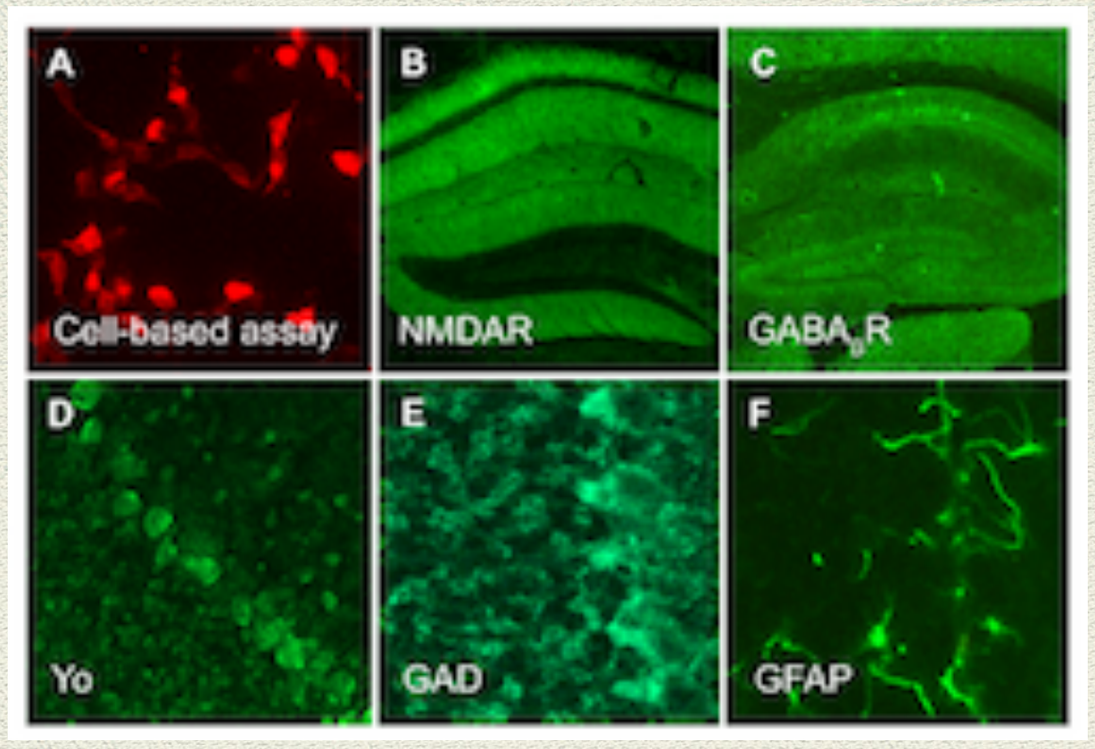
Clinical case

- 40 yr male; h/o ?mild brief febrile illness ~2 months back; followed by abrupt onset of altered behaviour with intermittent confusion, memory lapses, ataxia, transient aphasia and diplopia. No p/h/o psychiatric illness or SUD.
- Examination: not cooperative, diaphoresis+, irrelevant answers, singing spontaneously, hyper vigilant, fluctuating attention span, anxious, paranoid ideas+, insight absent, judgment impaired.
- EEG - NAD
- MRI brain - nodular T2 hyperintense lesions along the courses of the long tracts, cerebellar hemispheres, mid brain cerebral penduncle, left sub thalamic regions and few in supratentorial parenchyma
- Serum anti NMDA-R antibody positive —> responded to immunotherapy

Neurology masquerading as psychiatry

Potentially reversible psychosis: Insight into autoimmune encephalitis



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When to suspect autoimmune encephalitis

Herken J and Prüss H (2017) Red Flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients. Front. Psychiatry 8:25. doi: 10.3389/fpsyt.2017.00025

