Diagnosing autoimmune encephalitis in clinical practice: application and analysis of diagnostic algorithm in a single-center cohort.

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Background

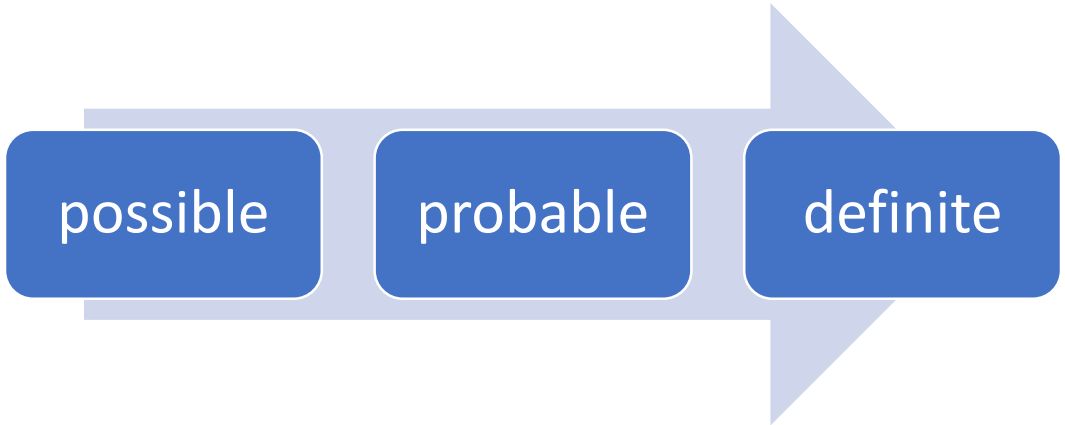
- **Early recognition** and **treatment** of autoimmune encephalitis (AE) are crucial for patients.

- Diagnosis of AE is often **difficult** and **time-consuming**.

Background

A clinical approach to diagnosis of autoimmune encephalitis

Francesc Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Iizuka, Sarosh R Irani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Reindl, Myrna R Rosenfeld, Kevin Rostásy, Albert Saiz, Arun Venkatesan, Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau



Background

- *«The next step will be to **test these guidelines in clinical practice**»*

  (Antoine JC, Lancet Neurology, Feb 2016)

- No published study has analyzed in detail the reasons for lack of criteria fulfillment in clinically defined AE in a real-world setting.

Aims

- ✓ To analyze the use and feasibility of this approach in a **real-world single-center setting**.

- ✓ To analyze the **most relevant factors** (among clinical, imaging and laboratory characteristics) to fulfillment or not fulfillment of the criteria

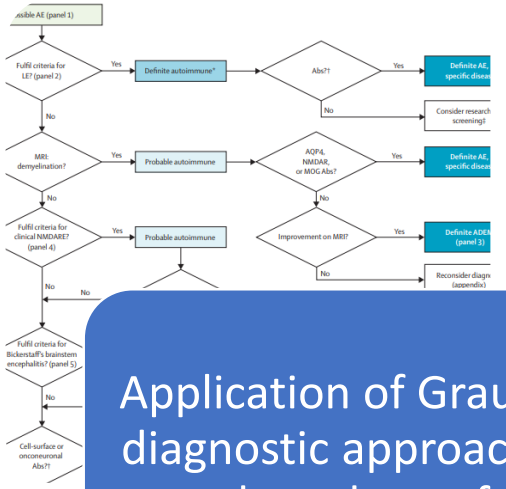
Methods

Retrospective research on medical records of patients discharged with diagnosis of AE (13.915 pts referred to our clinic between 2010 and 2018)

33 patients were found.

