

# Introduktion till autoimmuna/paraneoplastiska tillstånd i CNS

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# Schema för dagen

**Tema: Paraneoplastiska/Autoimmuna och infektiösa tillstånd i CNS**

**09.30 – 10.00**

Fika vid ankomst

**10.00 – 10.30**

Välkommen och introduktion till Paraneoplastiska tillstånd

*Anders Svenningsson*

**10.30 – 11.00**

Paraneoplastiska syndrom i CNS: Klinik och patofysiologi

*Clas Malmeström*

**11.00 – 11.15**

Frukt

Bensträckare/Frågestund

**11.15 – 12.00**

Diagnostiska metoder och utredning av paraneoplastiska syndrom

*Clas Malmeström*

**Lunch 12.00 – 13.00**



**Lunch 12.00 – 13.00**

**13.00 – 13.45**

CNS infektioner: Virala encefaliter och myeliter

*Marie Studahl*

**13.45 – 14.00**

Frukt

Bensträckare/frågestund

**14.00 – 14.45**

CNS infektioner: Borrelia och andra bakteriella infektioner i CNS

*Marie Studahl*

**14.45 – 15.15**

Fika

Bensträckare/frågestund

**15.15 – 16.00**

PML: Patofysiologi, diagnostik och behandling

*Anders Svenningsson*

**16.00 – 16.15**

Frukt

Bensträckare/frågestund

**16.15 – 17.00**

Autoimmuna epilepsitillstånd

*Johan Zelano*

**18.30**

ST-pub

ST-pub på Restaurang Ankdammen i Inre hamn

# Vad är ett paraneoplastiskt tillstånd?

- ◆ “Paraneoplastic neurologic syndromes are a heterogeneous group of disorders caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy, or side effects of cancer treatment”
  - ◆ Josep Dalmau, UpToDate
- ◆ Immunologisk reaktion mot ett onkoneuralt antigen som leder till neurologiskt syndrom beroende på var motsvarande antigen finns nervsystemet
- ◆ Kan drabba, CNS, PNS, NMJ och muskler

# Klassifikationer inom paraneoplastiskt tillstånd

- ◊ "Klassiska paraneoplastiska syndrom"
- ◊ "Icke klassiska paraneoplastiska syndrom"
  
- ◊ Antikroppar mot intracellulära antigen
- ◊ Antikroppar mot synaps-associerade antigen
- ◊ Antikroppar mot kanalproteiner eller andra ytproteiner



# Recommended diagnostic criteria for paraneoplastic neurological syndromes

F Graus, J Y Delattre, J C Antoine, J Dalmau, B Giometto, W Grisold, J Honnorat, P Sillevs Smitt, Ch Vedeler, J J G M Verschuuren, A Vincent, R Voltz, for the Paraneoplastic Neurological Syndrome Euronetwork

See Editorial Commentary, p 1090

*J Neurol Neurosurg Psychiatry* 2004;**75**:1135–1140. doi: 10.1136/jnnp.2003.034447

See end of article for other members of the Paraneoplastic Neurological Syndrome Euronetwork

See end of article for authors' affiliations

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**Background:** Paraneoplastic neurological syndromes (PNS) are defined by the presence of cancer and exclusion of other known causes of the neurological symptoms, but this criterion does not separate "true" PNS from neurological syndromes that are coincidental with a cancer.

**Objective:** To provide more rigorous diagnostic criteria for PNS.

**Methods:** An international panel of neurologists interested in PNS identified those defined as "classical" in previous studies. The panel reviewed the existing diagnostic criteria and recommended new criteria for those in whom no clinical consensus was reached in the past. The panel reviewed all reported onconeural antibodies and established the conditions to identify those that would be labelled as "well characterised". The antibody information was obtained from published work and from unpublished data from the different laboratories involved in the study.

**Results:** The panel suggest two levels of evidence to define a neurological syndrome as paraneoplastic: "definite" and "possible". Each level can be reached combining a set of criteria based on the presence or absence of cancer and the definitions of "classical" syndrome and "well characterised" onconeural antibody.