- Red flags 

1. Cerebrospinal fluid (CSF) lymphocytic pleocytosis or CSF-specific oligoclonal bands without evidence for infection
2. Epileptic seizures
3. Faciobrachial dystonic seizures
4. Suspected neuroleptic malignant syndrome
5. MRI abnormalities (mesiotemporal hyperintensities, atrophy pattern)
6. EEG abnormalities (slowing, epileptic activity or extreme delta brush)

When to suspect autoimmune encephalitis

Herken J and Prüss H (2017) Red Flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients. Front. Psychiatry 8:25. doi: 10.3389/fpsyt.2017.00025

- Yellow flags 

1. Decreased levels of consciousness
2. Abnormal postures or movements (orofacial, limb dyskinesia)
3. Autonomic instability
4. Focal neurological deficits
5. Aphasia or dysarthria
6. Rapid progression of psychosis (despite therapy)
7. Hyponatremia
8. Catatonia
9. Headache
10. Other autoimmune diseases (e.g., thyroiditis)

What is encephalitis

Susanna E et al. An evolving redefinition of autoimmune encephalitis, Autoimmunity Reviews, Volume 18, Issue 2, 2019, Pages 155-163.
Harry A et al. The immunobiology of autoimmune encephalitides, Journal of Autoimmunity, Volume 104, 2019, 102339.

- Encephalitis often refers to inflammation of brain parenchyma. Meningoencephalitis - meningeal involvement.
- Diagnosis as per Consensus Statement of the International Encephalitis Consortium requires evidence of:

A. An altered mental status lasting ≥24 h with no alternative cause identified (**major** criterion) along with 2 or more **minor** criteria, including

1. fever ≥38 °C within the 72 h before or after presentation,
2. generalized or partial seizures that were not fully attributable to a pre-existing seizure disorder,
3. a new onset of focal neurologic findings,
4. CSF pleocytosis (white blood cell count ≥5/mm3),
5. abnormality of brain parenchyma on neuroimaging, and abnormality on electroencephalography (EEG) not ascribable to other causes.

B. Two of these minor criteria were needed for a possible diagnosis of encephalitis and ≥ 3 for a probable or confirmed diagnosis.

- Last 15 years, significant advances in the identification of encephalitis aetiologies: bacteria, viruses, fungi, parasites and particularly autoimmune etiology.

Autoimmune Encephalitis (AE)

Vincent A et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004;127:701–12.
Dalmau J et al. Paraneoplastic anti-N-methyl-D aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61(1): 25–36.

- Limbic encephalitis first described in 1960s. Refers to the subacute onset of episodic memory loss, confusion, and agitation.

- Autoimmune encephalitis dates back to 1970s. In 2005, the first specific antibody subtype, anti-NMDAR, was identified by Dr Josep Dalmau and his team.

Immunological mechanisms: AE

Susanna E et al. An evolving redefinition of autoimmune encephalitis, Autoimmunity Reviews, Volume 18, Issue 2, 2019, Pages 155-163.

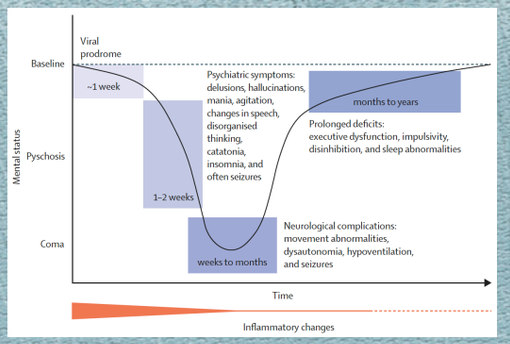
Mechanism	Antigens involved
Production of antibodies directed against intracellular antigens	Hu, MA2, glutamic acid antibodies against Hu (also defined type 1 anti-neuronal nuclear autoantibody, ANNA1), Ma2, glutamic acid decarboxylase (GAD)
Production of antibodies against synaptic receptors	N-methyl-D-aspartate (NMDA), γ-aminobutyric acid A (GABAAR), γ-aminobutyric acid B (GABABR), α-amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), metabotropic glutamate receptor 5 (mGluR5), dopamine 2 receptor
Production of antibodies targeting ion channels and cell surface proteins	Leucine-rich glioma inactivated-1 (LGI1), contactin-associated protein-like 2 (Caspr2), dipeptidyl-peptidase-like protein 6 (DPPX), myelin oligodendrocyte glycoprotein (MOG), aquaporin 4, ganglioside GQ1b