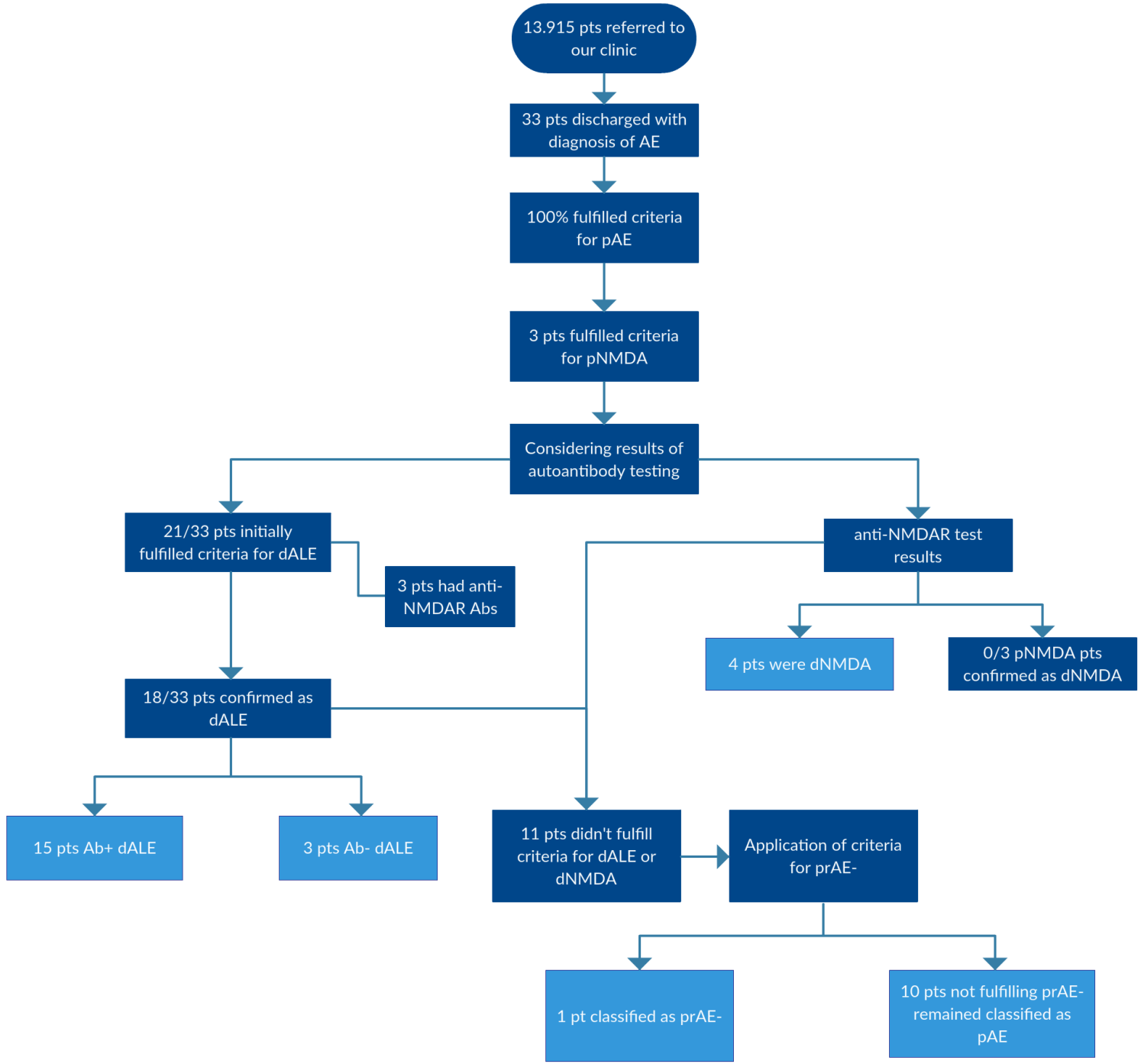
All the patients had undergone extensive search for neuronal antibodies both in serum and CSF[1].

58% was Ab+.



Application of Graus diagnostic approach to the cohort of patients and analysis of criteria fulfillment process

1. Cell-based essays were used. The following neuronal antibodies were tested: anti-N-methyl-D-aspartate-Receptor (NMDAR), anti-leucin-rich glioma-inactivated-1-protein (LGI-1), anti-contactin-associated protein-like 2 (CASPR2), anti-glutamic acid decarboxylase (GAD), anti-Ma1, anti-Ma2, anti-Yo, anti-Hu, anti-Ri and anti-CV2.


