A Neuroimmunology case

Presented at Medical Grand Rounds 29/11/2018

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Outline

- Case
- Background (including similar conditions)
  - Epidemiology
  - Theory-Pathophysiology + aetiology
  - Clinical presentation
  - Diagnosis
  - Treatment
  - Prognosis
- Media

CASE

19yo female

HPC:

- Presented to ED at Maitland with headaches, photophobia, flu-like symptoms and (low grade) fevers
- Change in behaviour with agitation, confusion + forgetfulness. Also started to develop slurred speech.

MHx:

- Generally fit and well
- Occasional headaches

Medications:

- OCP (Levlen)

SHx:

- Studied event management at TAFE and was working in retail
- Non smoker with no significant alcohol intake
- Boyfriend had recently travelled overseas and she was looking after his cat!

CASE

- **Examination**
  - BP140/70, HR 125, Sats 96%, RR25, Temp 37.8 degrees
  - GCS 12 –Mumbling incomprehensible words
  - Some rigidity noted

- **Impression:**
  - Meningitis/encephalitis

CASE

- **Investigations**
  - Bloods-WCC 17.3 (neutrophilia), UEC + LFT normal, CRP 8
  - CTB-normal
  - LP
    - WCC 111 (Mononuclear)
    - No growth

- **Management**
  - Empiric antibiotics and Acyclovir
  - Sedation for agitation
  - Transferred to JHH due to fluctuating level of consciousness/GCS
    - (Under care of Neurology)

CASE

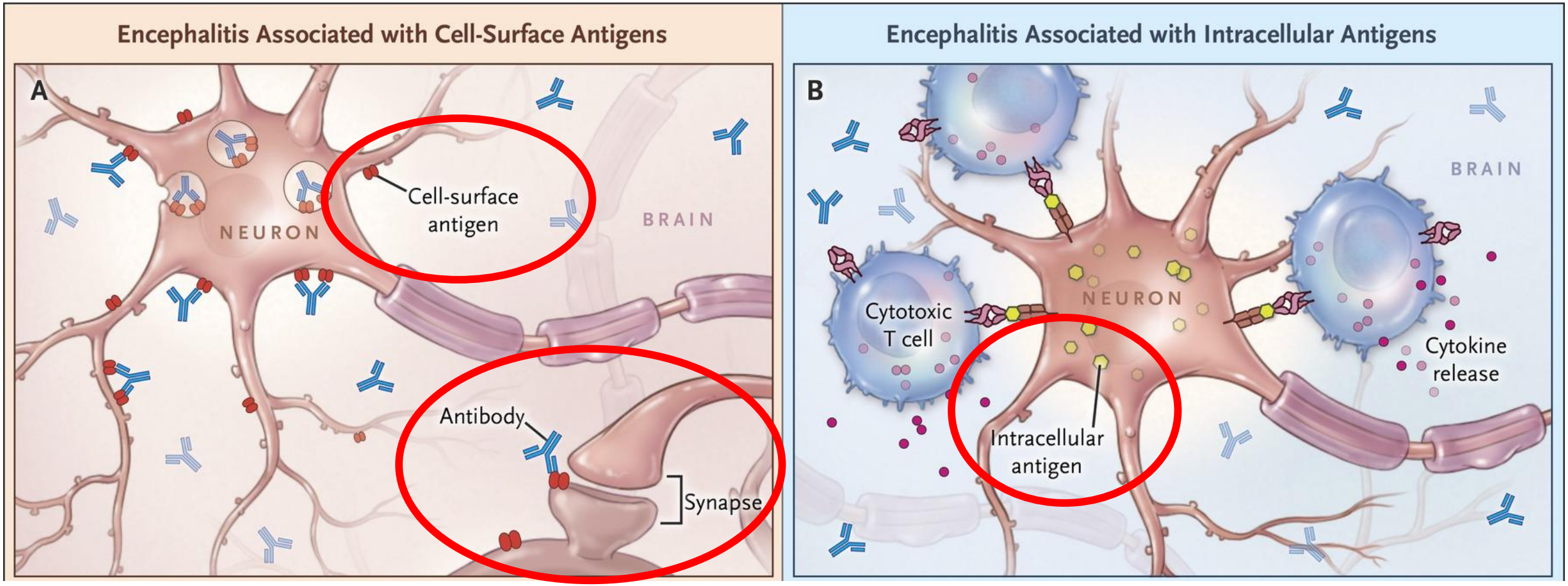
- At JHH
  - Rapid Response –reduced LOC on ward
  - Transferred to ICU
    - ?Seizure activity-commenced on Keppra
  - Further investigations
    - CSF PCR negative
    - MRI-normal
    - NMDAR antibodies DETECTED

What next?

Encephalitis

- Annual incidence ~5-8 cases per 100,000 persons
  - Most common causes:
    1. Infection (usually viral)
    2. Acute disseminated encephalomyelitis
    3. Autoimmune
       - Anti-NMDA Receptor encephalitis
  - In up to 50% of cases a cause cannot be established

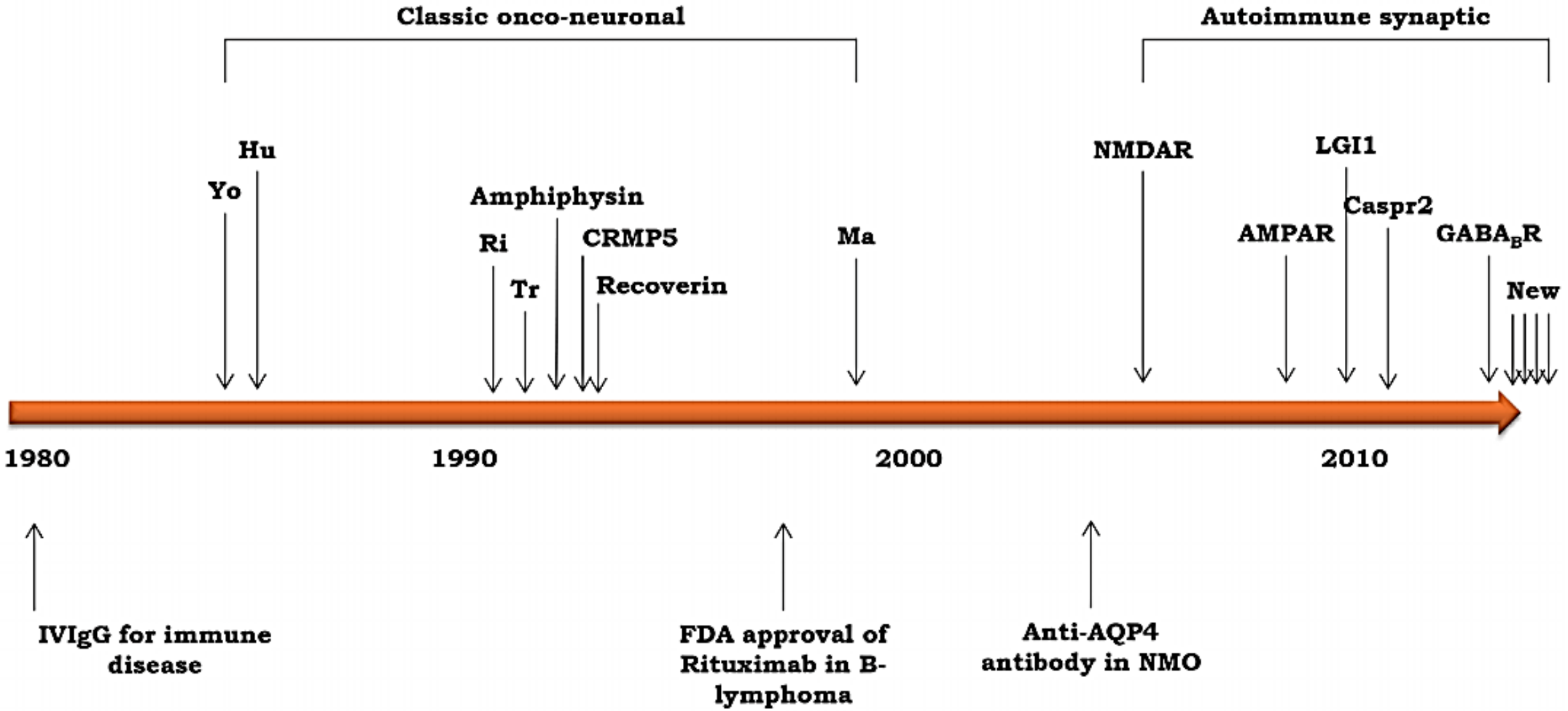
Autoimmune encephalitis



‘Limbic encephalitis antibodies’

Neuronal antibodies (classic onco-neuronal)
-paraneoplastic

Autoantibody-mediated encephalitis Nejm March 2018



The discovery of antibodies of autoimmune encephalitis; Journal of epilepsy research. Dec 2016

Antibody	Syndrome	Associated cancers
Well-characterized paraneoplastic antibodies ¶		
Anti-Hu (ANNA-1)	Encephalomyelitis including cortical, limbic, and brainstem encephalitis; cerebellar degeneration; myelitis; sensory neuronopathy; and/or autonomic dysfunction	SCLC, other
Anti-Yo (PCA-1)	Cerebellar degeneration	Gynecologic, breast
Anti-Ri (ANNA-2)	Cerebellar degeneration, brainstem encephalitis, opsoclonus-myoclonus	Breast, gynecologic, SCLC
Anti-Tr (DNER)	Cerebellar degeneration	Hodgkin lymphoma
Anti-CV2/CRMP5	Encephalomyelitis, cerebellar degeneration, chorea, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins Δ (Ma1, Ma2)	Limbic, hypothalamic, brainstem encephalomyelitis (infrequently cerebellar degeneration)	Testicular germ cell tumors, lung cancer, other solid tumors
Anti-VGCC ◇	Cerebellar degeneration	SCLC
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, lung cancer
Anti-PCA-2 (MAP1B)	Peripheral neuropathy, cerebellar ataxia, encephalopathy	SCLC
Anti-recoverin §	Cancer-associated retinopathy	SCLC
Anti-bipolar cells of the retina ¥	Melanoma-associated retinopathy	Melanoma
Partially characterized paraneoplastic antibodies ¶		
Anti-Zic 4	Cerebellar degeneration	SCLC
Anti-ANNA-3	Sensory neuronopathy, encephalomyelitis	No tumor or Hodgkin lymphoma

Available test panel=
Hu, Ri, Yo, CRMP5,
Ma1/2, Amphiphysin,
Sox1, VGCC

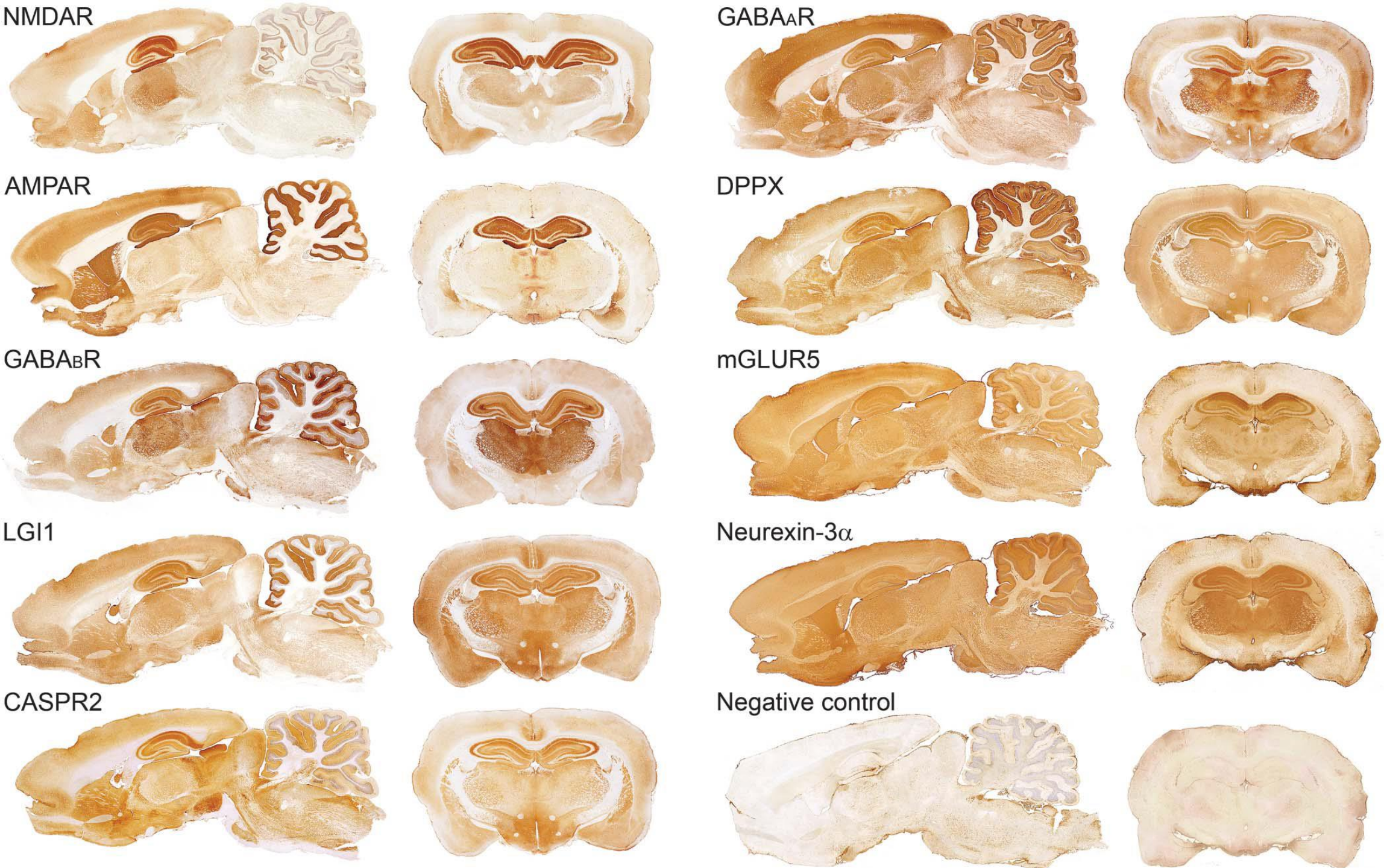
Neuronal antibodies (classic onco-neuronal)

