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To cite this article: Johann Steiner, Harald Prüss, Stephan Köhler, Thomas Frodl, Alkomiet Hasan & Peter Falkai (2020) Autoimmune encephalitis with psychosis: Warning signs, step-by-step diagnostics and treatment, *The World Journal of Biological Psychiatry*, 21:4, 241-254, DOI: [10.1080/15622975.2018.1555376](https://doi.org/10.1080/15622975.2018.1555376)

To link to this article: <https://doi.org/10.1080/15622975.2018.1555376>



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Published online: 28 Jan 2019.



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REVIEW ARTICLE



Autoimmune encephalitis with psychosis: Warning signs, step-by-step diagnostics and treatment

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ABSTRACT

Objectives: Despite intensive research, schizophrenia and schizoaffective disorders continue to be theoretical constructs that describe clinical syndromes and no pathophysiologically defined diseases. Moreover, there are no clear biomarkers at hand. Therefore, these diagnoses are still set up based on clinical ICD-10/DSM-5 criteria and the exclusion of alcohol/drug-associated, systemic or other brain organic causes.

Methods: Recently, autoimmune encephalitis with psychotic symptoms caused by specific antineuronal antibodies has been identified as a rare, but potentially treatable differential diagnosis. However, these inflammatory brain diseases are not reliably detected by our current routine diagnostic workup in psychiatry. This qualitative review provides structured diagnostic and therapeutic support for clinical practice.

Results: Disturbances of consciousness and orientation, catatonia, speech dysfunction, focal neurological signs, epileptic seizures/EEG abnormalities or autonomic dysfunction are warning signs in psychiatric patients which should always induce cerebrospinal fluid analysis with determination of antineuronal autoantibodies. Currently established immunotherapy strategies are summarised, taking into account international expert advice.

Conclusions: Guided by clinical warning signs, our qualitative review enables rapid and reliable diagnosis of definite autoimmune encephalitis. This is of high relevance for the affected individuals, since early and sufficiently intense immunotherapy often leads to a good prognosis despite severe illness.

ARTICLE HISTORY

Received 10 April 2018
Revised 6 November 2018
Accepted 26 November 2018

KEYWORDS

Antineuronal antibodies;
autoimmune encephalitis;
limbic encephalitis;
psychosis; schizophrenia

Schizophrenia spectrum disorders diagnosed by exclusion diagnostics in psychiatry

Despite intensive research, the pathophysiology of schizophrenia and schizoaffective disorders has not been clarified yet. Therefore, diagnostics in the sense of exclusion diagnostics is maintained in the recent editions of international and national classification schemes of mental illnesses (International Statistical Classification of Diseases and Related Health Problems 10/ICD-10 or Diagnostic and Statistical Manual of Mental Disorders 5/DSM-5: (APA 2013; Dilling et al. 2016). Disorders from this spectrum continue to be theoretical constructs that describe clinical syndromes and no clearly defined diseases, and there are no clear biomarkers at hand.

Clinical criteria comprising certain psychopathologic features and the disease course have been defined by

ICD-10 or DSM-5. Such data are collected by means of conversation and behavioural observation, procedures which are potentially subjective and influenced by the skill, individual perception and personal view of the doctor, as well as by the presentation of the complaint.

Exclusion diagnostics of alcohol-/drug-associated, systemic or other brain organic causes is based on a physical and neurological examination, if necessary neuropsychological testing (executive functions, memory and attention), routine blood testing, urine drug screening, breath/blood alcohol testing, electroencephalography (EEG) and brain structural imaging (magnetic resonance imaging (MRI) with T1 MP-RAGE, T2 and FLAIR sequences; a cranial computed tomography (cCT) scan should be performed in the case of MRI contraindications) at first manifestation, optionally supplemented

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by cerebrospinal fluid (CSF) analysis according to the AWMF guidelines of the German Psychiatric Association (Gaebel and Falkai 2005). We have recently proposed a differential diagnostic algorithm to facilitate thorough exclusion diagnostics (see Figure 1).

Immune alterations in a subpopulation of patients with schizophrenia spectrum psychosis

It has long been known that systemic autoimmune diseases with involvement of the central nervous system (e.g., systemic lupus erythematosus), a steroid-responsive encephalopathy in autoimmune thyroiditis (SREAT/Hashimoto's encephalopathy) or neuroinflammatory diseases such as multiple sclerosis or cerebral vasculitis can lead to organic schizophreniform psychosis (Steiner et al. 2018).

Notably, cluster analysis of multiplex immunoassay data revealed subtle changes of a variety of immune factors in the peripheral blood of a subgroup of

patients diagnosed with schizophrenia (Schwarz et al. 2014). Discreetly increased blood and CSF levels of pro-inflammatory cytokines or blood–CSF barrier disturbances may be observed in some patients who, according to our current psychiatric criteria, are diagnosed with schizophrenia or affective disorders (Endres et al. 2015; Goldsmith et al. 2016). In support of a possible link with the immune system, an epidemiological nationwide population-based study in Denmark showed that prior autoimmune disease increased the risk of schizophrenia by about 30%, while a history of hospitalisation with infection increased the risk of schizophrenia by about 60% (Benros et al. 2011). An increased production of autoantibodies and elevated B-cell counts have been found in a subpopulation of schizophrenia patients (Steiner et al. 2010; Ezeoke et al. 2013). It is unclear if such findings imply an involvement of immune mechanisms in the pathophysiology of a patient subgroup or if they are an epiphenomenon of other much more established concepts, e.g., considering schizophrenia as a neurodevelopmental disease.