Anti-NMDAR AE

Dalmau J et al, An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models, The Lancet Neurology,Vol 18, Issue 11, 2019, 1045-1057.

- Estimated incidence 1.5/million population/year.
- At onset, ~ 90% patients have prominent psychiatric or behavioural symptoms that can be difficult to differentiate from a primary psychiatric disease.
- Female predominance (F:M ratio ~8:2), age distribution (median 21 years, range <1–85 years.)
- ~80% patients improved or recovered after immunotherapy and (when needed) tumour removal.
- Early treatment and no admission to an intensive care unit were identified as predictors of good outcome.
- Within the first 2 years of the disease, 12% of patients had relapses that were usually less severe than the initial episode.

Anti-NMDAR AE



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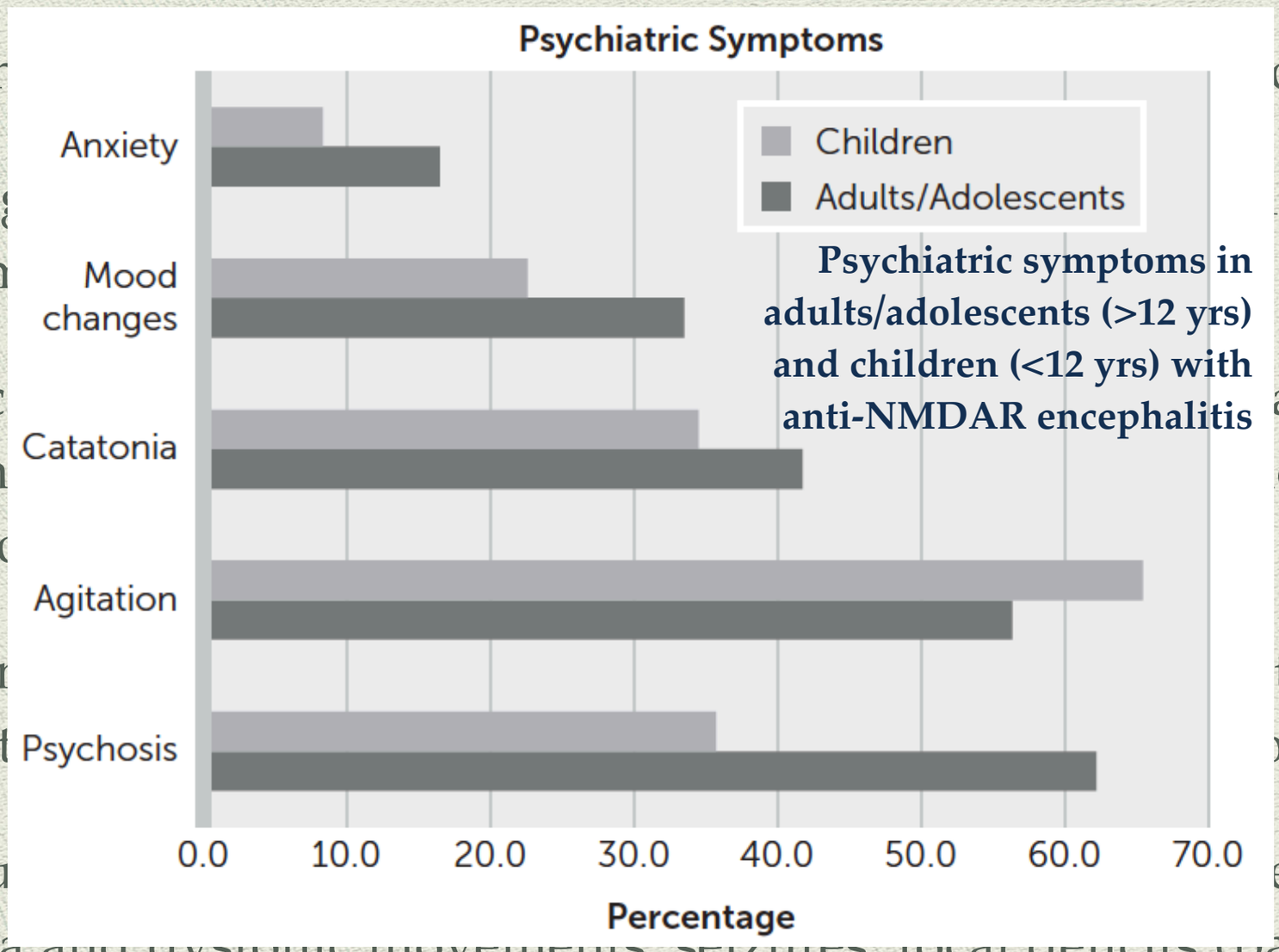
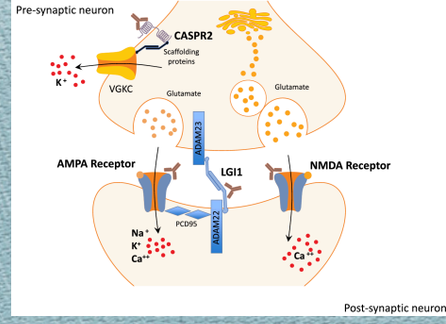
- Most commo or.
- Antibodies a ters synaptic function in lim
- Characteristic a, irritability, abnormal beh deations, and hypoventilati
- Due to predo tially referred to psychiatris leptics.
- Symptoms qu ent disorders, such as chorea and dystonic movements, seizures, focal deficits (paresis, ataxia), speech impairment, amnesia or coma.