**Conclusions:** The proposed criteria should help clinicians in the classification of their patients and the prospective and retrospective analysis of PNS cases.

**Table 1** Classical and non-classical paraneoplastic neurological syndromes

**Syndromes of the central nervous system**

(Encephalomyelitis)  
Limbic encephalitis  
Brainstem encephalitis  
Subacute cerebellar degeneration  
Opsoclonus-myoclonus\*  
 Optic neuritis†  
 Cancer associated retinopathy†  
 Melanoma associated retinopathy†  
 Stiff person syndrome  
 Necrotising myelopathy‡  
 Motor neuron diseases‡

**Syndromes of the peripheral nervous system**

Subacute sensory neuronopathy  
Acute sensorimotor neuropathy  
   Guillain-Barré syndrome‡  
   Brachial neuritis‡  
 Subacute/chronic sensorimotor neuropathies\*  
 Neuropathy and paraproteinaemia†  
 Neuropathy with vasculitis‡  
 Autonomic neuropathies  
   Chronic gastrointestinal pseudo-obstruction  
   Acute pandysautonomia‡

**Syndromes of the neuromuscular junction and muscle**

Myasthenia gravis†  
Lambert-Eaton myasthenic syndrome‡  
Acquired neuromyotonia‡  
Dermatomyositis‡  
 Acute necrotising myopathy‡

Classical syndromes are underlined.

\*Associated with onconeural antibodies only with particular tumour types.

†Syndromes not included in the present recommendations.

‡Neurological syndromes not associated with known onconeural antibodies.

Många “non-classical”  
syndrom.... !

**Table 2** Onconeural antibodies

Antibody	No of patients reported	Identified by more than one laboratory	Paraneoplastic neurological syndrome	Tumours	% of antibody positive patients without cancer* (number of patients studied)	Frequency in cancer patients without PNS (number studied)
<i>Well characterised onconeural antibodies</i>						
Anti-Hu (ANNA1)	>600	Yes	Encephalomyelitis; sensory neuronopathy; chronic gastrointestinal pseudo-obstruction; paraneoplastic cerebellar degeneration (PCD); limbic encephalitis	Small cell lung cancer (SCLC)	2% (200) <sup>5</sup>	16% (196 SCLC) (1% with titres similar to those patients with PNS) <sup>22</sup>
Anti-Yo (PCA1)	>200	Yes	Paraneoplastic cerebellar degeneration	Ovary, breast	2% (125) <sup>14 23-25</sup>	1% (107) <sup>26</sup>
Anti-CV2 (CRMP5)	>100	Yes	Encephalomyelitis; chorea; sensory neuronopathy; sensorimotor neuropathy; chronic gastrointestinal pseudo-obstruction; paraneoplastic cerebellar degeneration; limbic encephalitis	SCLC, thymoma <sup>27 28</sup>	4% (47)†	9% (74 SCLC) <sup>29</sup>
Anti-Ri (ANNA2)	61‡	Yes	Brainstem encephalitis	Breast, SCLC	3% (61) <sup>30-34</sup> §	4% (181 ovarian cancer) <sup>35</sup>
Anti-Ma2 (Ta)	55¶	Yes	Limbic/diencephalic encephalitis; brainstem encephalitis/PCD¶	Testicular, lung	4% (55) <sup>36</sup> ¶	0% (350)¶
Anti-amphiphysin	20‡	Yes	Stiff person syndrome; various syndromes	Breast SCLC	5% (20) <sup>37 38</sup>	0% (25 gynaecological cancer) <sup>39</sup> 1% (146 SCLC) <sup>40</sup>



## Table 4 Diagnostic criteria for paraneoplastic neurological syndromes (PNS)

### Definite PNS Var och en av nedanstående

1. A *classical* syndrome and cancer that develops within five years of the diagnosis of the neurological disorder.
2. A non-classical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission.
3. A non-classical syndrome with onconeural antibodies (well characterised or not) and cancer that develops within five years of the diagnosis of the neurological disorder.
4. A neurological syndrome (classical or not) with well characterised onconeural antibodies (anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin), and no cancer.