13.915 pts referred to our clinic
33 pts discharged with diagnosis of AE
100% fulfilled criteria for pAE
3 pts fulfilled criteria for pNMDA
Considering results of autoantibody testing
21/33 pts initially fulfilled criteria for dALE
3 pts had anti-NMDAR Abs
18/33 pts confirmed as dALE
15 pts Ab+ dALE
3 pts Ab- dALE
anti-NMDAR test results
4 pts were dNMDA
0/3 pNMDA pts confirmed as dNMDA
11 pts didn't fulfill criteria for dALE or dNMDA
Application of criteria for prAE-
1 pt classified as prAE-
10 pts not fulfilling prAE- remained classified as pAE

Possible AE

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

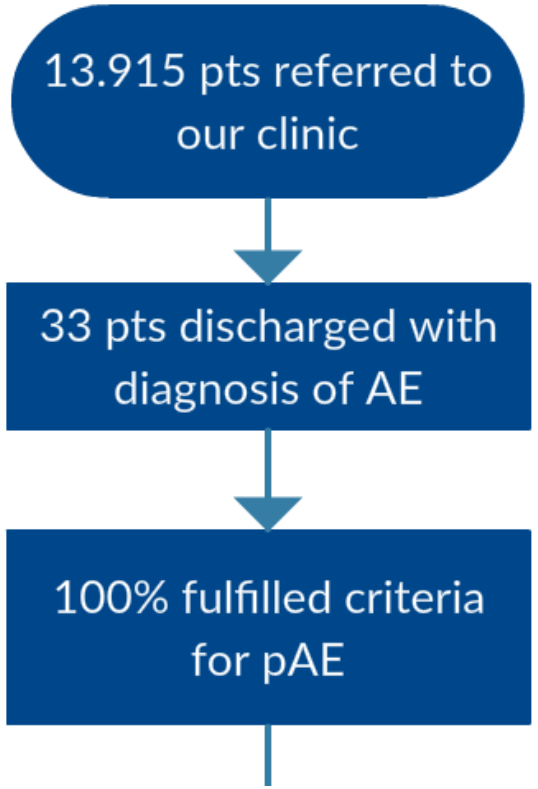
Diagnosis can be made when all three of the following criteria have been met:

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†

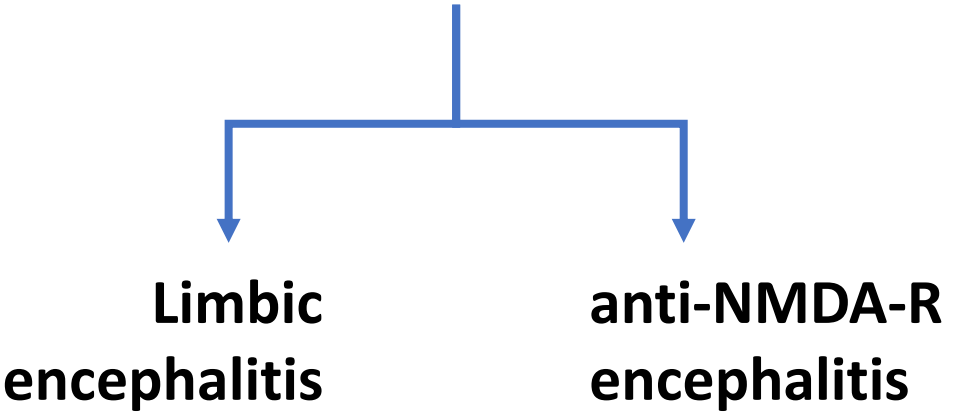
3 Reasonable exclusion of alternative causes (appendix)