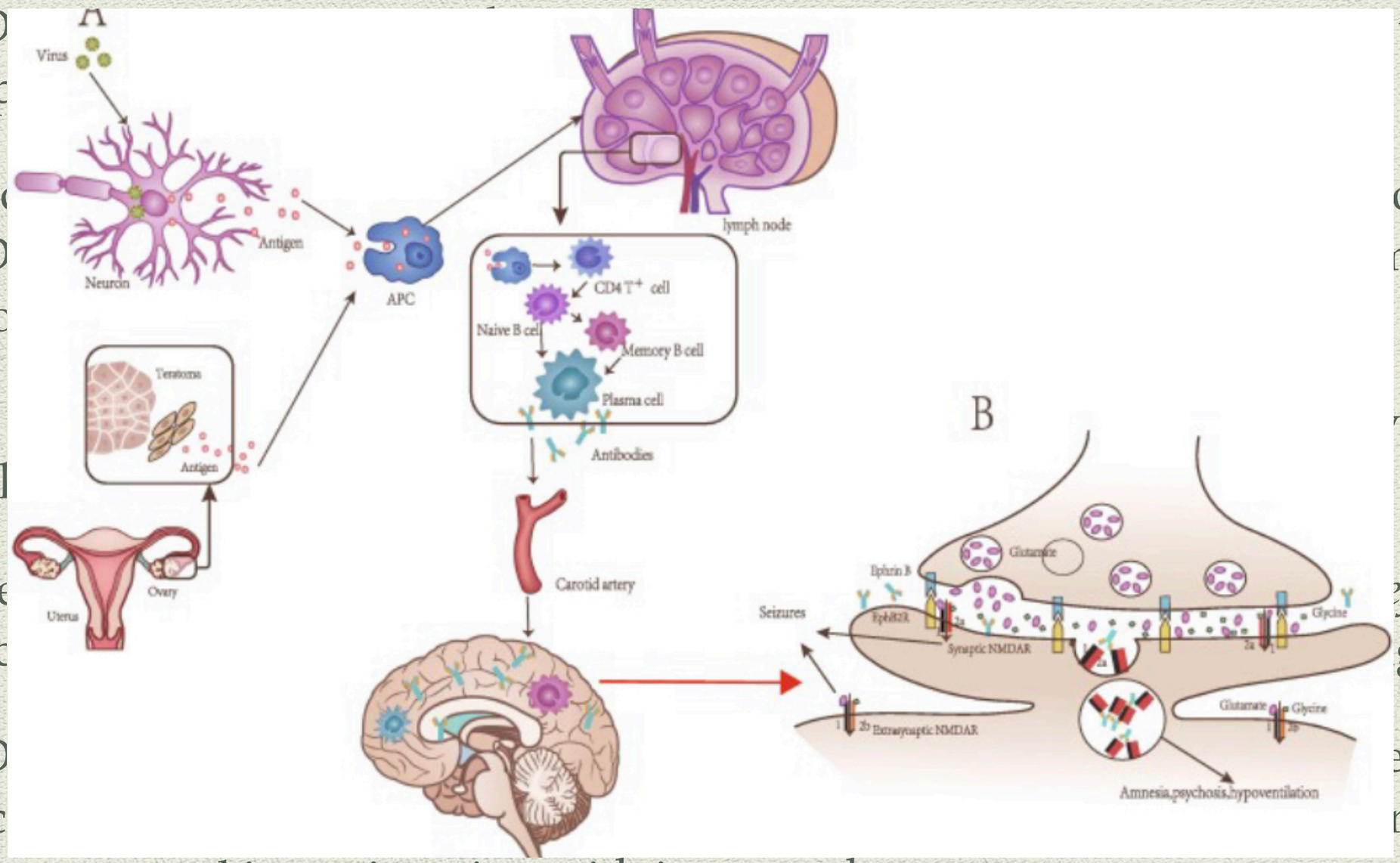
Psychiatric symptoms in adults/adolescents (>12 yrs) and children (<12 yrs) with anti-NMDAR encephalitis