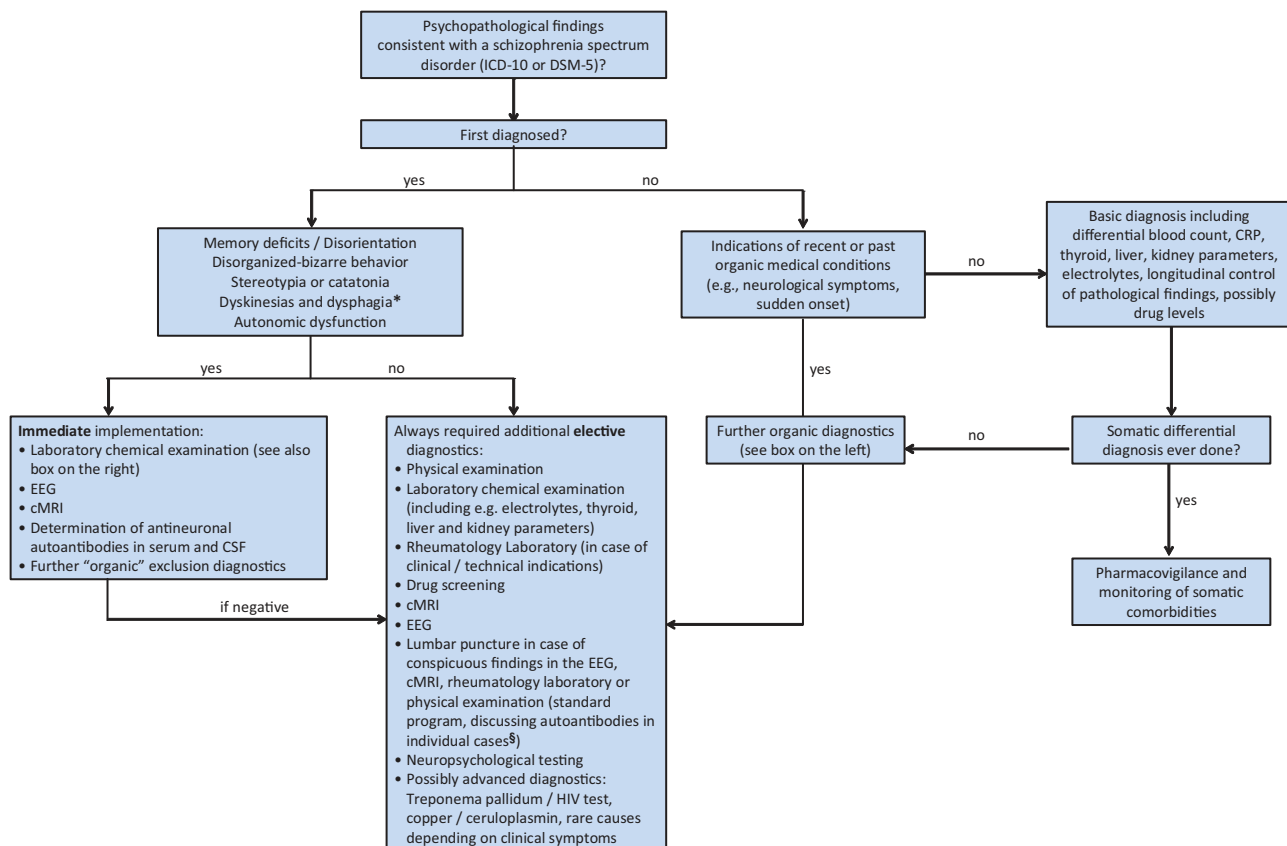


Figure 1. Comprehensive diagnostic algorithm to rule out organic disease with psychotic symptoms (adapted from Steiner et al. 2018). *The dyskinesias and dysphagia are not medically explainable and are not reversible by biperiden or discontinuation of the medication. §Notably, e.g., NMDA receptor encephalitis cannot be entirely excluded by the lack of the above-mentioned specific findings on EEG, by normal MRI, or by a normal basic CSF profile. Thus, in a more cautious approach, antineuronal autoantibody may be determined in all patients with clinical warning symptoms of encephalitis, regardless of unremarkable MRI, EEG and CSF cell count/oligoclonal bands.

Immune alterations may be associated with an activation of microglial cells in the brain (which are involved in the regulation of synaptic plasticity). Indeed, previous post-mortem studies observed an increased numerical density of microglial cells and neuroimmune mRNA expression levels, for instance in the dorsolateral prefrontal cortex in patient subgroups (Steiner et al. 2006; Steiner et al. 2008; Fillman et al. 2013; De Picker et al. 2017). In vivo data from translocator protein positron emission tomography (TSPO-PET) studies were inconsistent, but some were pointing in the same direction (De Picker et al. 2017). TSPO-PET studies may be partly confounded by the limited specificity of TSPO tracers for microglia, since astrocytes, some neuronal subtypes, as well as endothelial cells, can also express TSPO (Cosenza-Nashat et al. 2009). Dysfunction and loss of astrocytes, as opposed to astrogliosis, which is typical for classic neurodegenerative disorders, has been described in previous post-mortem studies and may partly explain conflicting TSPO-PET results in schizophrenia (Bernstein et al. 2015).