Autoimmune encephalitis syndromes with antibodies against neuronal cell surface/synaptic proteins

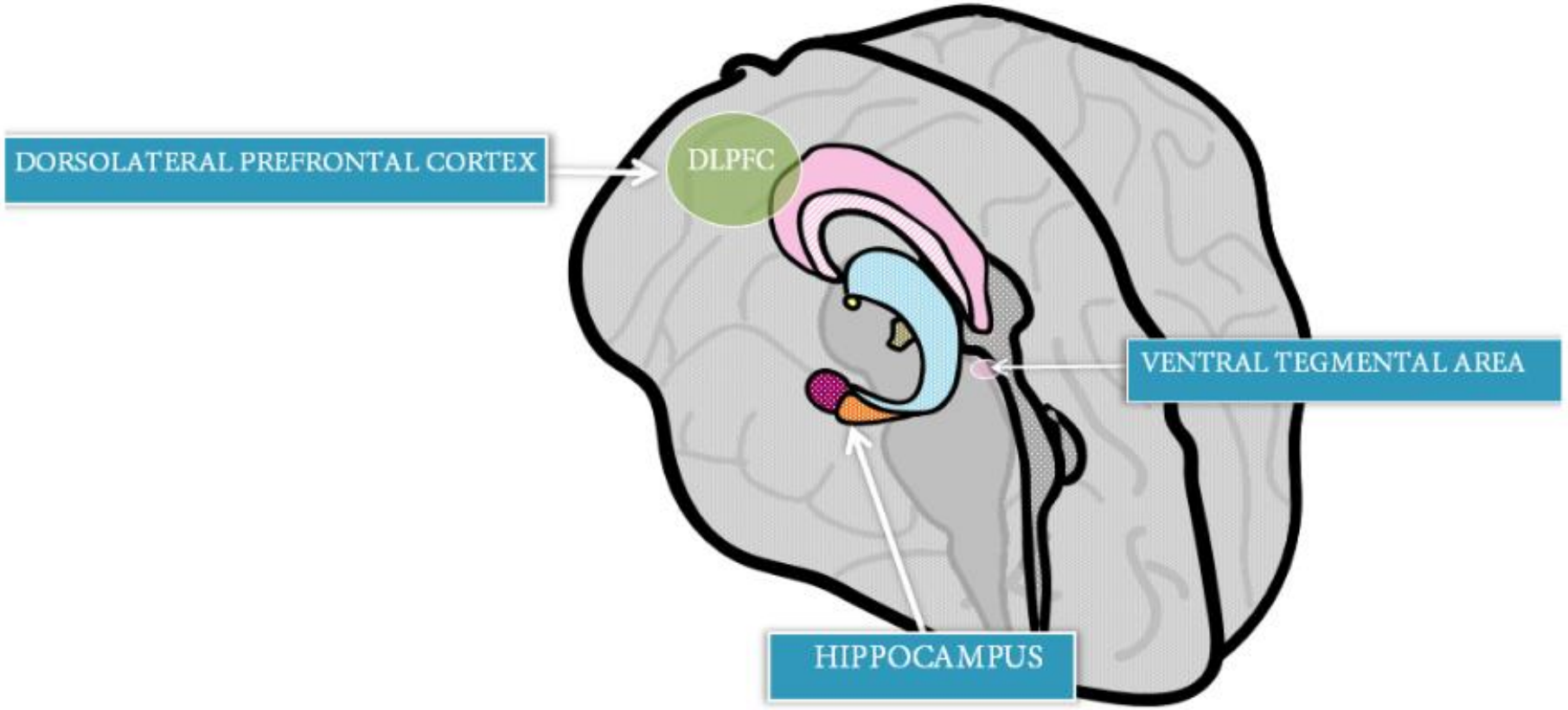
Antigen target	Clinical syndrome	Tumor or other associations
NMDAR	Multistage syndrome with psychosis, insomnia, memory and behavioral disturbances, seizures, dyskinesias, and autonomic dysfunction	Age-dependent presence of ovarian teratoma; rarely other tumors in older patients or males; often has viral-like prodrome
LGI1	Limbic encephalitis, seizures, facio-brachial dystonic seizures	5 to 10% (thymoma); 60% with hyponatremia
AMPAR	Limbic encephalitis, psychiatric disturbances	70% (variable solid tumors); relapses are common
GABA-A receptor	Rapidly progressive encephalopathy, refractory seizures, status epilepticus, epilepsia partialis continua	40% (thymoma); MRI with multifocal cortical-subcortical FLAIR and T2 abnormalities without contrast enhancement
GABA-B receptor	Seizures, limbic encephalitis	50% with cancer (mostly SCLC)
Caspr2	Morvan syndrome, limbic encephalitis, neuropathic pain, peripheral neuropathy, autonomic dysfunction, cerebellar ataxia, isolated neuromyotonia	Thymoma and variable solid tumors
IgLON5	REM and non-REM parasomnias, obstructive sleep apnea, stridor, brainstem dysfunction	No cancer association; often chronic and slowly progressive
DPPX	Encephalopathy with CNS hyperexcitability, hyperekplexia, myoclonus, tremor, often preceded by weight loss, diarrhea, or gastrointestinal symptoms	Two patients reported with B-cell neoplasms
GlyR	Encephalomyelitis with muscle spasms, rigidity, myoclonus, hyperekplexia	A past history of cancer and a concurrent cancer diagnosis have been reported
mGluR5	Encephalitis	Hodgkin lymphoma* or no tumor
mGluR1	Cerebellar ataxia	Hodgkin lymphoma or no tumor
Neurexin 3-alpha	Confusion, seizures, encephalitis, dyskinesias	No cancer association reported
Dopamine-2 receptor	Basal ganglia encephalitis	No cancer association reported

Available test panel= NMDAR, LGI1, AMPAR, GABAb, CASPR, IgLON5, DPPX

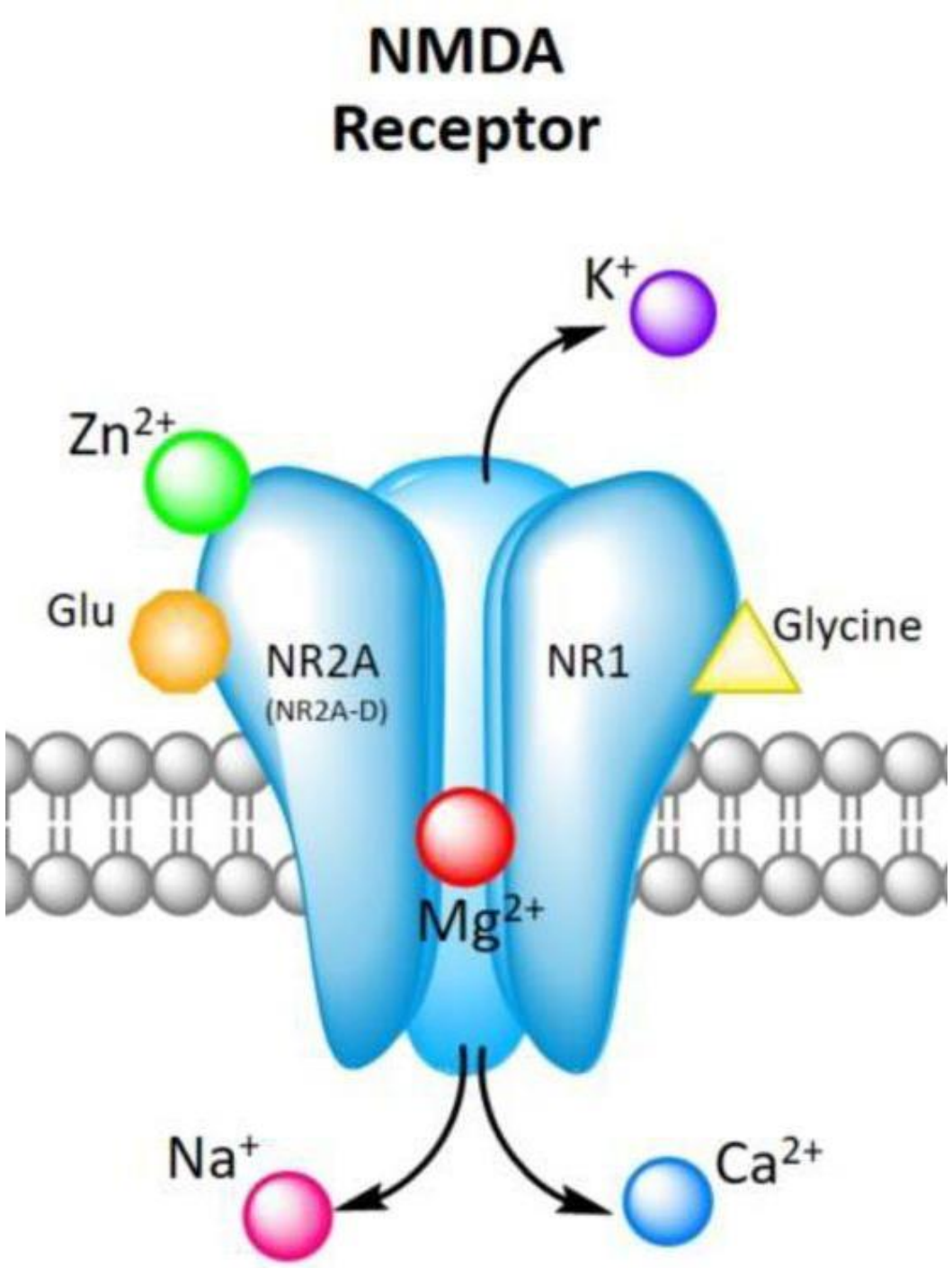
‘Limbic encephalitis antibodies’