### Possible PNS

1. A classical syndrome, no onconeural antibodies, no cancer but at high risk to have an underlying tumour.
2. A neurological syndrome (classical or not) with partially characterised onconeural antibodies and no cancer.
3. A non-classical syndrome, no onconeural antibodies, and cancer present within two years of diagnosis.

## Screening for tumours in paraneoplastic syndromes: report of an EFNS Task Force

M. J. Titulaer<sup>a</sup>, R. Soffietti<sup>b</sup>, J. Dalmau<sup>c</sup>, N. E. Gilhus<sup>d,e</sup>, B. Giometto<sup>f</sup>, F. Graus<sup>g</sup>, W. Grisold<sup>h</sup>, J. Honnorat<sup>i,j</sup>, P. A. E. Sillevs Smitt<sup>k</sup>, R. Tanasescu<sup>l</sup>, C. A. Vedeler<sup>d,e</sup>, R. Voltz<sup>m</sup>, and J. J. G. M. Verschuuren<sup>a</sup>

### Repetition of screening if initial screening is negative

Current recommendation is to repeat screening regularly every 6 months up to 4 years in patients with PNS and paraneoplastic antibodies [11]. First repetition of screening should be carried out after 3 or 4 months if suspicion of a malignancy remains high. In patients with LEMS, a large cohort study shows that 2 years of screening is sufficient [7]. Screening by thoracic X-ray or tumour markers is not reliable.

**Recommendation**—If initial screening is negative in a patient with PNS and paraneoplastic antibodies, second screening should be repeated after 3–6 months, followed by regular screening every 6 months for 4 years. In patients with LEMS, 2 years is sufficient. X-ray or blood sampling is not reliable (good practice point).

## Recommendations/Good practice points

1. Nature of antibody, and to a lesser extent the clinical syndrome, determine the risk and type of an underlying malignancy.
2. As most PNS are not specifically related to one antibody, testing for several paraneoplastic antibodies simultaneously will improve the yield, avoiding loss of time before a malignancy is detected.
3. Screen for SCLC by CT-thorax followed by FDG-PET or integrated FDG-PET/CT.
4. Screen for thymoma by CT-thorax (followed by FDG-PET) or integrated FDG-PET/CT.
5. Screen for breast cancer by mammography, followed by MRI-breast. If negative followed by FDG-PET/CT.
6. Screen for ovarian teratoma by TV US, followed by CT/MRI-pelvis/abdomen. If negative, followed by CT-thorax.
7. Screen for ovarian carcinoma by TV US and CA-125, followed by CT-pelvis/abdomen or integrated FDG-PET/CT.
8. Screen for testicular tumour by US,  $\beta$ -HCG and AFP, followed by CT of the pelvic region. Biopsy is recommended in men under the age of 50 with classical PNS and microcalcifications on US.
9. If tumour screening is negative and the neurological condition is worsening, exploratory surgery and eventually preventive removal of the ovaries is warranted in post-menopausal women with an anti-Yo-associated PNS.
10. Additional laboratory investigations have extra value if the antibody and the associated PNS are related to both a paraneoplastic and a non-paraneoplastic subtype (like LEMS and myasthenia gravis). Positive markers raise suspicion of a tumour, but normal values do not exclude malignancy as sensitivity is low to moderate.
11. If no paraneoplastic antibodies are found, the patient has a classical PNS and the neurological condition is deteriorating, screening according to the most likely site, guided by the type of PNS with conventional methods, and if negative by total-body FDG-PET, is recommended.