Autoimmune encephalitis as a potentially overlooked differential diagnosis of psychosis

In recent years, autoimmune encephalitis¹ with psychotic symptoms has been established as a diagnostic entity in clinical neurology and psychiatry. This type of organic psychoses is an important differential diagnosis of schizophrenic and schizoaffective disorders. Its mental symptoms are associated with certain anti-neuronal autoantibodies directed against synaptic and neuronal cell surface antigens (focus of this review, see Table 1: NMDA (N-methyl-D-aspartate) receptor, LGI1 (leucine-rich glioma inactivated 1), Caspr2 (contactin-associated protein 2), AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, DPPX (dipeptidyl-peptidase-like protein-6), GABA (gamma-aminobutyric acid receptor), mGluR5 (metabotropic glutamate receptor 5) and GlyR (glycine receptor)). Autoimmune encephalitis as a differential diagnosis of schizophrenic and schizoaffective disorders refers to a small subgroup of psychotic patients; especially to a rather acute first-onset phase. The longer the disease course, the less likely is encephalitis a phenocopy of schizophrenia. However, one should still be cautious because of possible exceptions. For example, a case of NMDA receptor encephalitis has been described that was treated as catatonic schizophrenia for about 1.5 years and responded well to immunotherapy despite the long course of the disease (Endres et al. 2015).

Antibodies against intracellular neuronal antigens (onconeural antibodies) usually occur as paraneoplastic syndromes in the context of cancer (e.g., Anti-Hu, Ri, Yo, CV2/CRMP5, Ma1, Ma2/Ta, amphiphysin, Tr, PCA-2, ANNA-3 and SOX1) are rarely associated with psychotic syndromes and therefore not the main focus of this work.

Epidemiology

Notably, different forms of encephalitis are relatively rare but potentially treatable causes of neuropsychiatric symptoms. A recently published epidemiological study from the USA showed no significant difference in the overall prevalence of infectious encephalitis (11.6/100,000) or viral subcategory (8.3/100,000) in January 2014 compared to autoimmune encephalitis (13.7/100,000; Dubey et al. 2018). The incidence (years 1995–2015) of infectious and autoimmune encephalitis was 1.0/100,000 and 0.8/100,000/year, respectively (Dubey et al. 2018). Antibodies against NMDA receptors (4%) and the voltage-gated potassium channel complex (VGKC complex, 3%) appear to play the biggest role in autoimmune encephalitis in Northern Europe (Granerod et al. 2010). Unfortunately, autoimmune encephalitis not presenting with a full-blown clinical picture is often not detected reliably in routine psychiatric diagnostics. A more refined differential diagnostic approach is medically indicated in psychiatric care because immune therapies are available for autoimmune encephalitis. Severe neuropsychiatric deficit can occur if these treatments are not applied.

NMDA receptor autoantibodies in patients diagnosed with schizophrenia

In addition, several studies have shown that different isotypes of serum antibodies to the NMDA receptor are present in 3–10% of patients diagnosed with schizophrenia (Zandi et al. 2011; Steiner et al. 2013; Ando et al. 2016; Lennox et al. 2017). However, studies suggested no significant difference in the prevalence of these autoantibodies in patients with schizophrenia compared to controls (Masdeu et al. 2012; Dahm et al. 2014; Steiner et al. 2014; de Witte et al. 2015). A larger study found a relatively high prevalence of between 10 and 20% of Ig (immunoglobulin) A and IgM NMDA receptor antibodies and 1% of IgG NMDA receptor antibodies in serum from blood donors and people without known neuropsychiatric disease (mostly titres of <1: 320) (Dahm et al. 2014). Autoantibodies to other synaptic and neuronal cell surface antigens were

Table 1. Important types of autoimmune encephalitis with specific antibodies against synaptic and neuronal cell surface proteins and increased risk of psychosis (Pettingill et al. 2015; Steiner et al. 2015; Lancaster 2016; Steiner et al. 2018).