NMDAR
GABAAR
AMPAR
DPPX
GABABR
mGLUR5
LGI1
Neurexin-3α
CASPR2
Negative control

Key regions affected in NMDA receptor encephalitis

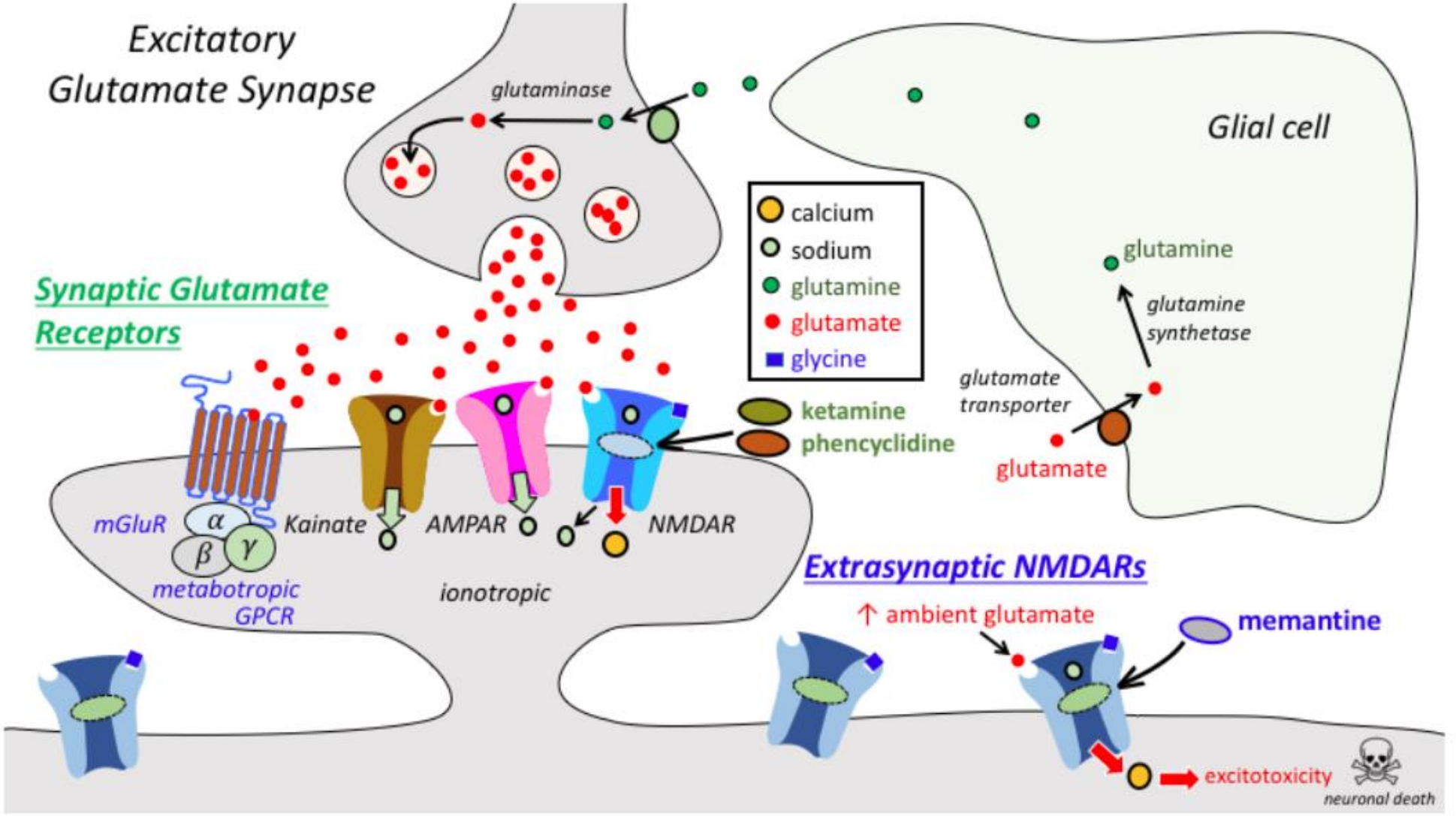


- The NMDA receptor is highly expressed in the forebrain, limbic system and hypothalamus



- N-Methyl-D-aspartic acid
- Ionotropic glutamate receptor-ligand gated cation channel
- The NMDA receptor requires both glutamate and the co-agonist glycine for the efficient opening of the ion channel.
- Composed of 2 subunits-NR1 and NR2
- Plays a role in memory and pain.
- The activation of NMDA receptors has been associated with hyperalgesia, neuropathic pain, and reduced functionality of opioid receptors.
- Ketamine, Methadone and memantine are NMDA antagonists.
- The channel is affected by psychoactive drugs + alcohol.
- Anti-NMDA IgG(1) usually binds to NR1 subunit.

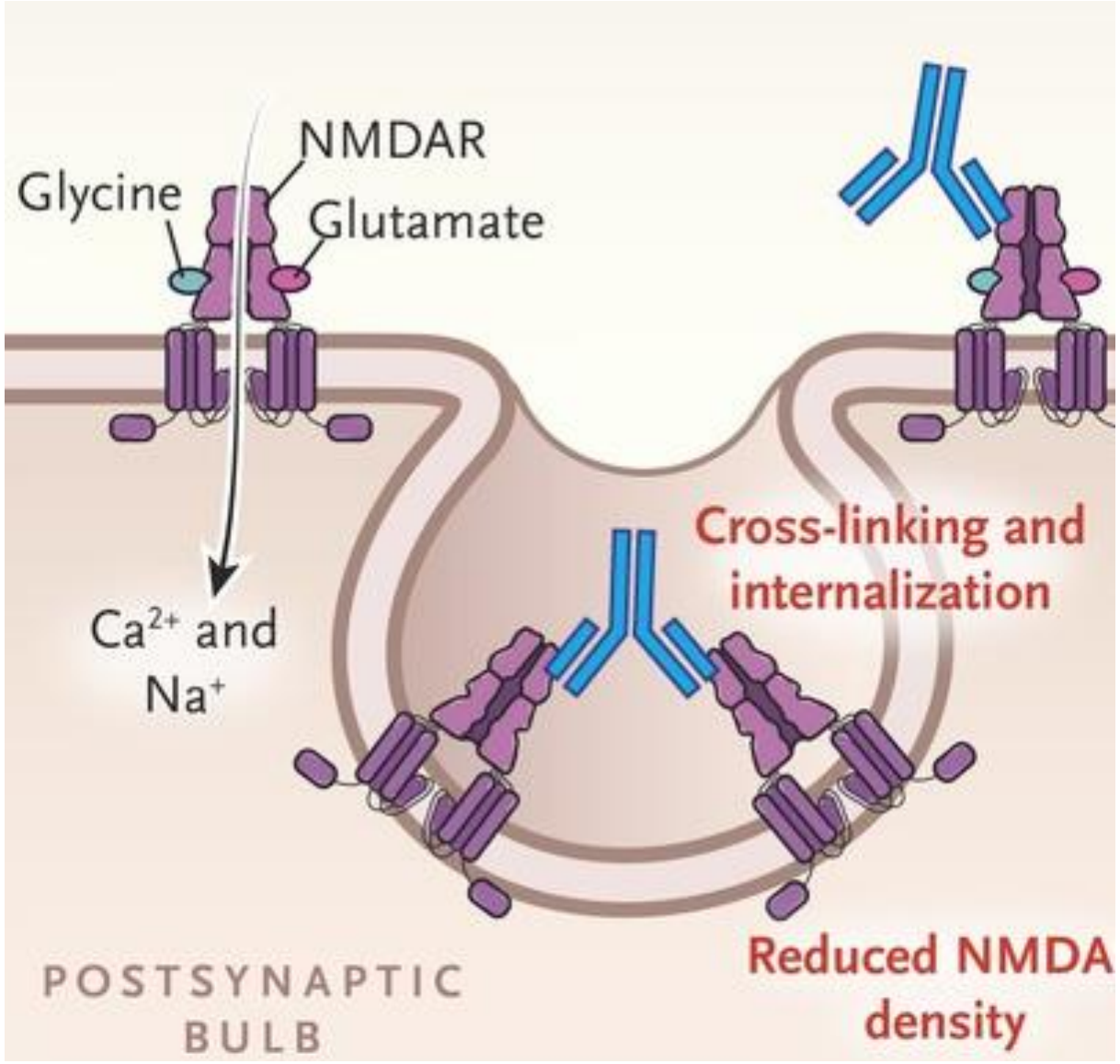
NMDA Receptor



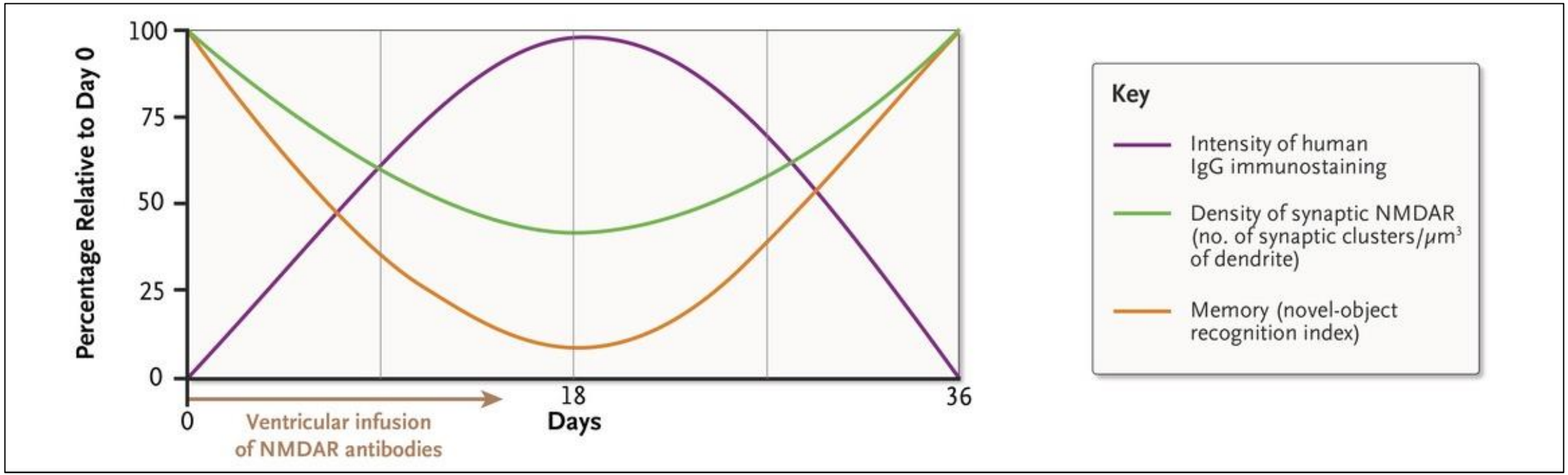
- NMDA Receptors can be divided into synaptic (post synaptic membrane) and extrasynaptic.
- Synaptic NMDA receptors are coupled to different downstream signaling cascades compared to extrasynaptic NMDA receptors.
- Excessive stimulation of extrasynaptic receptors results in excitotoxicity and cell death.

Anti-NMDA Receptor antibodies

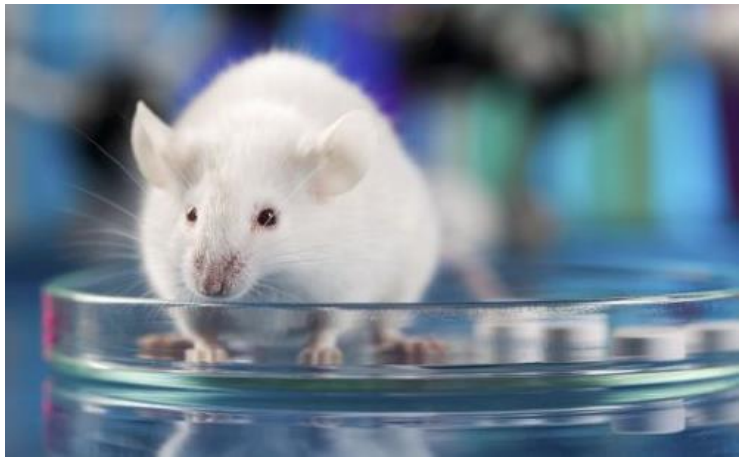
- Pathogenic
- Receptor binding leads to internalisation of receptors.
- Reduced receptor number on postsynaptic neuronal dendrites causes synaptic dysfunction (and psychotic symptoms characteristic of anti-NMDAR encephalitis).
- Of note internalisation of receptors occurs with no significant neuronal death or immune activation (unlike other neuronal antibodies)
    - This correlates with the eventual recovery in these patients (as new receptors are synthesised and inserted into the membrane).