# 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*

Encephalitis is a severe inflammatory disorder of the brain with many possible causes and a complex differential diagnosis. Advances in autoimmune encephalitis research in the past 10 years have led to the identification of new syndromes and biomarkers that have transformed the diagnostic approach to these disorders. However, existing criteria for autoimmune encephalitis are too reliant on antibody testing and response to immunotherapy, which might delay the diagnosis. We reviewed the literature and gathered the experience of a team of experts with the aims of developing a practical, syndrome-based diagnostic approach to autoimmune encephalitis and providing guidelines to navigate through the differential diagnosis. Because autoantibody test results and response to therapy are not available at disease onset, we based the initial diagnostic approach on neurological assessment and conventional tests that are accessible to most clinicians. Through logical differential diagnosis, levels of evidence for autoimmune encephalitis (possible, probable, or definite) are achieved, which can lead to prompt immunotherapy.

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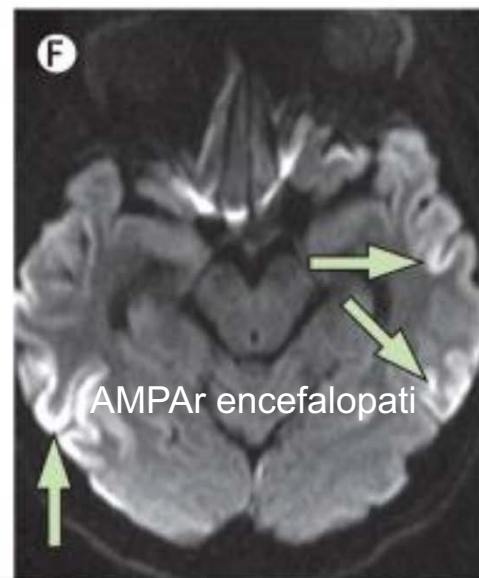
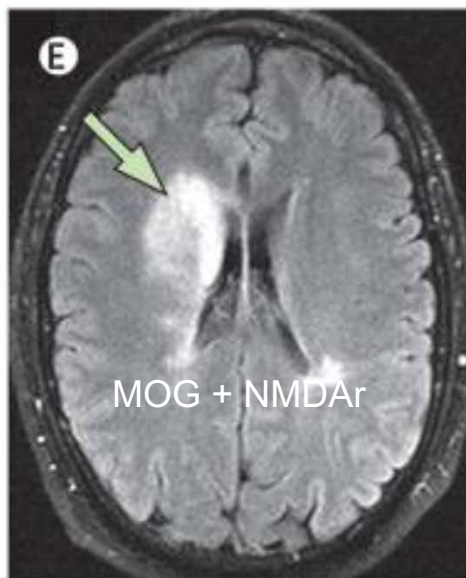
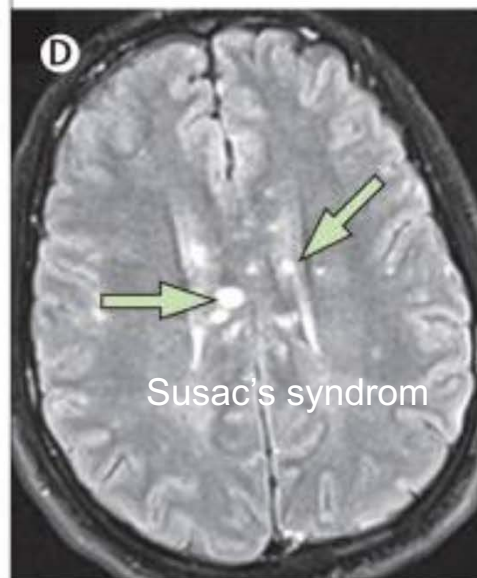
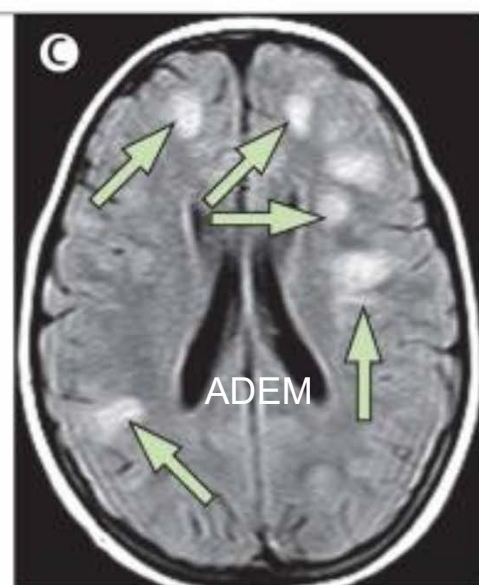
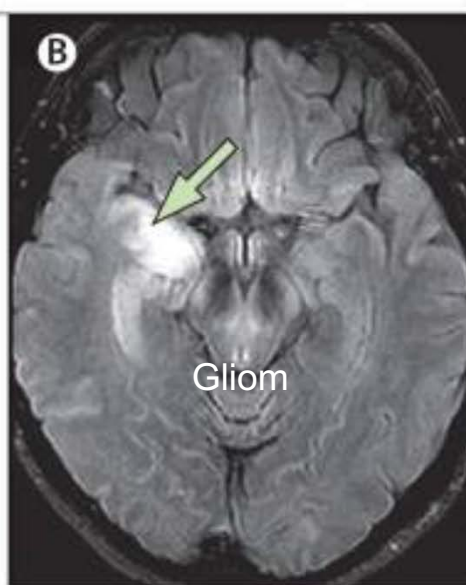
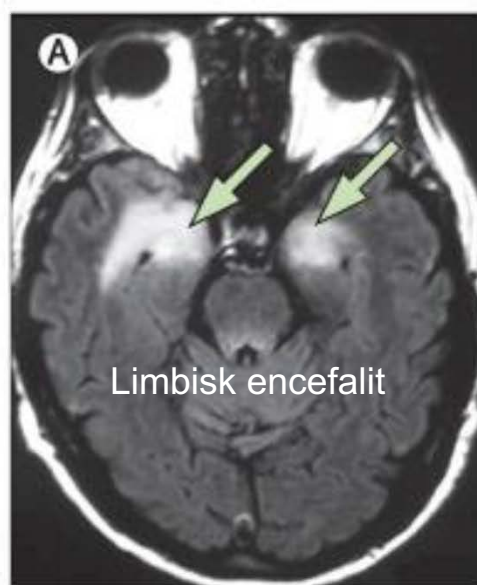
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# Kliniska kriterier för ett antal immunmedierade encefaliter