Antigen	Function	Clinical symptoms	Peculiarities	Age/sex distribution	Typical patient ^a	Tumor association	Therapy
NMDA/N-methyl-D-aspartate receptor (NR1a/GluN1)	Transmembrane protein, ionotropic neurotransmitter receptor for glutamate, ligand-gated ion channel, mediates excitatory glutamatergic synaptic neurotransmission	Memory deficits, schizophreniform psychosis/catatonia , epileptic seizures/perioral dyskinesia/dystonia, impaired consciousness, hypoventilation	Cerebral MRI often unremarkable, mostly pleocytosis in the CSF, slowing in the EEG	All ages, peak in childhood and adolescence, ratio female/male = 4/1	Onset in young (female) patients <30 years or children	In women often ovarian teratoma (in about 40%)	Intravenous immunoglobulins, plasmapheresis, rituximab, possibly cyclophosphamide, severe courses with relapses possible
LGI1/leucine-rich glioma inactivated 1	Transmembrane protein, associated with voltage-gated potassium channels	Memory deficits, schizophreniform psychosis/catatonia , faciobrachial dystonic seizures (=unilateral, short-lived dystonic posturing of the upper limb and face)	Mesiotemporal hyperintensity in cerebral MRI, hyponatremia	Older adults (>40 years), ratio female/male = 1/2	Onset in (male) patients, typically >55 years, faciobrachial dystonic seizures hyponatremia	Thymoma and lung cancer possible (in about 5–10%)	High-dose steroids may be sufficient, sometimes required for months
Caspr2/contactin-associated protein 2	Transmembrane protein, involved in cell adhesion processes, associated with voltage-gated potassium channels	Neuromyotonia, Morvan syndrome (= insomnia, autonomic excitement, neuromyotonia + symptoms of 'limbic encephalitis', e.g., memory deficits, psychosis , epileptic seizures), (painful) small-fibre neuropathy	Similar to LGI1, no hyponatremia	Older adults (> 40 years), ratio female/male = 1/4	Onset in (male) patients >40 years, Morvan syndrome, (painful) small-fibre neuropathy	Thymoma and lung cancer possible (in about 20%)	Steroids, rituximab, cyclophosphamide, unfavourable prognosis
AMPA/ α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor	Transmembrane protein, ionotropic neurotransmitter receptor for glutamate, ligand-gated ion channel, important for synaptic plasticity	Memory deficits, psychosis , epileptic seizures	CSF mostly unremarkable	Older adults (>40 years), ratio female/male = 9/1	Onset of in (female) patients >40 years, epileptic seizures, thymoma, lung or breast cancer	Thymoma, lung or breast cancer (in about 70%)	Steroids, rituximab, cyclophosphamide, unfavourable prognosis frequent relapses
DPPX/dipeptidyl-peptidase-like protein-6	Membrane protein, binds to voltage-gated potassium channels and influences their biological function	Memory deficits, central hyperexcitability (myoclonus, exaggerated startle, diffuse rigidity, irritability), psychosis/catatonia , epileptic seizures	Therapy refractory diarrhoea	Older adults (>40 years), ratio female/male = 1/2	Onset in (male) patients >40 years, central hyperexcitability therapy refractory diarrhoea,	Lymphoma (<10%)	Response to immunotherapy described

(continued)

Table 1. Continued.

Antigen	Function	Clinical symptoms	Peculiarities	Age/sex distribution	Typical patient ^a	Tumor association	Therapy
GABA/gamma-aminobutyric acid receptor	Transmembrane protein in neurons, metabotropic (works through second messenger) neurotransmitter receptor for GABA, leads to activation of ligand-gated potassium channels, which induces an inhibitory postsynaptic signal	Memory deficits, therapy refractory epileptic seizures, hallucinations/anxiety	Mesiotemporal hyperintensity in cerebral MRI, CSF pleocytosis	Adolescents to older age, ratio female/male $\approx$ 1/1	Onset of therapy refractory epileptic seizures in adolescence to older age	GABA-A: Thymoma (about 25%) GABA-B: small-cell lung cancer (about 50%)	Response to immunotherapy described
mGluR5/metabotropic glutamate receptor 5	Transmembrane protein in neurons, G protein-coupled metabotropic (works through second messenger) neurotransmitter receptor for glutamate, mediates excitatory activation of NMDA receptors	Memory deficits, changes in behaviour and personality, emotional instability, psychosis	Ophelia syndrome (=Hodgkin lymphoma with autoimmune limbic encephalitis)	Younger adults (about 30 years), ratio female/male = 1/2	Onset in younger (female) patients, Ophelia syndrome	Hodgkin lymphoma (about 70%)	Response to immunotherapy described
GlyR/glycine receptor	Transmembrane protein in neurons, ionotropic receptor for glycine, ligand-gated ion channel, makes the membrane permeable for chloride ions	Memory deficits, central hyperexcitability, changes in behaviour and personality, psychosis	Progressive encephalomyelitis, rigidity and myoclonus (PERM), Stiff-Person Syndrome	Middle-aged and older adults, ratio female/male $\approx$ 1/1	Onset of stiffness in trunk and limb muscles in middle-aged and older adults	Rare (thymoma, lung cancer, Hodgkin lymphoma)	Response to immunotherapy described

The older term 'limbic encephalitis' suggests that areas of the limbic system are mainly affected (hippocampus, cingulate gyrus, amygdala, insula and frontobasal brain areas), as shown in the initial description of the syndrome. However, in clinical practice, inflammatory brain changes are rarely limited to limbic areas, so the term 'limbic encephalitis' is being abolished.

^aThis column can be helpful in deciding which autoantibody tests may have the highest yield in certain patient populations.

Table 2. Diagnostic criteria for possible autoimmune encephalitis when all three of the following criteria have been met (adapted from Graus et al. 2016)

1. Subacute onset (rapid progression < 3 months) of working memory deficits (short-term memory loss), altered mental status (decreased or altered level of consciousness, lethargy, or personality change) 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 >5 Zellen/ μ L)^a
 - cMRI features suggestive of encephalitis: hyperintense signal on T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both
3. Reasonable exclusion of alternative causes^b

^aAttention regarding pre-analytic requirements: only short time interval between lumbar puncture and analysis of the cerebrospinal fluid (ideally <30 min), otherwise 'false-normal cell count' due to cell lysis.