*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

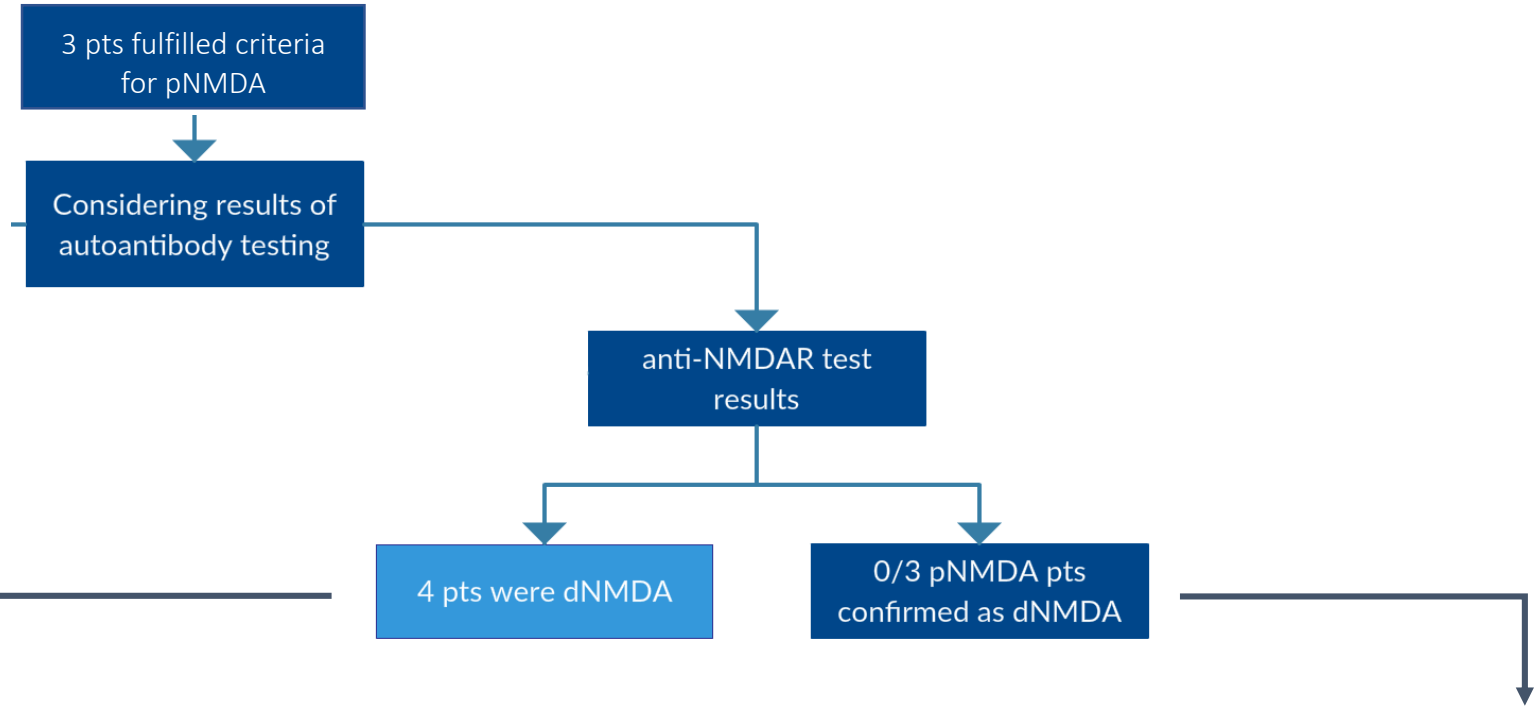


- All the subjects (**33/33**) fulfilled criteria for **possible AE** (pAE)
- **Most common features**:
  1. Typical **MRI** abnormalities (73%)
  2. **Seizures** (67%)
- **CSF pleocytosis** was found in only **24%** of the examined patients

Possible Autoimmune Encephalitis (pAE)



Anti-NMDA-R encephalitis



- **Definite anti-NMDAR** encephalitis (dNMDA) was diagnosed in **4 patients** with detection of the autoantibody.
- Surprisingly, **none of these subjects had fulfilled criteria for pNMDA**

- 2 patients were later diagnosed with dALE (LGI-1 and anti-GAD); one patient remained classified as pAE.