- ◊ “Possible autoimmune encephalitis”
- ◊ “Definite autoimmune limbic encephalitis”
- ◊ “Definite acute disseminated encephalomyelitis (ADEM)”
- ◊ “Diagnostic criteria for anti-NMDA receptor encephalitis
- ◊ Diagnostic criteria for Bickerstaff ’s brainstem encephalitis
- ◊ Diagnostic criteria for Hashimoto’s encephalopathy
- ◊ Criteria for autoantibody-negative but probable autoimmune encephalitis



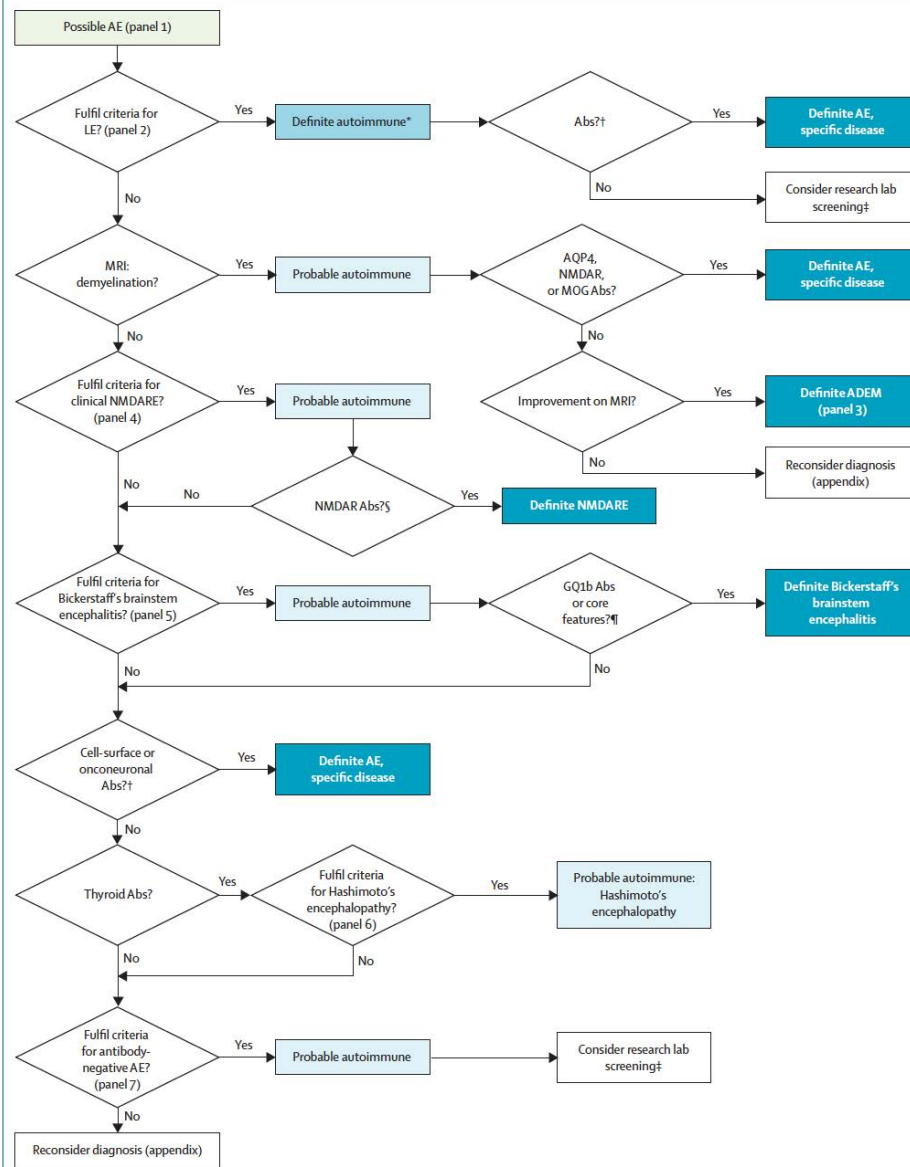
## Panel 1: Diagnostic criteria for possible autoimmune encephalitis

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<sup>3</sup>)
  - 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.