Anti-NMDA receptor antibodies-pathogenicity



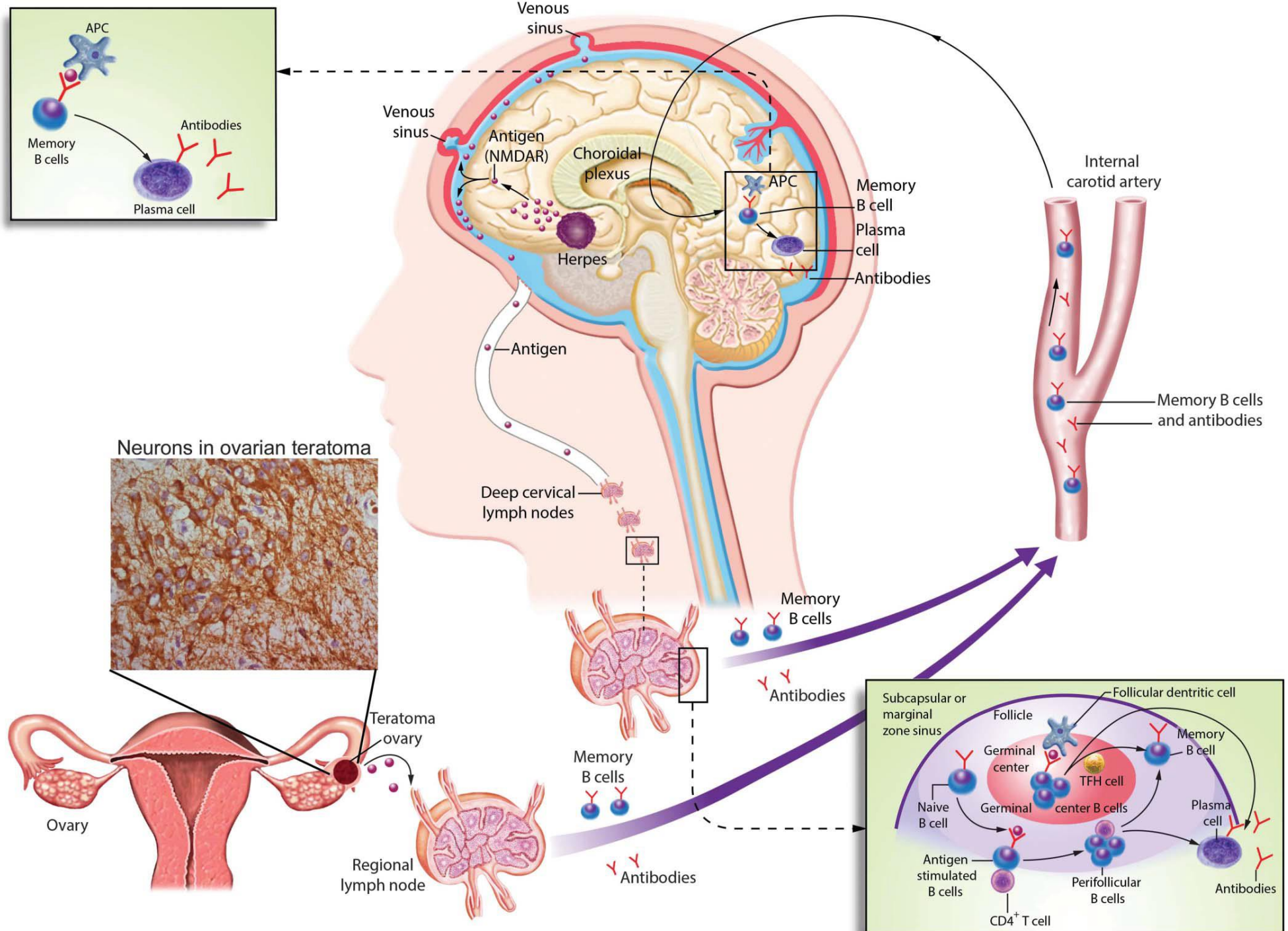
Brain 2015 Jan: **Human *N*-methyl D-aspartate receptor antibodies alter memory and behaviour in mice**



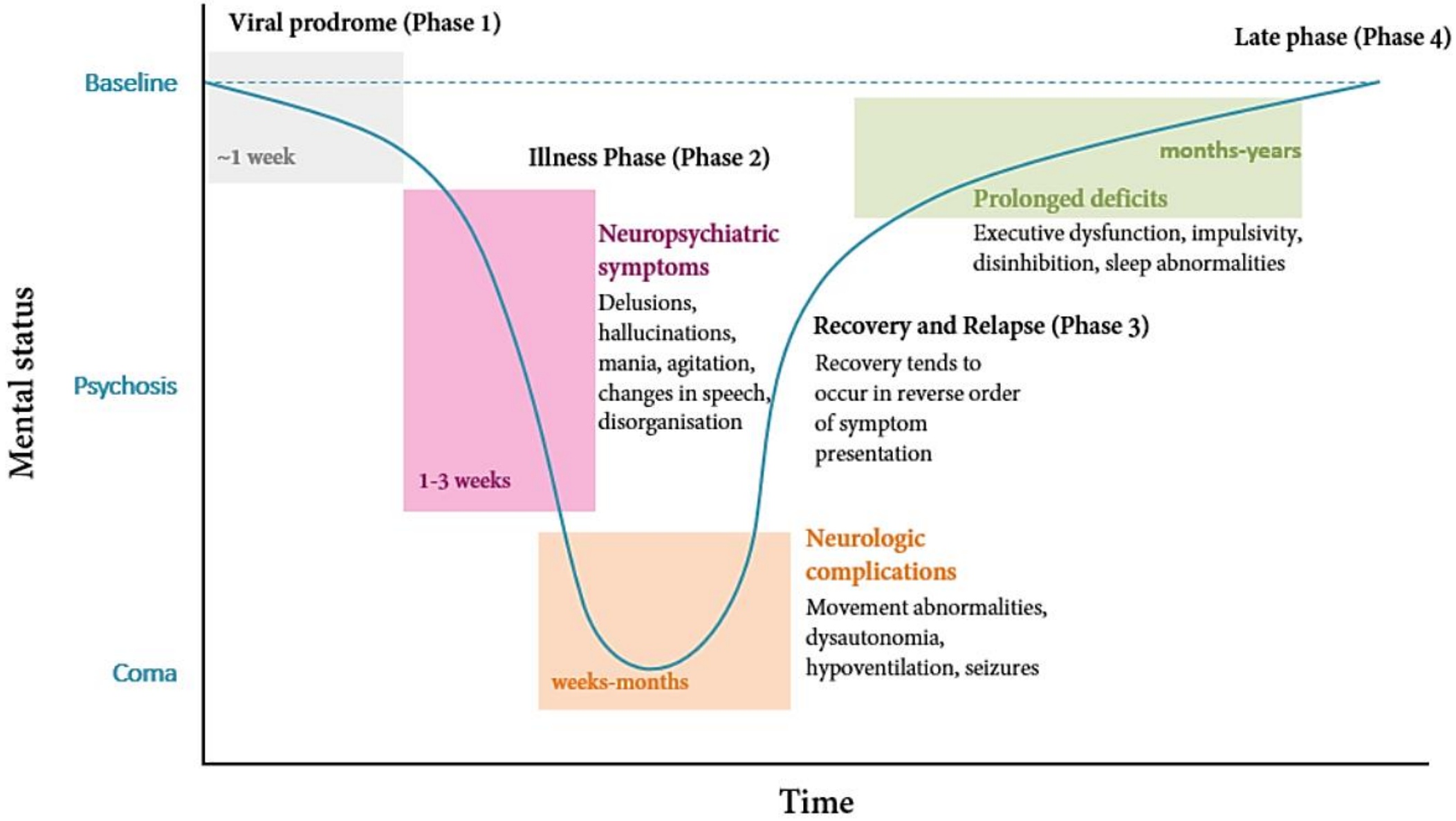
Aetiology

- It has been postulated that the autoimmune response is initiated by antigens released
    - during/post infection
        - viral destruction of neurons (e.g. herpes simplex)
        - Bacterial infection-Mycoplasma
    - by tumours
        - Up to 50% women (25-30 age group) have underlying tumour, <5% men
            - >90% Ovarian Teratomas. Carcinoma more common in older patients.
    - Or by unknown mechanisms
- Genetic susceptibility
    - a number of risk alleles known/identified for HSV encephalitis
    - anti-NMDAR encephalitis with HLA-I allele B*07:02 (p = 0.039) Ann Neurol 2018

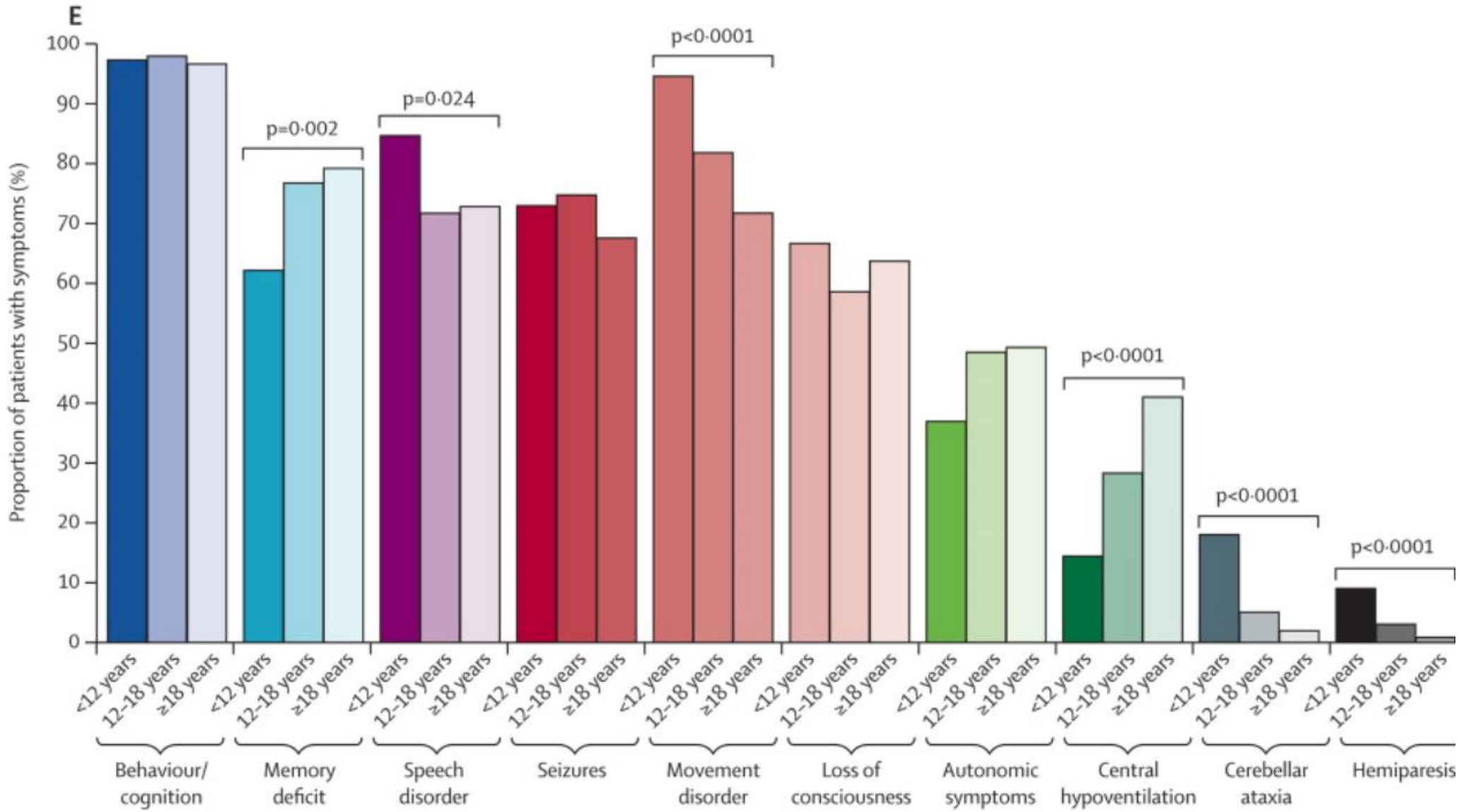
Mediators of inflammation 2017: Anti-N-Methyl-D-aspartate Receptor Encephalitis: A Severe, Potentially Reversible Autoimmune Encephalitis, Liu et al.
Eur J Clin Microbiol Infect Dis (2009): Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis, M. S. Gable et al


APC
Memory B cells
Antibodies
Plasma cell
Venous sinus
Venous sinus
Antigen (NMDAR)
Choroidal plexus
Herpes
APC
Memory B cell
Plasma cell
Antibodies
Antigen
Deep cervical lymph nodes
Internal carotid artery
Memory B cells and antibodies
Neurons in ovarian teratoma
Teratoma ovary
Ovary
Regional lymph node
Memory B cells
Antibodies
Memory B cells
Antibodies
Subcapsular or marginal zone sinus
Follicle
Follicular dentritic cell
Germinal center
Memory B cell
TFH cell
Naive B cell
Germinal center B cells
Plasma cell
Antigen stimulated B cells
Perifollicular B cells
Antibodies
CD4+ T cell

Presentation



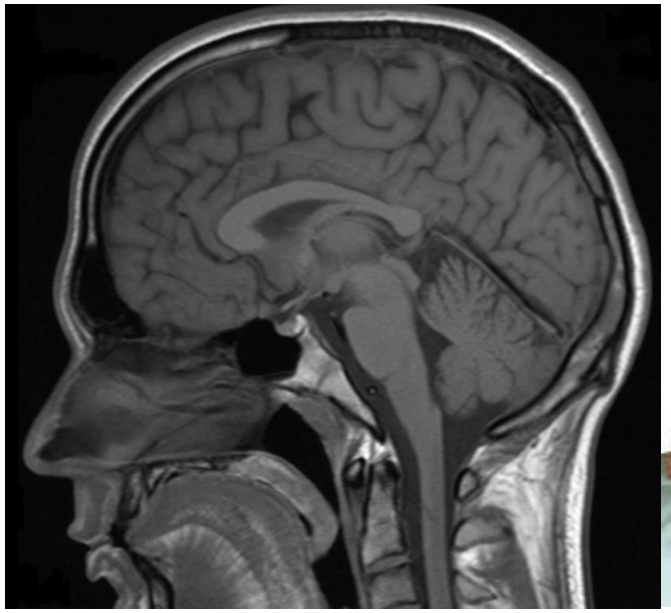
S Kayser, M., & Dalmau, J. (2011). Anti-NMDA receptor encephalitis in psychiatry. *Current psychiatry reviews*, *7*(3), 189-193.

