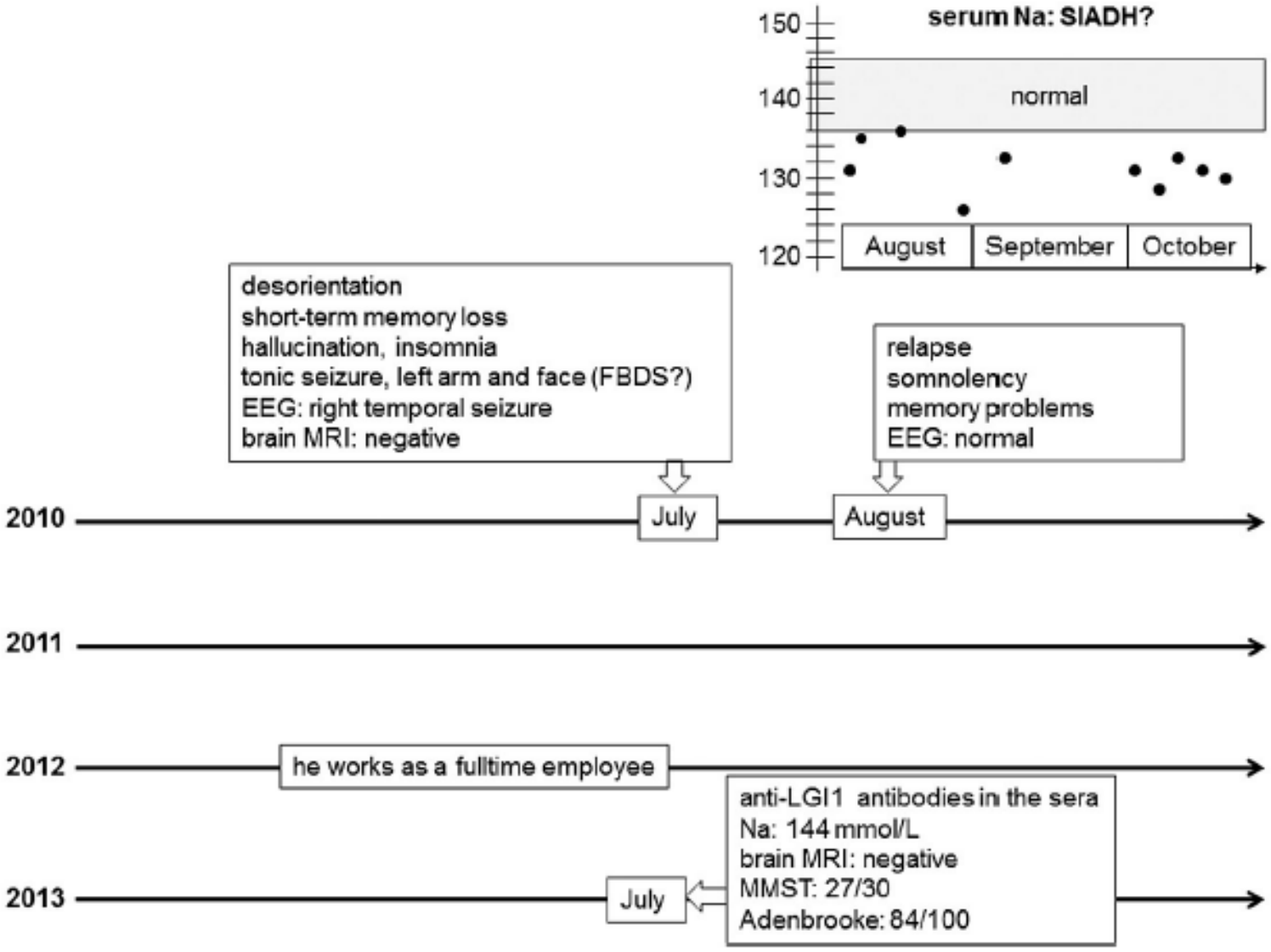




LGI1 encephalitis: FBDS

video

LGI1 encephalitis: natural course



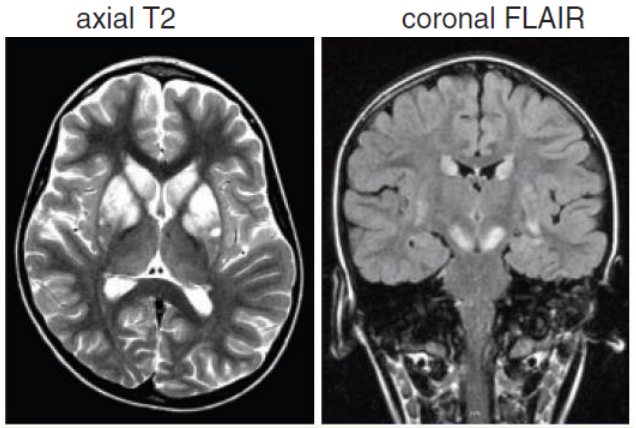
J Neurol Sci, 2014, 343:198

autoimmmune basal ganglia encephalitis

- preceding EBV, respiratory viruses, influenza, Mycoplasma
- parkinsonism
- orolingual and limb tremor, cogwheel rigidity
- dystonia maybe present, oculogyric crisis in one-third
- chorea, ballism in subgroups
- pyramidal signs, cranial nerve deficits in some
- sleep disturbance, mostly hypersomnolence
- dysautonomia
- psychiatric (OC, psychosis)

dopamin-2 receptor antibody

- basal ganglia encephalitis 12/17 children (70%)
- 0.4-15 years, sex even
  - fever in 9
  - CSF pleiocytosis in 6, no Ab
  - MRI abnormal in 50% (BG, SN)
  - no tumors, preceeding infection 50%



- Sydenham chorea 30%
- Tourette's syndrome 9%
- PANDAS 0%

Neuropediatrics, 2013, 44:336; Brain, 2012, 135:3453

Ab-mediated encephalitis: take home message

recognize the syndrome
- LE
- especially in the elderly

identify clues for specific syndrome
- „plus"
- hyponatremia
- age
- FBDS
- facial dyskinesias

ask for „multiple" antibody screening
- onconeural (one serum: 5)
- NSAbs (one serum: 6)
- check both serum and CSF
- multiple NSAb and onconeural Abs

think of differential diagnosis
- consider age, history
- ANCA, CRP, ESR
- ANA, dsDNS, ENA, ACL/APL
- LDH, HSV

→ **treat early**
- plasma exchange

→ **consider 2nd line**
- NMDAR

→ **repeat tumor screenings**

→ **consider relapse**
- maintanance treatment?

→ **treat empirically, if no Abs?**
- if strong suspicion: IVIG, PE, MP

thank you very much

Am J Psychiatry, 2013