^bExclusion of alternative causes: infectious encephalitis (neurotropic viruses: e.g., CMV, EBV, HSV, influenza, measles, mumps, rubella or VZV; other pathogens: e.g., *Borrelia*, *Chlamydia*, *Mycoplasma*, *Candida albicans* and *Toxoplasma gondii*) or sepsis, rheumatoid diseases (e.g., lupus erythematosus or sarcoidosis), metabolic and toxic encephalopathies (e.g., hepatic or renal), mitochondrial diseases, cerebrovascular diseases, tumours or Creutzfeldt-Jakob disease.

rarely detectable in the serum of neuropsychiatric patients (anti-Caspr2 0.9%, and anti-LGI1/AMPA receptor/DPPX each <0.1%); CSF was not studied in these individuals (Dahm et al. 2014).

The key point is that these papers reporting IgM, IgA and other serum responses used different methods than those employed to diagnose NMDA receptor encephalitis (presence of specific serum and cerebrospinal fluid IgG NR1a antibodies, cross-validation with different assay systems) (Graus et al. 2016). If the standard methods for diagnosing NMDA receptor encephalitis are applied to patients with schizophrenia the overall positive rate of detected cases with encephalitis is very low. For instance, the criteria for NMDA receptor encephalitis (including CSF analysis and cross-validation of results) were met only by two out of 121 patients with an initial diagnosis of schizophrenia (Steiner et al. 2013).

CSF data are only available from three retrospective cohorts (Steiner et al. 2013; Endres et al. 2015; Oviedo-Salcedo et al. 2018). In addition to the already mentioned study by Steiner et al. (2013), Endres et al. (2015) observed four cases with autoantibodies against synaptic and neuronal cell surface antigens (one anti-NMDA receptor, three anti-voltage-gated potassium complex (LGI1 and Caspr2)) in 125 psychotic patients. Most of these patients had a schizophreniform or schizoaffective syndrome, few had other presumed diagnoses, e.g., viral encephalitis. The third study found no NMDA receptor, AMPA receptor, Caspr2, LGI-1 or GABA-B receptor antibodies in the CSF of 124 patients with schizophrenia-spectrum disorders (Oviedo-Salcedo et al. 2018). The results for the intracellular onconeuro-nal and synaptic antibodies were also negative (amphiphysin, Yo, Hu, Ri, CV2 and Ma antibodies). However, schizophrenia patients showed higher frequencies for intrathecal oligoclonal bands.

Warning signs for autoimmune encephalitis

According to a retrospective analysis of 100 cases with various forms of definite autoimmune encephalitis at the Charité (Berlin, Germany), psychiatric abnormalities including psychotic symptoms are the most common clinical symptoms at the time of first manifestation of autoimmune encephalitis (60%) (Herken and Prüss 2017). One-third of the patients examined were at first hospitalised in a psychiatric ward. The mean time between the first onset of symptoms and the autoantibody test was often long, but could be reduced by improved clinical awareness from 483 days (years 2007–2012) to 74 days (years 2013–2016).

Certain clinical warnings of encephalitis in patients with psychiatric disorders should trigger an advanced differential diagnosis (overview in Figure 2). It should be noted that there is no single standard for the diagnosis of autoimmune encephalitis. We rely on an expert consensus of neuroimmunologists; see Tables 2 and 3: (Graus et al. 2016) and its reception by English psychiatrists (Al-Diwani et al. 2017), a recent opinion article (Ehrenreich 2017), the above mentioned retrospective study at the Charité (Herken and Prüss 2017) and our previously published German review paper on this topic (Steiner et al. 2018). This includes:

- a rapid progression of psychotic and/or affective symptoms despite psychopharmacotherapy,
- consciousness/orientation/memory impairment
- catatonia
- speech dysfunction
- neurological deficits, epileptic seizures
- autonomic dysfunction or
- hyponatremia.