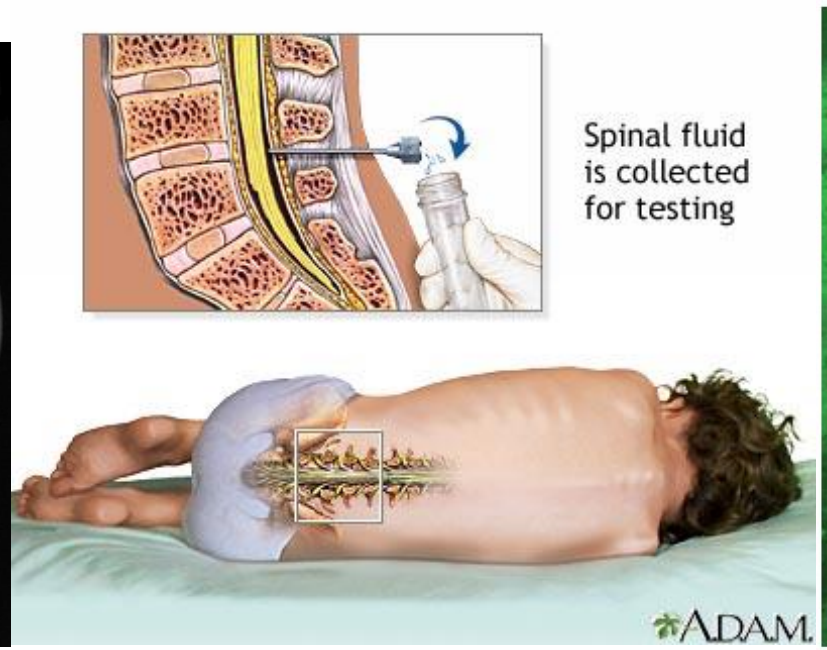


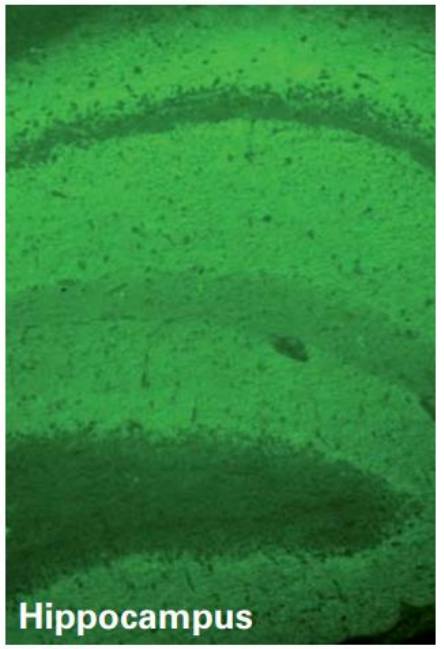
Titulaer, et. al., 2013

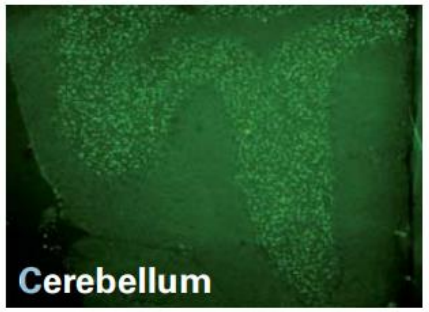
Diagnosis

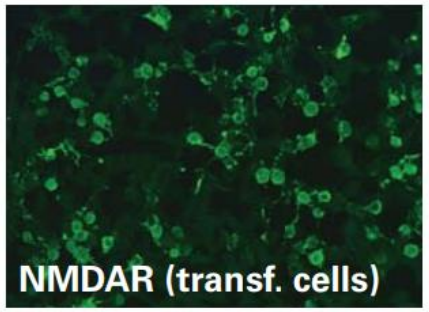
- Diagnosis is made using a combination of clinical presentation, imaging (MRI preferred), EEG, CSF analysis and serological investigations











Diagnosis-initial screening

- Serology
  - FBC, UEC, LFT, CRP
  - EBV, Streptococcus, Mycoplasma pneumoniae serology
  - ~~Lyme (Borrelia), Rabies, others~~
  - ~~ANA, ANCA, APLAs~~
  - ~~Toxins, Ammonia~~
  - ~~Thyroid antibodies~~
  - Neuronal and Limbic encephalitis antibodies

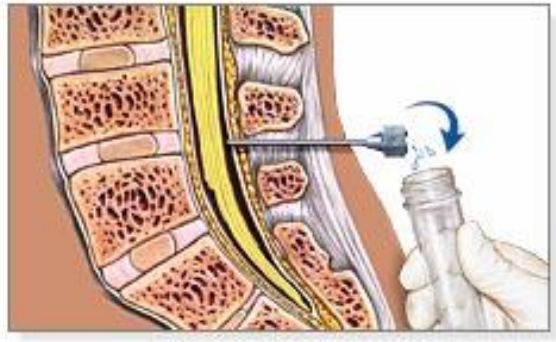
- CSF analysis
  - Biochemistry-Protein, glucose, cell count with differential, ~~cytology~~
  - Bacterial culture + gram stain
  - ~~Fungal culture, crytococcal antigen~~
  - Viral PCR testing
    - HSV, VZV, Enterovirus, HHV6
  - ~~VDRL~~
  - Oligoclonal Band profile
  - CSF antibody testing (as per serum)
  - ~~14-3-3 protein~~

NB: Should be guided by
- Presentation
- History/risk factors
  - Immunocompromised
  - travel
- Imaging

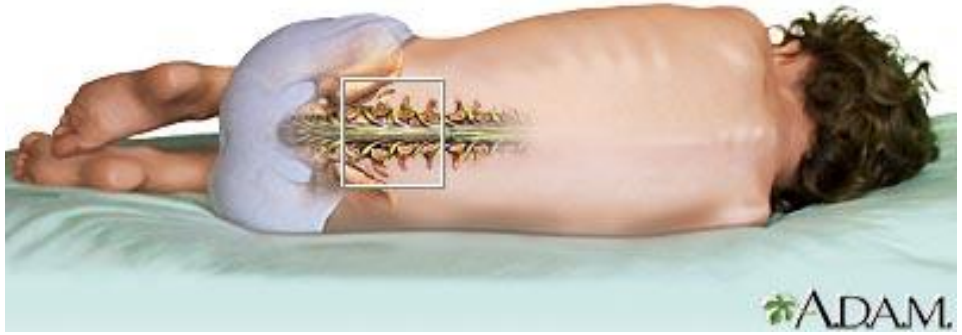
- i.e. exclusion of other disorders

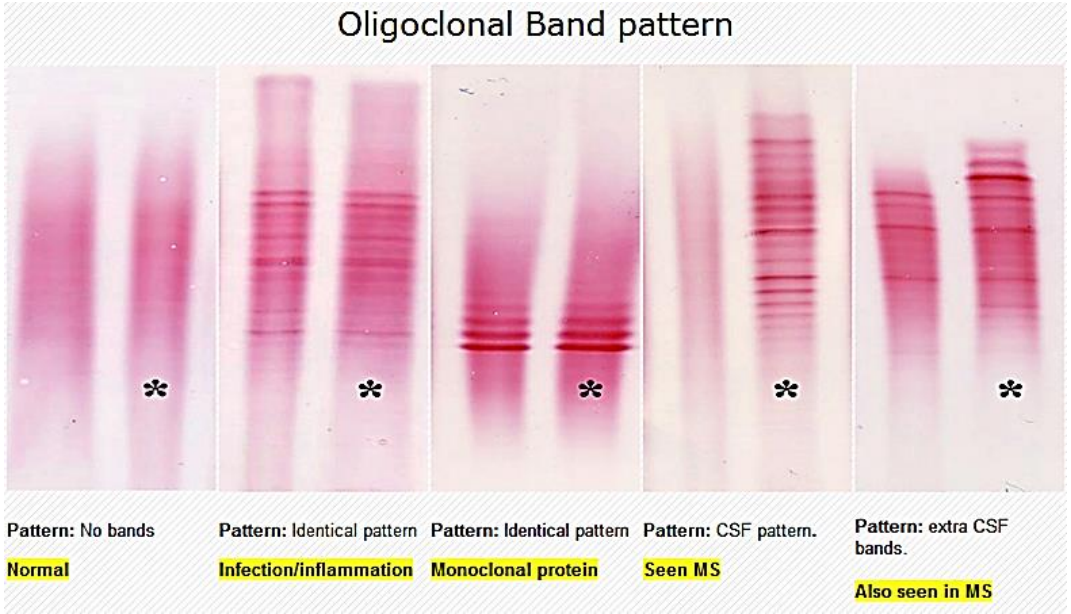
CSF

- Pleocytosis on cell count consistent
- OCB-traditionally requested to assist with diagnosis of Multiple Sclerosis.
- CSF OCBs indicate release of antibodies within CSF which can occur in a range of other conditions including CNS inflammation secondary to anti-NMDA receptor antibodies.
- CSF proteins and indices also provide information regarding integrity of the BBB and presence of immunoglobulin.



Spinal fluid is collected for testing





IMMUNOLOGY - CSF INDICES & PROTEINS Specimen type:CSF

Albumin	0.17	(< 0.35)	g/L
CSF IgG	0.06 H	(< 0.03)	g/L
CSF IgG / Albumin	35 H	(0 - 20)	%
Albumin ratio	4.5	(0.8 - 8.4)	
CSF / Serum IgG ratio	4.4	(1.0 - 7.0)	
IgG Index	1.0 H	(0.3 - 0.7)	
IEF done?	YES		

Isoelectric focussing :
See comment below

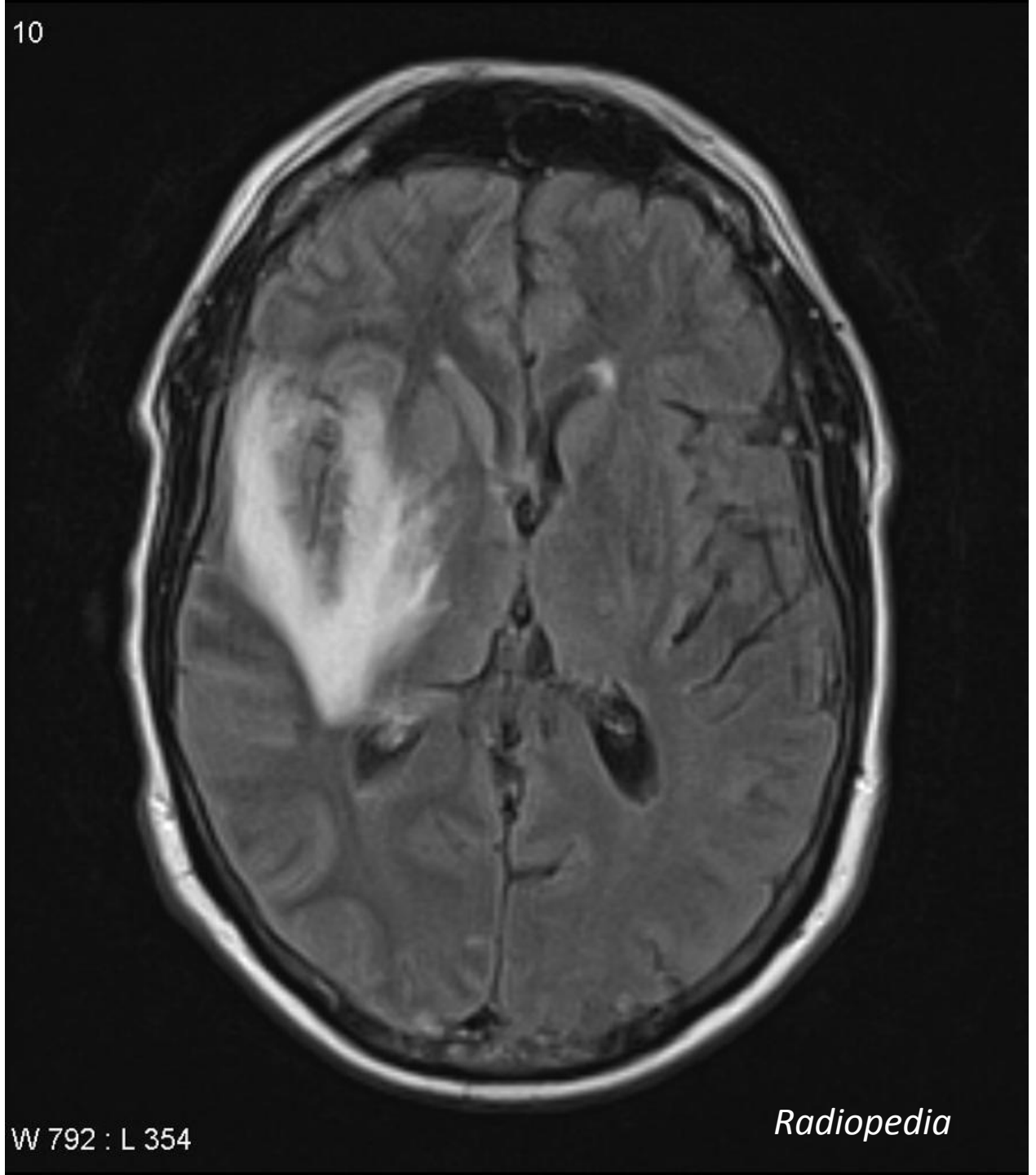
COMMENT :
CSF OCB comment: Oligoclonal IgG banding present in CSF but not serum and abnormal indices above suggest local (CNS) IgG production, and is consistent with inflammatory demyelination.