Anti-NMDAR AE



Harry A et al. The immunobiology of autoimmune encephalitides, Journal of Autoimmunity, Volume 104, 2019, 102339.

- NMD… the post-synap…
- Neur… on of the NMD… nate and excito…
- If the … recovers and th…
- Howe… *eficits* due to exc… ging).
- NMD… eratomas, espec… ms upon tumour removal in conjunction with immunotherapy.



Anti-NMDAR AE

Dalmau J et al, An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models, The Lancet Neurology,Vol 18, Issue 11, 2019, 1045-1057.

- Neuronal antibody testing helps confirm the diagnosis.
- In clinical laboratories, this test is a cell based assay (CBA) in which a patient's CSF or serum reactivity against NMDARs is examined using a human embryonic kidney cell line (HEK 293) that expresses the receptors.
- Any CBA technique, either with fixed or live cells, if used without confirmatory tests (eg, brain immunostaining) might lead to false-positive or false negative results (in 2–14% of cases). These drawbacks are avoided if CSF is used.

Anti-NMDAR AE

Dalmau J et al, An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models, The Lancet Neurology,Vol 18, Issue 11, 2019, 1045-1057.

Diagnostic criteria of anti-NMDAR encephalitis

Probable

- Rapid onset (<3 months) of at least four of the six major groups of symptoms:
  - Abnormal (psychiatric) behaviour or cognitive dysfunction
  - Speech dysfunction (pressured speech, verbal reduction, or mutism)
  - Seizures
  - Movement disorder, dyskinesias, rigidity, or abnormal postures
  - Decreased level of consciousness
  - Autonomic dysfunction or central hypoventilation
- And at least one of the laboratory studies:
  - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
  - CSF with pleocytosis or oligoclonal bands
- Or three of the above groups of symptoms and identification of a systemic teratoma
- Exclusion of recent history of herpes simplex virus encephalitis or Japanese B encephalitis, which might result in relapsing immune-mediated neurological symptoms

Definite

- One or more of the six major groups of symptoms and IgG GluN1 antibodies (antibody testing should include CSF); if only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to a cell-based assay)
- Exclusion of recent history of herpes simplex virus encephalitis or Japanese B encephalitis, which might result in relapsing immune-mediated neurological symptoms

Anti-NMDAR AE

Rössling, R., Prüss, H. SOP: antibody-associated autoimmune encephalitis. *Neurol. Res. Pract.* **2,** 1 (2020).

Diagnostic algorithm

Obtain history, clinical symptoms

- Subacute onset (< 3 months)
- Disturbed consciousness
- Working memory deficits
- Autonomic symptoms
- Aphasia/ Dysarthria
- Catatonia, suspected NMS
- New epileptic seizures
- Psychiatric symptoms/ behavioural changes
- Dyskinesia, facio-brachial dystonic seizures
- New focal neurological signs
- Hyponatremia
- Other autoimmune disorders

Suspected AE

No → **Exclusion of alternative causes**
- Viral encephalitis
- NMO, MS, ADEM
- Intoxication
- Vasculitis
- Prion disease
- Psychiatric disease
- Meningitis

Yes →

EEG
- Epileptic activity
- Slow wave activity (esp. including temporal lobes)

CSF
- Pleocytosis
- Increased protein
- Oligoclonal bands

MRI
- Contrast enhancing lesions
- Atrophy
- T2/FLAIR hyperintensities in medial temporal lobes

MRI, EEG, CSF can be normal in AE!

Anti-NMDAR AE

Rössling, R., Prüss, H. SOP: antibody-associated autoimmune encephalitis. *Neurol. Res. Pract.* **2,** 1 (2020).

…Diagnostic algorithm

Exclusion of alternative causes
- Viral encephalitis
- NMO, MS, ADEM
- Intoxication
- Vasculitis
- Prion disease
- Psychiatric disease
- Meningitis

Antibody detected ? Serum / CSF

No

Ongoing clinical suspicion ?

Yes

Research lab - new Ab?

No

Ongoing clinical suspicion ?

Yes

Exclusion of AE

Yes

Antibody negative AE

Yes

Compatible with clinical syndrome ?

No

Evidence of classical PNS?
Limbic encephalitis
Encephalomyelitis
Cerebellar degeneration
Opsoclonus-myoclonus

MRI
T2/FLAIR hyperintensities in medial temporal lobes

Yes

Surface Ab

Onconeural Ab

Tumor screening

Probable AE

Definite AE

Definite PNS

Definite Limbic encephalitis

Therapy
symptomatic
immunotherapy
tumor therapy

Therapy of AE

Rössling, R., Prüss, H. SOP: antibody-associated autoimmune encephalitis. Neurol. Res. Pract. 2, 1 (2020).

- Therapy depends on the clinical syndrome and the underlying antibody.
- Early therapy is critical.
- First-line therapy in antibody-mediated AE comprises:
  1. high-dose intravenous methylprednisolone (1gm/d i.v. for 5 days),
  2. therapeutic apheresis (at least 5 times every other day, in cases with predominant CSF antibodies usually 7–10 treatments needed),
  3. intravenous immunoglobulins (2 g/kg body weight over 3–5 days).
- If no treatment effect after two weeks, initiate second-line therapy.

Therapy of AE

Rössling, R., Prüss, H. SOP: antibody-associated autoimmune encephalitis. Neurol. Res. Pract. 2, 1 (2020).