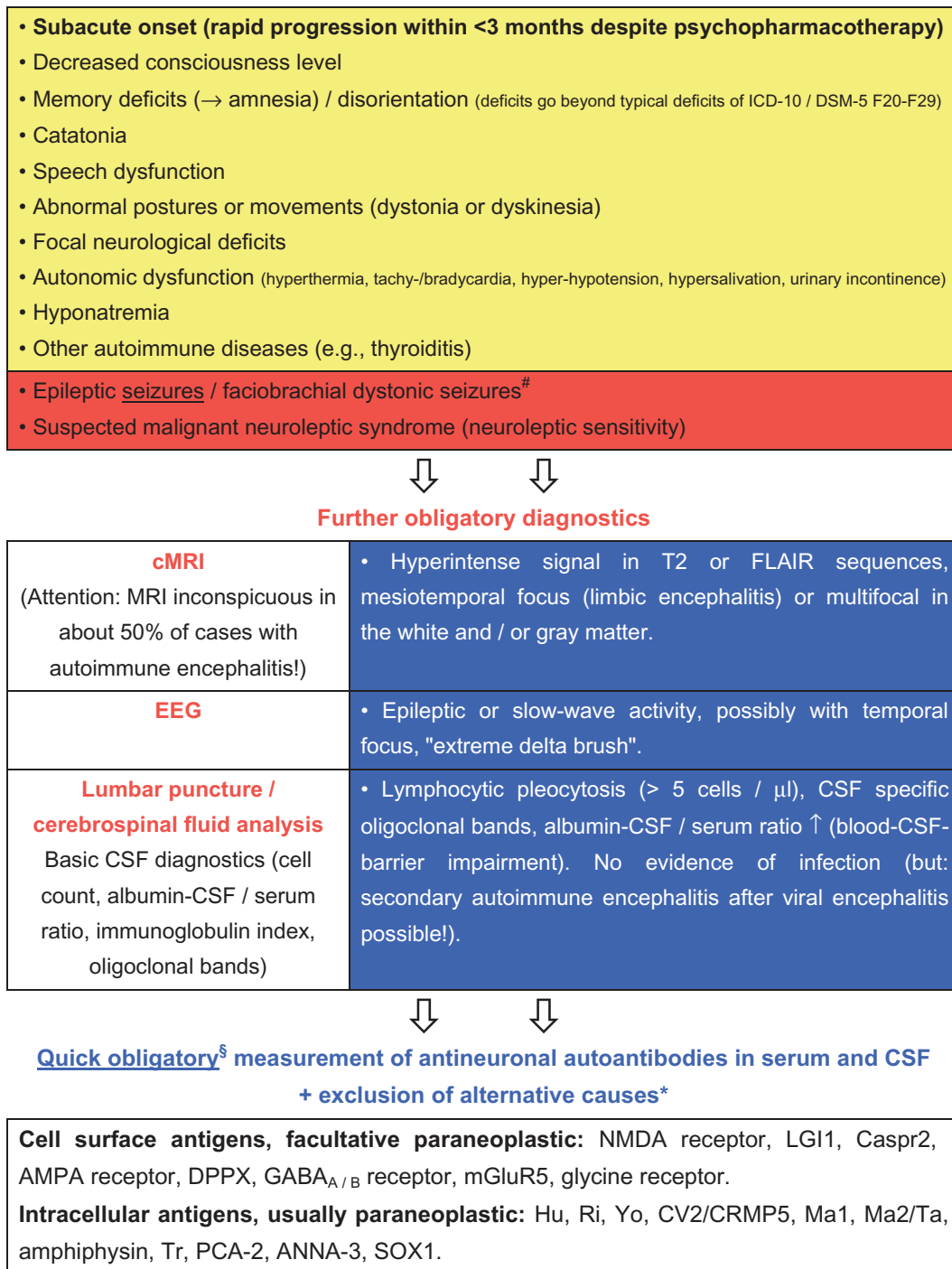


Figure 2. Clinical warnings (yellow/red) of possible autoimmune encephalitis in patients with psychotic symptoms and step-by-step diagnostic procedure (adapted from Graus et al. 2016; Steiner et al. 2018).

Annotations: [#]Faciobrachial dystonic seizures are characterised by unilateral, short-lived dystonic posturing of the upper limb and face which are caused by autoantibodies to leucine-rich glioma-inactivated 1 (LGI1) protein, a component of the voltage-gated potassium channel complex (Irani et al. 2013).

^sNotably, e.g., NMDA receptor encephalitis cannot be entirely excluded by the lack of the above-mentioned specific findings on EEG, by normal MRI, or by a normal basic CSF profile. Thus, in a more cautious approach, antineuronal autoantibody may be determined in all patients with clinical warning symptoms of encephalitis, regardless of unremarkable MRI, EEG and CSF cell count/oligoclonal bands. ^{*}Exclusion of alternative causes: infectious encephalitis (neurotropic viruses: e.g., CMV, EBV, HSV, influenza, measles, mumps, rubella, VZV; other pathogens: e.g., *Borrelia*, *Chlamydia*, *Mycoplasma*, *Candida albicans* and *Toxoplasma gondii*) or sepsis, rheumatoid diseases (e.g., lupus erythematosus and sarcoidosis), metabolic and toxic encephalopathies (e.g., hepatic and renal), mitochondrial diseases, cerebrovascular diseases, tumours and Creutzfeldt-Jakob disease (Graus et al. 2016).

Table 3. Criteria for autoantibody-negative but probable autoimmune encephalitis when all four of the following criteria have been met (adapted from Graus et al. 2016)

1. Subacute onset (rapid progression < 3 months) of working memory deficits (short-term memory loss), altered mental status (decreased or altered level of consciousness, lethargy, or personality change) or psychiatric symptoms
2. Exclusion of well-defined syndromes of autoimmune encephalitis (e.g., typical limbic encephalitis, Bickerstaff 's brainstem encephalitis or acute disseminated encephalomyelitis)
3. Absence of well-characterised autoantibodies in serum and CSF, and at least two of the following criteria:
 - cMRI features suggestive of encephalitis: hyperintense signal on T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter or both
 - CSF pleocytosis,^a CSF-specific oligoclonal bands or elevated CSF IgG index or both
 - Brain biopsy showing inflammatory infiltrates and excluding other disorders (e.g., tumour)
4. Reasonable exclusion of alternative causes^b

^aAttention regarding pre-analytic requirements: only short time interval between lumbar puncture and analysis of the cerebrospinal fluid (ideally <30 min), otherwise 'false-normal cell count' due to cell lysis.

^bExclusion of alternative causes: infectious encephalitis (neurotropic viruses: e.g., CMV, EBV, HSV, influenza, measles, mumps, rubella or VZV; other pathogens: e.g., *Borrelia*, *Chlamydia*, *Mycoplasma*, *Candida albicans* and *Toxoplasma gondii*) or sepsis, rheumatoid diseases (e.g., lupus erythematosus or sarcoidosis), metabolic and toxic encephalopathies (e.g., hepatic or renal), mitochondrial diseases, cerebrovascular diseases, tumours or Creutzfeldt-Jakob disease.