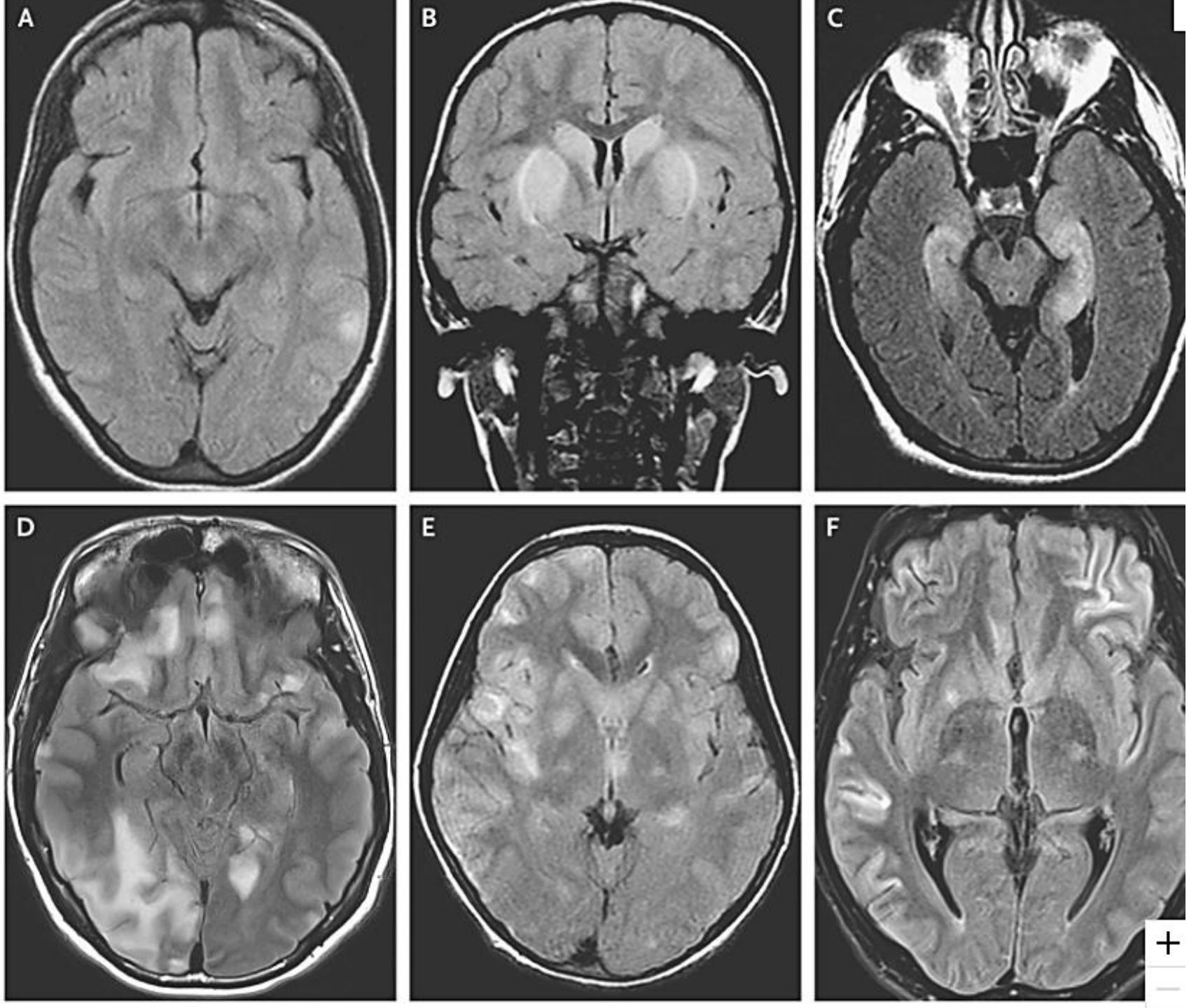
Imaging

Viral encephalitis

- Temporal Lobe
  - HSV
  - HHV6/7

  - Onco-neuronal encephalitides esp. VGKC Antibodies





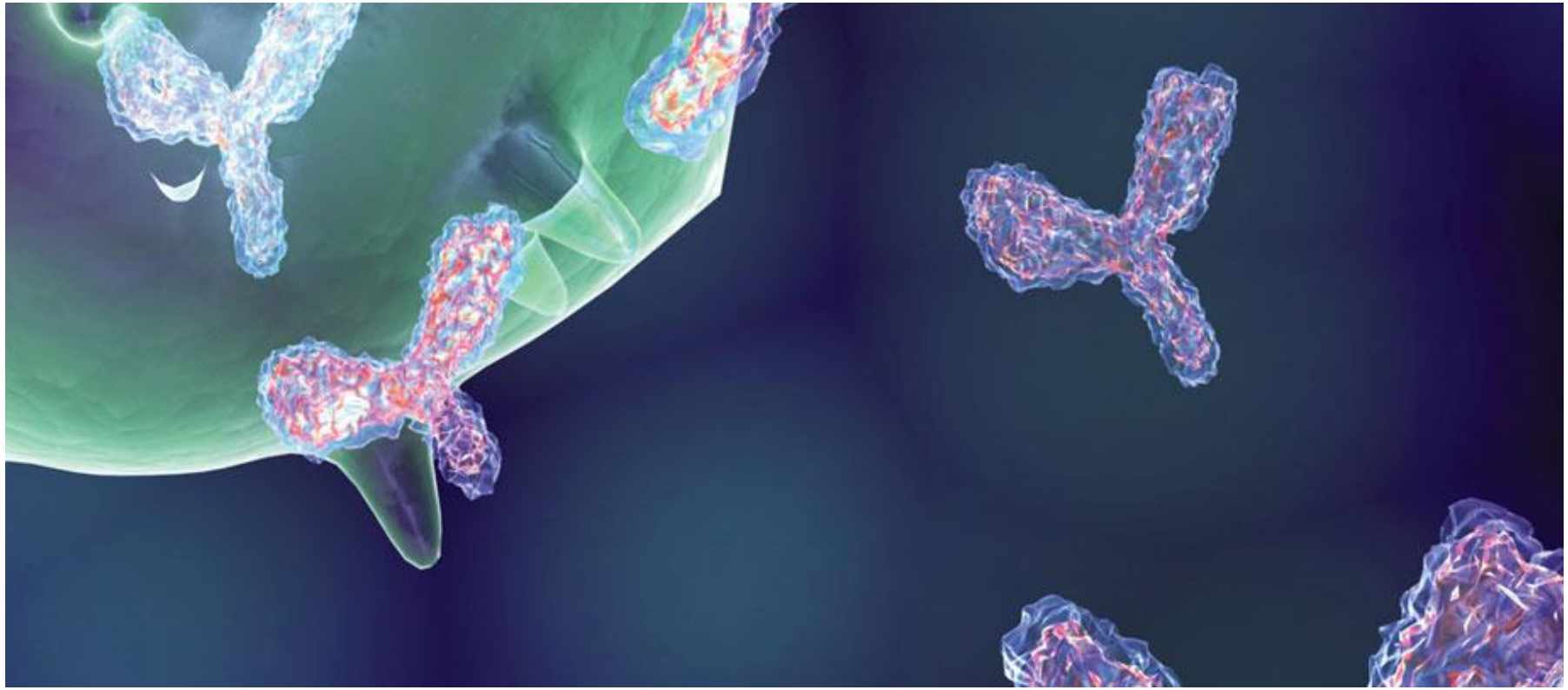
- A- Anti-NMDAR encephalitis
- B- Basal ganglia encephalitis
- C- Limbic encephalitis
- D- Encephalitis with antibodies to $GABA_AR$
- E- Acute disseminated encephalomyelitis associated with antibodies against myelin oligodendrocyte glycoprotein
- F- Severe encephalitis with AMPAR antibodies

Imaging-associated malignancy?

- The detection of systemic tumours is very important, not only because systemic tumours can be fatal in cases of delayed treatments, but also because the removal of the tumour can facilitate the recovery from autoimmune encephalitis.
- Sometimes, the size of the cancer or tumour is too small to allow its detection when the initial neurological symptoms and signs appear; repeated follow-up assessments are necessary.

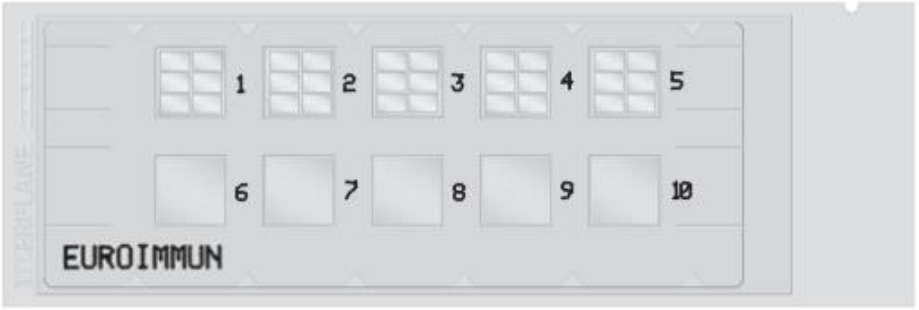
- Main imaging (once NMDARE confirmed)=
  - CT Chest, abdomen, pelvis
  - Pelvic USS (females)

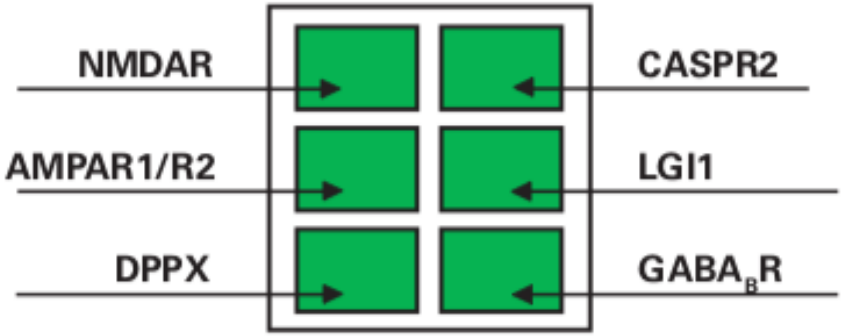
Auto-antibody detection



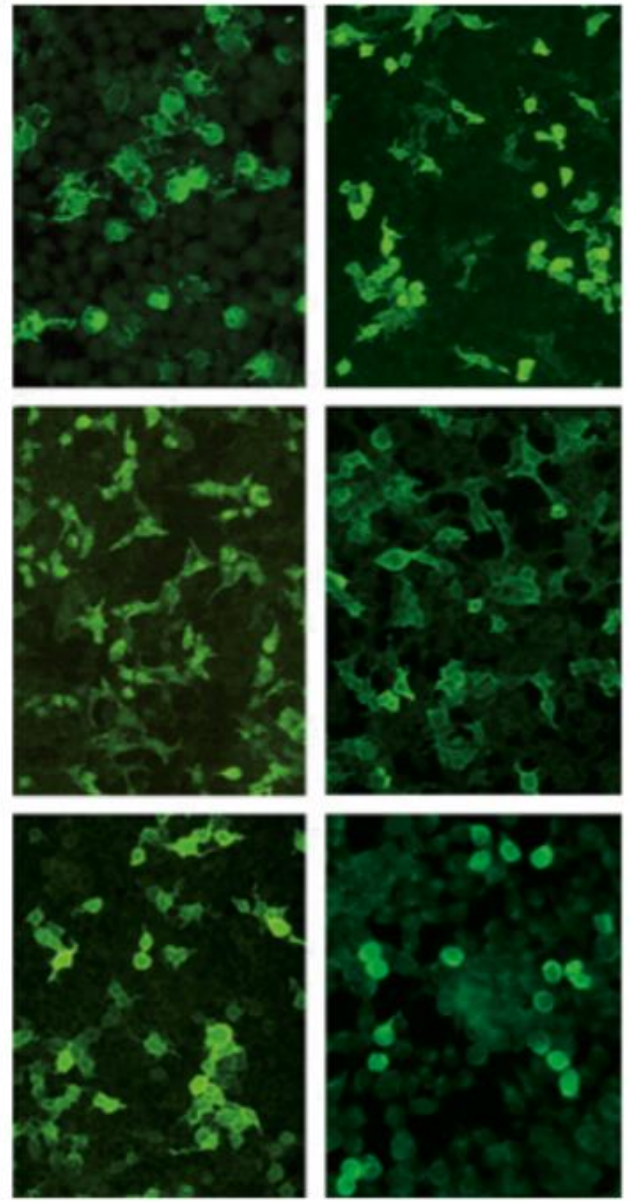
Diagnostic confirmation

Anti-NMDA receptor antibody detection





- **<u>Up to 30% of samples are positive only in CSF</u>**, hence negative or equivocal results in serum should prompt CSF testing if clinical suspicion is high.
- Analytical sensitivity-unknown, Specificity ~100%*-CSF N.B. >serum (also other conditions)
- No MBS-item number-$120 or $60 for individual antigens.