Anti-NMDA-R encephalitis

Panel 4: **Diagnostic criteria for anti-NMDA receptor encephalitis**

Probable anti-NMDA receptor encephalitis*

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

1 Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
   - Abnormal (psychiatric) behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation

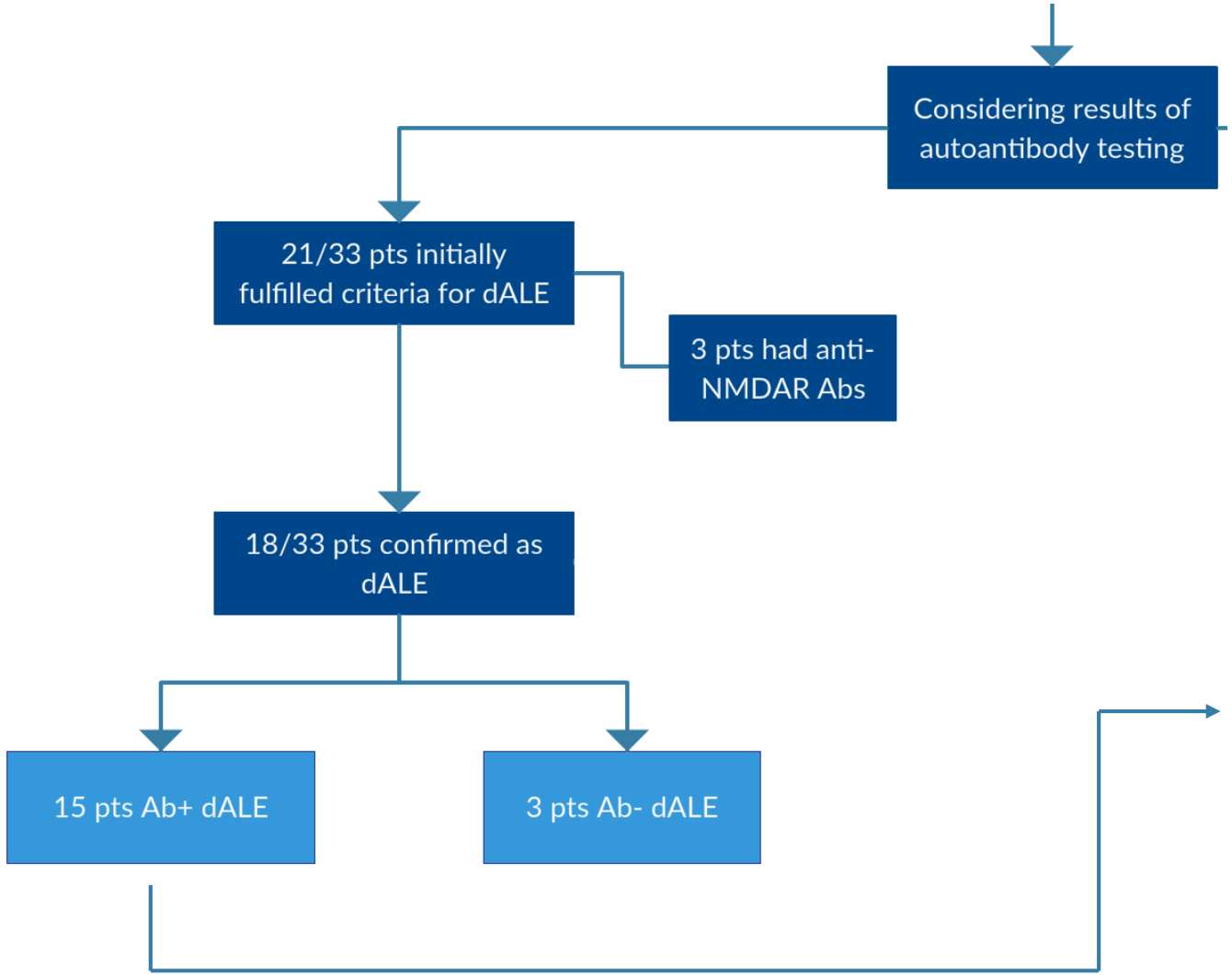
2 At least one of the following laboratory study results:
   - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands