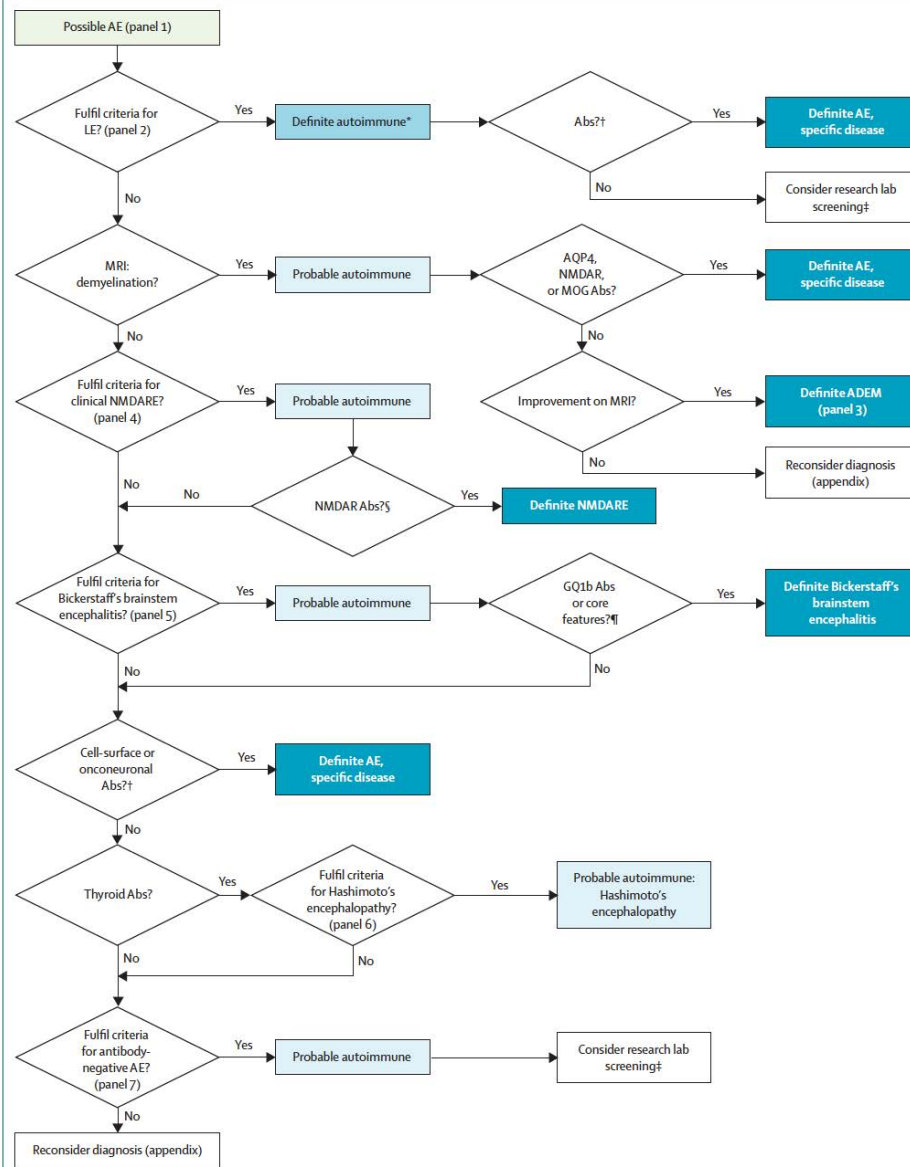


## Panel 2: Diagnostic criteria for definite autoimmune limbic encephalitis


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<sup>3</sup>)
  - 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. †<sup>18</sup>F-Fluorodeoxyglucose (<sup>18</sup>F-FDG) PET can be used to fulfil this criterion. Results from studies from the past 5 years suggest that <sup>18</sup>F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal-appearing medial temporal lobes.<sup>44,45</sup>



## Earlier treatment of NMDAR antibody encephalitis in children results in a better outcome

Susan Byrne, PhD,  Cathal Walsh, PhD, Yael Hachon, MRCPCH, Eyal Muscal, MD, Joseph Jankovic, MD, Amber Stocco, MD, Russell C. Dale, PhD, Angela Vincent, MD, MSc, FRCPATH, FRS, Ming Lim, PhD,\* and Mary King, FRCPCH\*

**Table 1** Comparison of the clinical features between children who recovered completely and those who did not

	Complete recovery at follow-up (n = 33)	Incomplete recovery at follow-up (n = 47)	p Value
Median time of follow-up, mo (IQR)	12 (5-24)	12 (4-24)	0.864
Range, mo	2-54	1.3-36	
Median age at symptom onset, y (IQR)	9 (3.4-14)	8 (5-13)	0.791
Range, y	2.3-17	1.3-16	
Median mRS score at nadir (IQR)	5 (4-5)	4 (3-5)	0.2
Range	3-5	3-5	
Percentage in each group given empiric therapy	89	73	0.175
Median time from symptom onset to treatment, d (IQR)	15 (7-21)	21 (15-40)	0.014 <sup>a</sup>
Range, d	3-182	5-365	
Number of therapies required to induce remission, % (n)			0.968
1	25 (8)	9.5 (4)	
2	40.6 (13)	54.8 (23)	
3	25 (8)	21.4 (9)	
4 or more	9.4 (3)	14.3 (6)	
Median mRS score at follow-up (IQR)	0 (0-0)	2 (1-3)	



# Misstänkt autoimmun encefalit, behandlingsalgoritm