Transfected cells: antibodies against NMDAR and CASPR2 (top), AMPAR1 and LGI1 (middle), AMPAR2 und GABAB-R (bottom)

Treatment

- Based largely on retrospective series and expert opinion, since few clinical trials have been conducted.
- The current approach includes immunotherapy and removal of the immunological trigger such as teratoma, when applicable.
- Most patients are treated with steroids, IVIG, or plasma exchange, and if there is no clinical response Rituximab or Cyclophosphamide are used (second line).
- Of note, studies suggest an increased susceptibility to the adverse effects of neuroleptic agents (e.g. neuroleptic malignant syndrome).

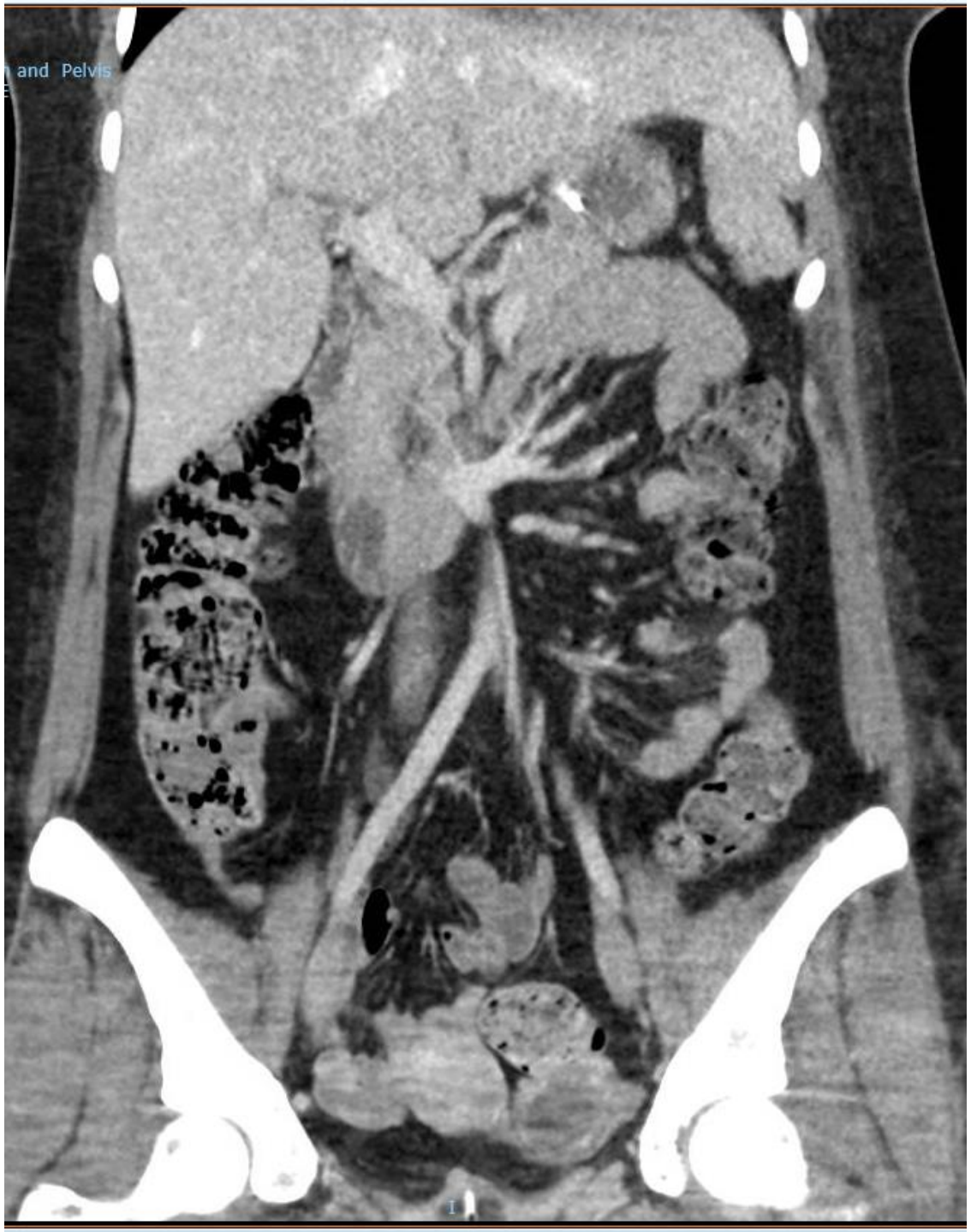
Prognosis

- The speed of recovery, degree of residual deficit, and frequency of relapse vary according to the type of autoimmune encephalitis.
- In a series of 577 patients with anti-NMDAR encephalitis,
  - 53% had clinical improvement within 4 weeks, and
  - 81% had substantial recovery (i.e. mild or no residual symptoms) at 24 months.
  - (Mortality up to 20%)
- For all types of autoimmune encephalitides, prompt immunotherapy has been associated with a favourable outcome; spontaneous clinical improvement is infrequent.
- In those associated with malignancy, particularly with antibodies to intracellular antigens, the rate of response to immunotherapy is lower. Outcomes are better with surgery.
- Frequency of relapses range from 12-35%.
- Relapses often occur when immunotherapy is reduced or discontinued and may herald the recurrence of the associated tumour, or a tumour that was missed in the initial episode.
- However, antibody titres correlate imperfectly with the course of the disease and may remain detectable (albeit at a low titre) after clinical recovery.

Back to ICU…

CASE

- In ICU
  - deteriorated with desaturations requiring intubation
  - CT CAP, Pelvic USS performed



CASE-Imaging reports

Abdomen and pelvis:

There is a moderate volume of gas in the urinary bladder, which is o
the indwelling catheter.

A rounded cystic structure is seen in the left adnexa, which is bette
recent ultrasound.

The small and large bowel loops, kidneys, adrenal glands, spleen, li
pancreas have a normal appearance. The aorta, IVC and portal vein

No destructive osseous lesion is seen.

Comment:

1. No evidence of malignancy is identified.

2. There is complete left lower lobe collapse with subsegmental atelectasis elsewhere.

Pelvic ultrasound

Transvaginal ultrasound was performed. Note is made of the transabdominal ultrasound 19/09/2018 and CT 20/09/2018.

There are again two anechoic cystic structures within the left ovary. These measure 25 mm and 30 mm respectively. The 30 mm lesion has a collapsed morphology and likely represents a partially collapsed cyst. There are no suspicious features. There is no free fluid. The ovary has normal vascularity.

The right ovary measures 6 cc and demonstrates several physiological follicles.

The uterus is anteverted normal size. The endometrium measures 3 mm.

Conclusion

Left ovarian lesions likely represent benign dominant follicles. There are no features to suggest teratoma/dermoid.

Best management???

CASE

- Left oophorectomy

- Treated with Pulsed methylprednisolone x 5/7
- 5 doses IVIG

- Rituximab x 2 (2 weeks apart)
- Single dose cyclophosphamide

CASE

- Histology report

This is a mature cystic teratoma with a neural component associated with a lymphocytic infitrate. A neural component with a lymphocytic infiltrate is described in anti-NMDAR encephalitis associated with mature cystic teratoma.

DIAGNOSIS
Left ovary and tube
- mature cystic teratoma

CASE-progress

- Slow progress in ICU with T1RF (and sputum plugging) requiring tracheostomy x 6/52
- Following transfer to ward she continued to make a slow recovery
  - significant short term amnesia and ongoing confusion with disorientation.
  - impulsive + ataxic gait; requiring a frame and supervision.
- Transferred to rehab yesterday!

The future?

- Markers
  - CSF
    - Neopterin, Beta 2 macroglobulin, Light chains, Cytokines

- Treatments
  - Severe refractory NMDA receptor encephalitis
    - Tocilizumab

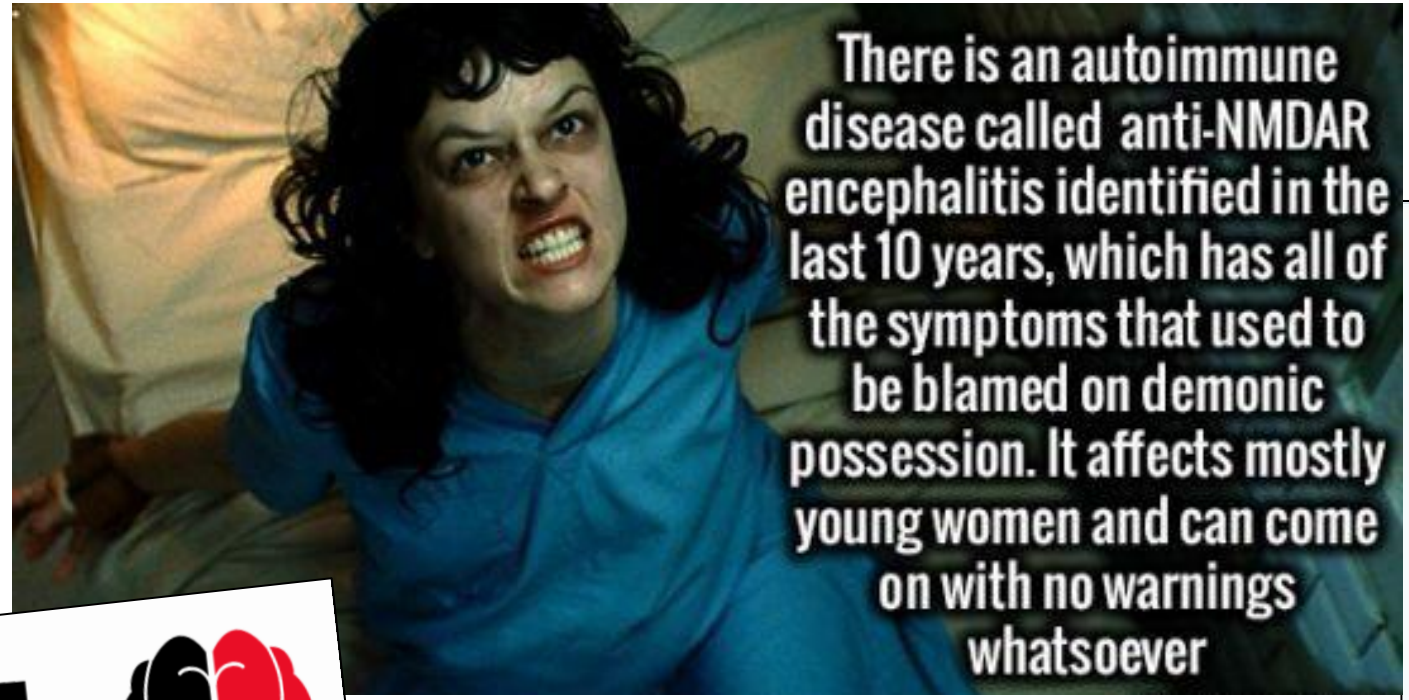
      Tocilizumab in Autoimmune Encephalitis Refractory to Rituximab: An Institutional Cohort Study. Neurotherapeutics 2016
    - Bortezomib

      Bortezomib in Severe Refractory Anti–NMDA Receptor Encephalitis: Neurology May 2018
    - Intrathecal Methotrexate