3 Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

- **Clinical criterion** (at least 4/6 symptoms) **limited correct diagnosis in these patients**

Definite limbic AE (dALE)



Antibody	No. patients
LGI-1	10
GAD	2
Ma2	2
Hu	1

Definite limbic AE (dALE)

***Panel 2:* Diagnostic criteria for definite autoimmune limbic encephalitis**

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

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
3. At least one of the following:
   - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes (appendix)

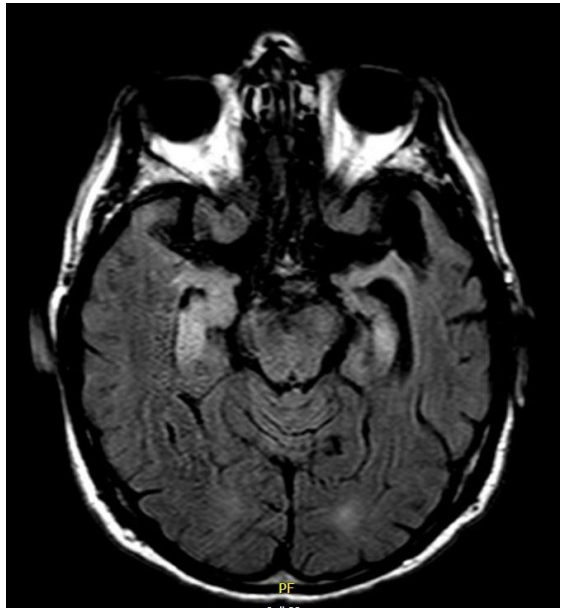
*If one of the first three criteria is not met, a diagnosis of definite limbic encephalitis can be made only with the detection of antibodies against cell-surface, synaptic, or onconeural proteins. †^{18}Fluorodeoxyglucose (^{18}F-FDG) PET can be used to fulfil this criterion. Results from studies from the past 5 years suggest that ^{18}F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal-appearing medial temporal lobes.[44,45]

- In these patients, **EEG and MRI** alone gave useful information for diagnosis in **94%** of cases
- **CSF pleocytosis** contributed to diagnosis only in **28%**
- MRI alterations are necessary and must be bilateral in Ab-negative patients → in **4 Ab-negative** MRI was positive but **unilaterally; 9 patients had negative MRI.**

Definite limbic AE (dALE)

- **Can MRI be negative when diagnosing limbic encephalitis? Yes**, if neuronal Abs are found.
- **Bilateral involvement at MRI was a major limiting factor** for diagnosis of definite limbic AE in absence of antibodies

bilateral



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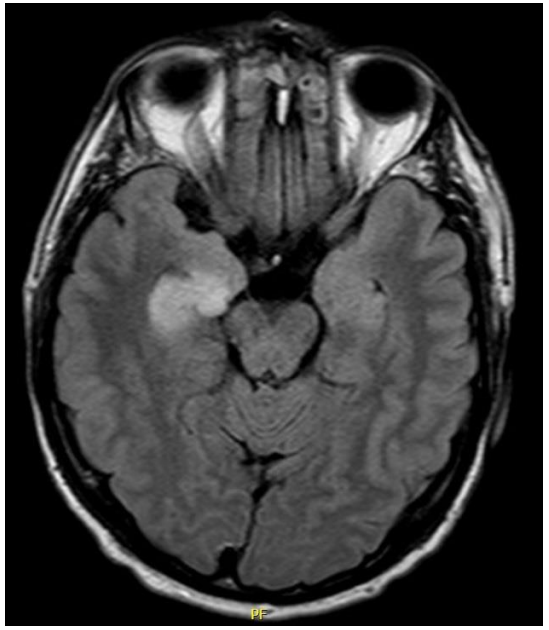


unilateral or negative

However, involvement is NOT requested for Ab+ patients
Several antibodies are being discovered over the years → reconsidering this criterion?