Step-by-step diagnostic workup

As illustrated in Figure 2, we recommend the following procedure:

If there are clinical warnings of possible autoimmune encephalitis in patients with psychotic symptoms, cerebral MRI, EEG and routine CSF diagnostics should be mandatory. If at least one of the following findings is present, there is a high degree of suspicion of autoimmune encephalitis: hyperintense signal in T2 or FLAIR sequences, mesiotemporal focus (limbic encephalitis) or multifocal in the white and/or grey matter, epileptic or slow-wave activity, possibly with temporal focus, 'extreme delta brush'² in the EEG or lymphocytic pleocytosis, CSF-specific oligoclonal bands or blood–CSF barrier impairment.

In this case, extended diagnostics with determination of anti-neuronal autoantibodies in serum and CSF, as well as a parallel microbiological-virological CSF diagnostics (see below, triggering of autoimmune encephalitis or blood–brain barrier impairment by viral infections) should be performed. Standards for antibody diagnostics using indirect immunofluorescence are cell-based biological assays, which are now available in many routine laboratories. Ideally, specimens from patients with suspected CNS autoimmunity, but negative antibody findings in cell-based assays, should be re-analysed in research laboratories using rodent brain sections.

Interpretation of the antibody findings

Generally, the titre of antineuronal antibodies is determined by the maximum dilution level (e.g., 1:100) at which a reaction of the patient sample to the test cells is still detectable.

The decisive factor is whether the antibodies reach their targets in the brain. They may get there either

by local (intrathecal) production or by a (temporary) impairment of the blood–brain barrier from the blood (Ehrenreich 2017). *The positive detection of well-characterised anti-neuronal antibodies in CSF is therefore always considered as pathological.*

The isolated detection of low titres of antineuronal antibodies in serum without clinical/CSF evidence for encephalitis, however, is insufficient for the diagnosis of autoimmune encephalitis and does not justify the implementation of an immunomodulatory therapy. In fact, IgG-NMDA receptor antibodies were also detected in approximately 1% of people without neuropsychiatric disease (more rarely, others of the antineuronal antibodies mentioned in Figure 2 (Dahm et al. 2014)). Furthermore, a longitudinal study of 228 patients with psychosis showed that cases with low serum antibodies to the neuronal antigens NMDA receptors, LGI1, Caspr2 or GABA receptors without clinical signs of encephalitis remitted during a 6-month course similarly well as seronegative cases even without immunotherapy (Lennox et al. 2017).

Various factors, for example viral infections, systemic autoimmune diseases, neuroimmune diseases (e.g., multiple sclerosis), hypoxic or traumatic brain damage as well as the 'physiological' blood–brain barrier impairment in old age could promote the transfer of the antibodies into the brain. Therefore, in the case of suspected NMDA receptor encephalitis, *a proven blood–brain barrier impairment (albumin-CSF/serum ratio as surrogate marker) in the context of high-positive serum antibodies and clinical encephalitis symptoms may be also diagnostically sufficient (cut-off unclear, possibly IgG NMDA receptor serum antibody titres ≥ 1:320) even in cases with negative CSF NMDA receptor antibody titres (Ehrenreich 2017; Steiner et al. 2018).* It should be noted that, in addition to antibodies of the IgG type, IgA and IgM antibodies against GluN1

(NR1a) may show some pathophysiological significance, which awaits further investigation (Prüss et al. 2012; Castillo-Gomez et al. 2016; Dalmau et al. 2017).

Notably, the superiority of CSF for antineuronal antibody testing was primarily shown for NMDA receptor antibodies, in which 10–20% of patients have detectable antibody levels in CSF only. However, some other common antibodies, such as against LGI1 and Caspr2, are always present in serum and may be absent in CSF (van Sonderen et al. 2016; McCracken et al. 2017). Thus, positive serum detection by commercial assays is sufficient for these antibodies. However, if available, both specimens reduce the risk of overlooking pathogenic antibodies, and CSF detection increases the plausibility that the respective antibodies are relevant for the clinical syndrome.

Antibody-negative autoimmune encephalitis

The negative predictive value of serum antibody diagnostics is limited, as, in about 50% of cases in which clinical testing and MRI are suggestive of autoimmune encephalitis, none of the known antibodies can be detected in patient serum (Dubey et al. 2018). For such cases, Graus et al. (2016) defined criteria that allow the diagnosis of autoimmune encephalitis even in the absence of an antibody (see Table 3), particularly as the number of autoantibodies tested varies greatly between laboratories.

Seronegativity is believed to be due to autoantibodies that have either not yet been detected, are not included in the assay or are found only in the CSF. Perhaps current laboratory assays are not sensitive enough either. Furthermore, the strong immunoadsorbing property of the brain can lead to a binding of autoantibodies to their respective antigens, thereby limiting their detection in serum and CSF (Castillo-Gomez et al. 2016). Alternatively, autoimmunity may be due to an as-yet undefined innate or T-cell-mediated autoimmunity, rather than circulating autoantibodies (Najjar et al. 2018).

For 'seronegative' encephalitis classified as 'definite' due to the clinical criteria, the same immunotherapy is recommended as for antibody-associated forms. In the case of 'probable' or 'possible' encephalitis (categories according to Graus et al. (2016)), the response to a probative immunotherapy (e.g., steroid sensitivity after a sufficiently long treatment) would be conceivable as a criterion for clinical diagnosis. However, this is questionable in view of the extremely different response of various forms of autoimmune encephalitis to steroids,

as well as the increased risk of steroid administration in people with psychotic disorders.