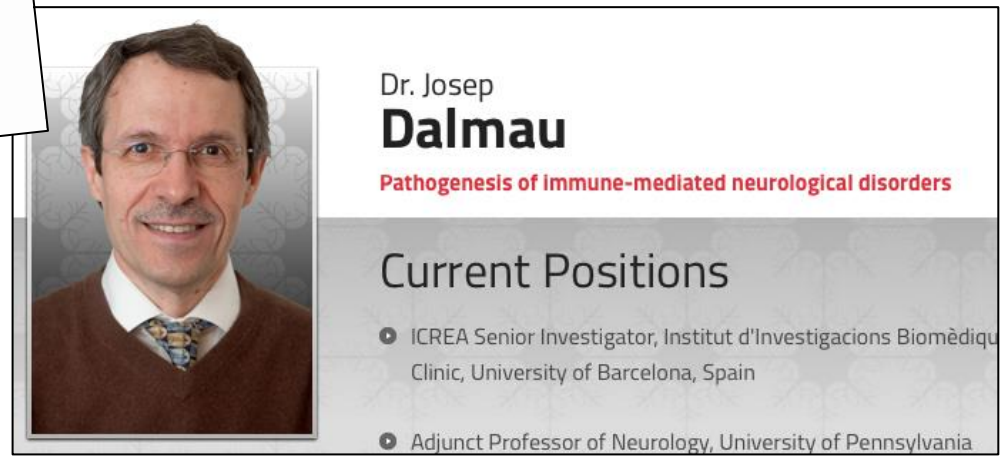
      *Successful treatment of NMDARA associated encephalitis using intrathecal methotrexate. Neurology April 2016**
    - Others

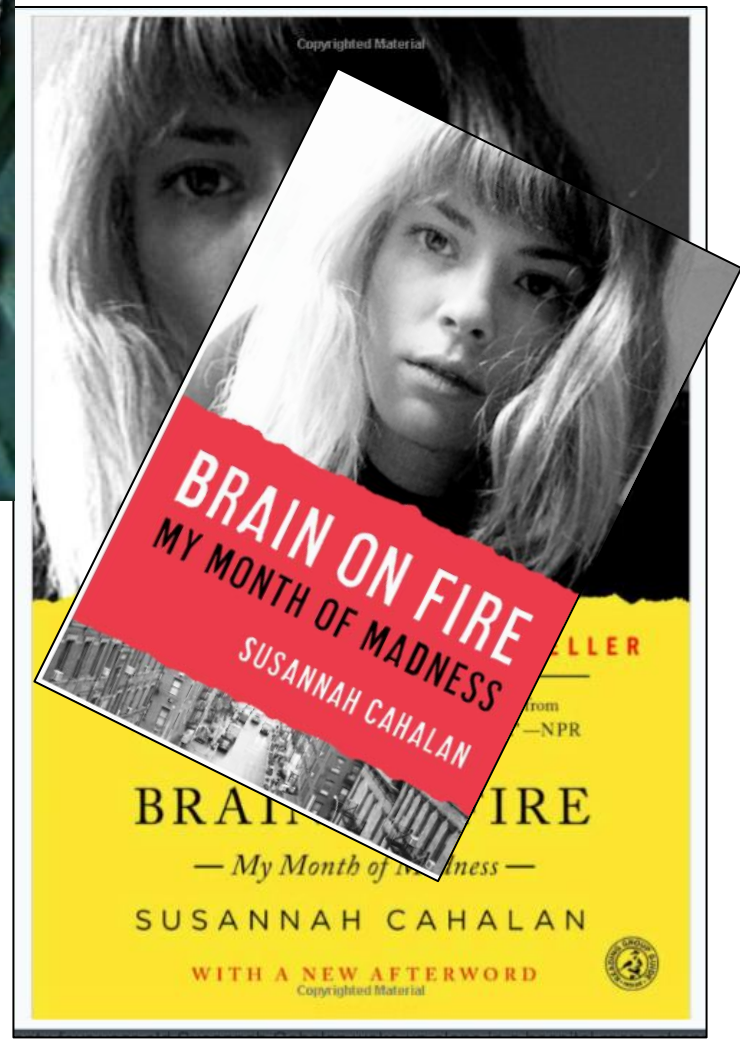
- Awareness
- Other autoantibodies to be detected?

Media



The Anti-NMDA Receptor Encephalitis ©Foundation Inc.





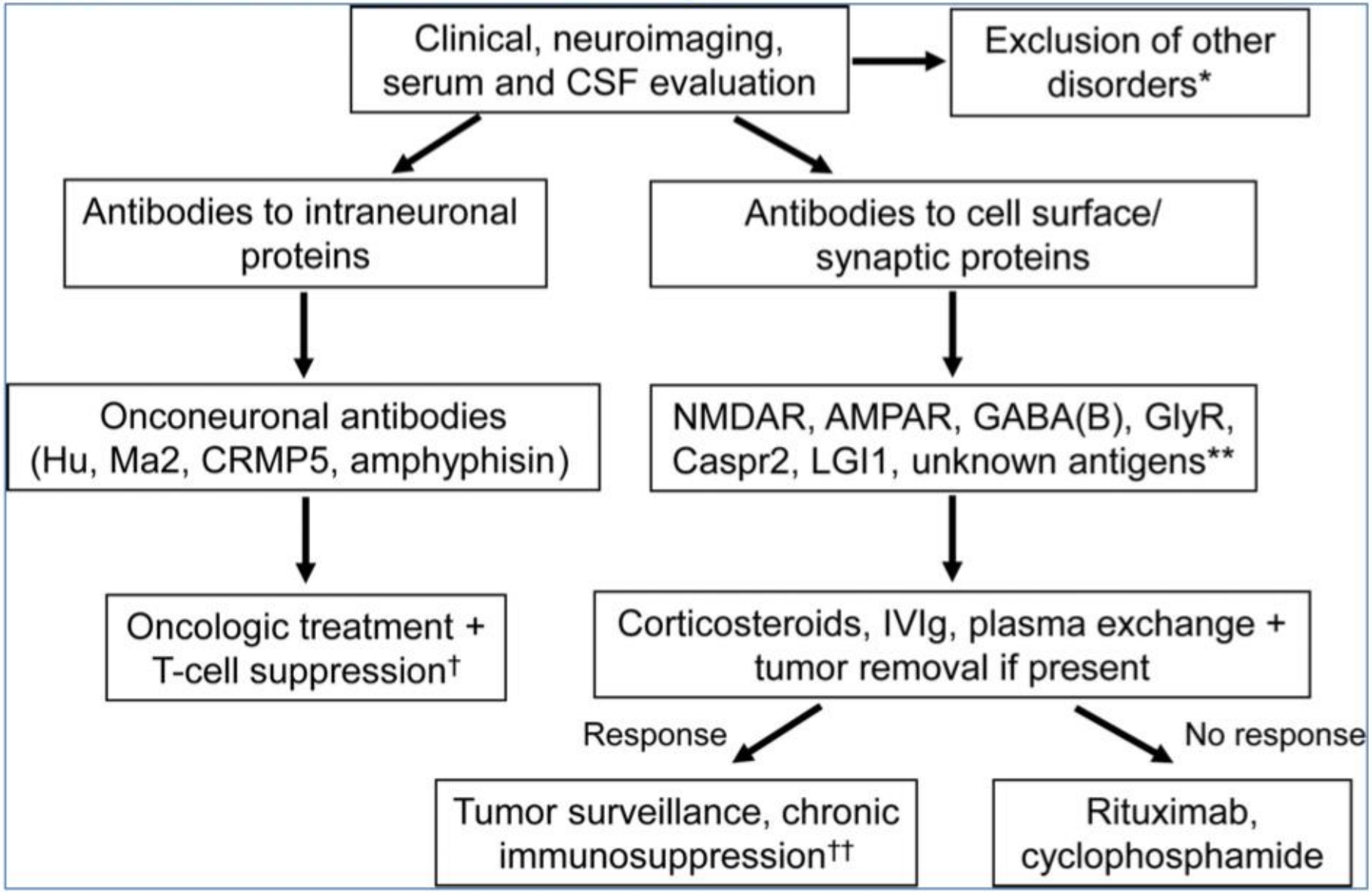

NETFLIX

Summary

- Autoimmune encephalitis is divided into 2 main categories; classic onco-neuronal encephalitis that is generally paraneoplastic, and limbic encephalitis of which anti-NMDA receptor encephalitis is one of the most common forms.
- Autoantibodies within these categories can causes syndromes other than encephalitis.
- NMDA receptor encephalitis has a multiphasic presentation, usually with a prodrome, psychiatric followed by neurological symptoms and subsequent slow resolution (with treatment).
- Up to 50% females and <5% males with anti-NMDA receptor encephalitis have an underlying malignancy (ovarian teratomas being most common).
- EBV and Mycoplasma infections have also been associated with development of these antibodies.
- Anti-NMDA receptor antibody detection is most sensitive and specific in CSF (~30% cases missed, and antibodies detectable in other conditions in serum).
- Early recognition and treatment with immunosuppression (and surgery when appropriate) leads to better outcomes.
- ~80% of patients with anti-NMDAR encephalitis recover within 2 years, leaving ~20% with persistent morbidity or mortality. This severe form of encephalitis is a particularly important area of ongoing research.

Summary

Algorithmic approach to diagnosis and treatment of encephalitis with antibodies to intracellular or cell surface neuronal antigens



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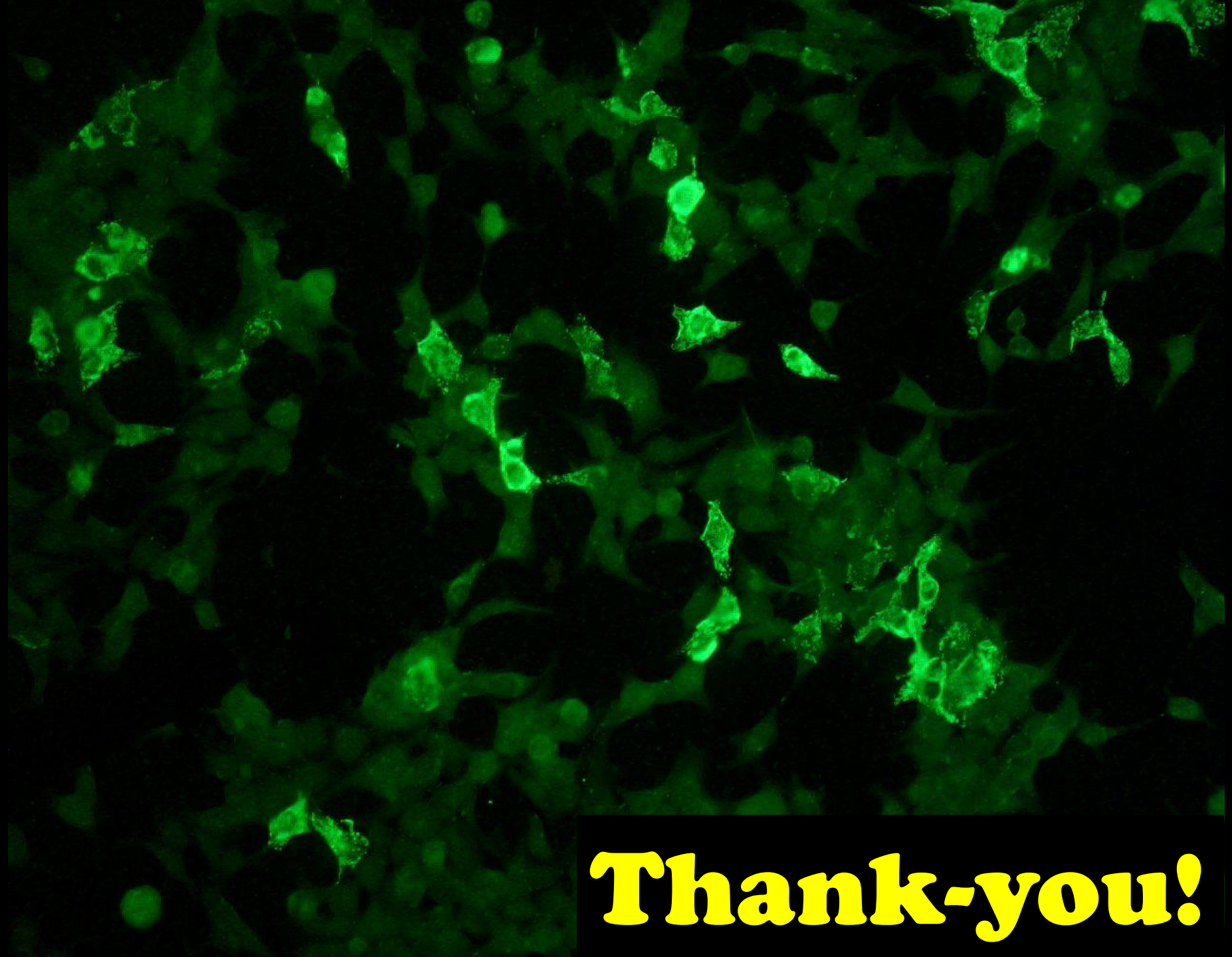

Thank-you!

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- Radiopedia