Probable Ab-negative AE (prAE-)

***Panel 7*: Criteria for autoantibody-negative but probable autoimmune encephalitis**

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

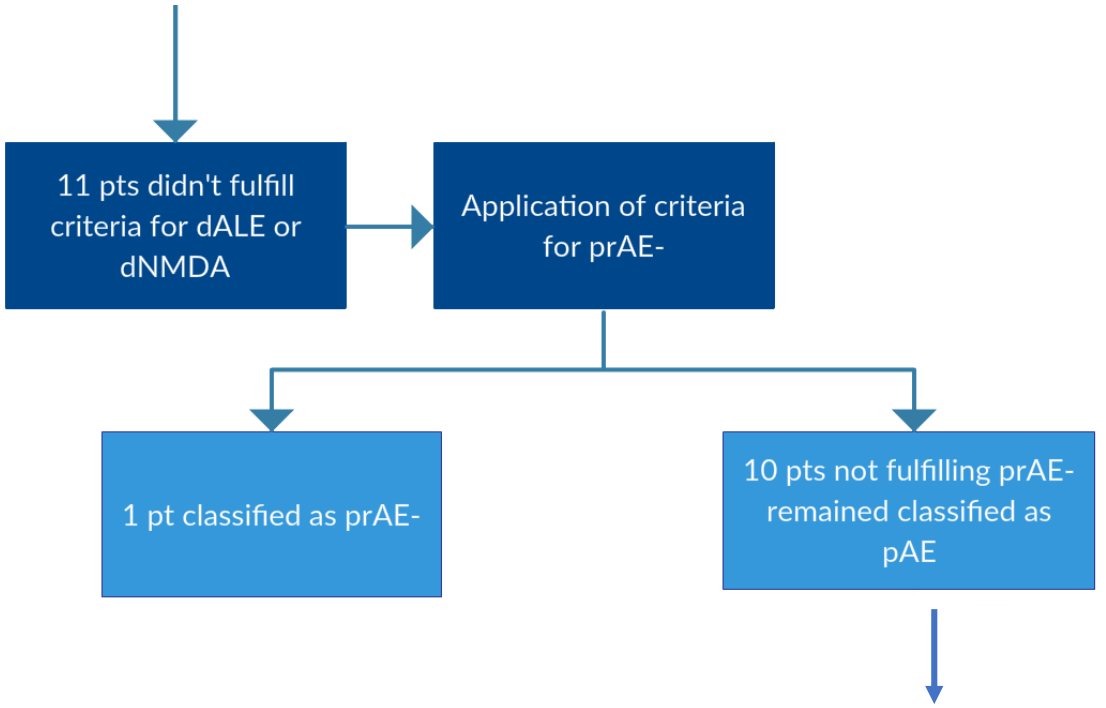
1 Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms

2 Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)

3 Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:
- MRI abnormalities suggestive of autoimmune encephalitis*
- CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both*
- Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)

4 Reasonable exclusion of alternative causes

*Some inherited mitochondrial and metabolic disorders can present with symmetric or asymmetric MRI abnormalities and CSF inflammatory changes resembling an acquired autoimmune disorder.[102]



- No patient had a cerebral biopsy → invasive procedure with limited diagnostic value
- Newly-found antibodies or in-house laboratory essays were not tested → common problem in practice

Conclusions

- ✓ Our study is an example of **practical application of Graus criteria** and it may shed light on several aspects regarding this approach in a **real-world single-center setting**.

- ✓ **EEG and MRI** played a **central role** in diagnosing both pAE and dALE, while CSF was useful mainly to rule out other conditions.

- ✓ When applying criteria for **probable anti-NMDA-R**, the number of symptoms required **limited correct diagnosis** → specificity and sensitivity may need validation in proper larger studies

Conclusions

- ✓ **Negative/unilateral vs bilateral MRI alterations in limbic encephalitis:** what to do?

- ✓ **Patients not fulfilling criteria for probable or definite AE**: what to do? **Reconsidering diagnosis**?
  Autoimmune etiology suggested by fulfilling of pAE criteria and clinical judgement → *to treat or not treat?*
  Referring to third-level central laboratory?

- ✓ **Larger studies on prospective cohorts** may be more helpful to explore possible important issues.

Thank you!

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