- Second-line therapy used by majority: rituximab (1gm, at day 1 and day 15 followed by 6 months intervals).
- Cyclophosphamide is another option for second-line therapy and might be combined with rituximab.
- Many other treatments have been used with variable success, including mycophenolat mofetil, methotrexate or azathioprine.
- Promising new data suggest that the proteasome inhibitor bortezomib might be a valuable option in patients with surface antibody-mediated AE. daratumumab, tocilizumab or autologous stem cell transplantation.
- If high antibody titres persist parallel to clinical symptoms: repeated apheresis should be considered.
- Antibody-mediated AE can be monophasic, i.e. maintenance treatments can often be stopped after 1–3 years.

Therapy of AE

Rössling, R., Prüss, H. SOP: antibody-associated autoimmune encephalitis. Neurol. Res. Pract. 2, 1 (2020).

- Comparative studies of the respective therapeutic option are still lacking.

- Early initiation of immunotherapy is crucial not only regarding the acute phase of the disease, but also for long-term outcome.

- As shown in patients with NMDAR encephalitis, long-term outcome might be impaired by persistent cognitive deficits.

Therapy of AE

Rössling, R., Prüss, H. SOP: antibody-associated autoimmune encephalitis. Neurol. Res. Pract. 2, 1 (2020).

- Evidence of a tumour requires, if possible, prompt and complete removal to withdraw the auto-antigen that is ectopically produced on tumour cells.
- Symptomatic therapy depends on the form of AE.
- Antiepileptic therapy is frequently required as AE commonly leads to epileptic seizures.
- Antiepileptic drugs should be tapered after the encephalitic phase given that in surface antibody-mediated AE seizures are mainly acute-symptomatic.
- Psychotic symptoms often require transient treatment with antipsychotic drugs, which might also be tapered after the initial disease phase.
- With status epilepticus, autonomic symptoms or major behavioural abnormalities, patients regularly require intensive care unit treatment including sedation and mechanical ventilation.
- Physiotherapy and speech therapy can further help to improve the outcome.

Prognosticating AE

Broadley J et al. Prognosticating autoimmune encephalitis: A systematic review. Journal of Autoimmunity 96 (2019) 24–34.

Conclusions drawn from the data obtained in referenced review regarding possible correlations with outcome in autoimmune encephalitis due to any antibody and in anti-NMDAR encephalitis. Relationships are described as being likely, possible, unlikely, inconclusive or not sufficiently studied.

Association with poor outcome in		
Variable	Autoimmune encephalitis	Anti-NMDAR encephalitis
Age	Unlikely	Unlikely
Sex	Unlikely	Unlikely
Autonomic dysfunction	Inconclusive	Not sufficiently studied
Altered conscious state	Unlikely	Possible
Status epilepticus	Unlikely	Unlikely
Presence of neoplasm	Inconclusive	Unlikely (may have positive influence on remission)
MRS on presentation	Unlikely	Not sufficiently studied
MRS nadir	Possible	Unlikely
Antibody titer	Inconclusive	Inconclusive
CSF abnormalities	Unlikely	Inconclusive
MRI abnormalities	Unlikely	Unlikely
Use of immunotherapy	Not sufficiently studied	Likely
Delay in immunotherapy	Likely	Likely
ICU admission	Not sufficiently studied	Likely
Mechanical ventilation	Not sufficiently studied	Unlikely

Conclusion

Rössling, R., Prüss, H. SOP: antibody-associated autoimmune encephalitis. Neurol. Res. Pract. 2, 1 (2020).

- In patients with suspected antibody-associated AE, it is essential to analyse the patient's history for the aforementioned red/yellow flags.
- Standard diagnostic work-up includes EEG, MRI, CSF analysis and testing for anti-neuronal autoantibodies.
- 'Definite AE' or 'definite PNS' can be diagnosed when a detected antibody is compatible with the clinical syndrome.
- Treatment should be initiated as soon as possible and must not await pending antibody analysis.
- Consultation of an AE specialist (neurologist) is generally recommended before/after confirmation of the diagnosis of AE.

Let’s discuss !

–Dr Ashutosh Shah