Non-specificity of clinical symptoms

A summary of the clinical signs, features, the typical age distribution, possibly associated tumours and therapy in various autoimmune encephalitis forms by various antibodies against synaptic and neuronal cell surface proteins can be found in Table 1.

However, if the disease has not been manifested in its full form, the symptoms are often not specific for the autoantibody type. Most oligosymptomatic courses show a wide overlap with established neuropsychiatric conditions (Steiner et al. 2018). Of course, epileptic seizures are also a possible consequence of infectious encephalitis, metabolic encephalopathy or congenital epilepsy. Focal neurological deficits may occur, e.g., as a result of vascular lesions, rheumatological diseases, multiple sclerosis, brain tumours and metastases. Neurodegenerative or prion diseases are associated with a variety of abnormalities in EEG, MRI and CSF, and symptoms that may be similar to autoimmune encephalitis (Steiner et al. 2018).

Viral encephalitis as differential diagnosis

Finally, it should be noted on herpes simplex encephalitis (HSE) with temporal brain affection that, on the one hand it is an important differential diagnosis. On the other hand, viral diseases (e.g., herpes simplex or influenza) can trigger a malfunction of the immune system and disruption of the blood–brain barrier with secondary development of NMDA receptor encephalitis (Armangue et al. 2014; Ehrenreich 2017; Prüss 2017b). The detection of herpes encephalitis thus does not exclude the existence or onset of autoimmune encephalitis, which should be treated with immunotherapy after acyclovir treatment in the case of positive antineuronal autoantibodies. Generally, the production of antineuronal autoantibodies may occur as a secondary response to the viral disease. This means that, as a precaution, virological diagnostics should also be performed when detecting NMDA receptor autoantibodies in the CSF (see above).

Significance of EEG and CSF diagnostics

It should be emphasised at this point that the cMRI is unsuspicious in about 50% of patients with autoimmune encephalitis despite severe illness (Dalmau et al. 2011). In the CSF and in the EEG, however, about

90% show relevant abnormalities (see step-by-step diagnostic workup and [Figure 2](#); Dalmau et al. 2011). Therefore, in the case of clinical suspicion of autoimmune encephalitis, EEG and CSF diagnostics should always be done.

Functional impairment of the brain, for example, in the context of encephalitis or encephalopathies that have not (yet) led to visible brain structural changes in the cMRI, can be well detected by EEG.

In view of the physiological role of the blood–brain barrier, inflammatory processes of the brain and neurodegenerative diseases can be detected only to a very limited extent by blood analyses alone. In the context of the clinical warnings presented in [Figure 2](#), CSF diagnostics should always be offered to patients with primary psychiatric symptoms. Despite the currently not scientifically proven added value of screening tests for the clinical situation described here, we recommend that every person with a first psychotic episode should be offered a lumbar puncture with a comprehensive clarification of infectious, autoimmune and other central causes. The low risks associated with the lumbar puncture must be balanced against the added diagnostic value in these severely ill patients.

Therapy

The treatment of patients should be multidisciplinary and involve psychiatrists and neurologists, as well as neuroimmunologists and oncologists. For more detailed background information regarding immunosuppressive therapies in autoimmune encephalitis we refer to the following references: Lancaster (2016), Dalmau et al. (2017), Prüss et al. (2017a), Varley et al. (2017), and Shin et al. (2018).

Based on our own clinical experience and taking into account international expert advice, *immunosuppression* by corticosteroid therapy (1 g (methyl) prednisolone/day for 5 days) or intravenous human immunoglobulin administration (0.4 g/kg/day for 5 days) or immunoadsorption or plasmapheresis for rapid removal of the pathogenic autoantibodies are treatments of first choice in patients with definite autoimmune encephalitis (expert opinion: Graus et al. 2016; Lancaster 2016; Dalmau et al. 2017; Prüss 2017a; Varley et al. 2017). It should be noted that, because of the described risk of steroid-induced mania or psychosis, there should be a clear indication for immunosuppressive corticosteroid therapy (Gable and Depry 2015). If autoimmune encephalitis is confirmed and therapy fails, the treatment should be extended within a few days, preferably with rituximab ($2 \times 1,000$ mg i.v.

or s.c. at intervals of 2–4 weeks). Refractory cases may also require combination with cyclophosphamide (750 mg/m^2 body surface every 4 weeks), mycophenolate mofetil or methotrexate to achieve clinical response (expert opinion: Lancaster 2016; Dalmau et al. 2017; Prüss 2017a; Varley et al. 2017). In addition to the clinical improvement, an improvement of pathological cMRI and EEG findings may be used to assess the success of the therapy. Antineuronal serum and CSF antibody titres should decrease with adequate response (control after a few weeks).

In particular, antipsychotics with low extrapyramidal adverse effects are suitable for the *symptomatic pharmacotherapy* of psychotic symptoms, since the risk of neuroleptic-induced dyskinesia or malignant neuroleptic syndrome is increased in patients with autoimmune encephalitis (Lejoste et al. 2016). Short-acting benzodiazepines can be used for anxiolysis and sedation, and at higher doses for the treatment of catatonic syndrome.

In general, with clear detection of antineuronal antibodies a tumour search (whole-body CT, PET, MRI, sonography, mammography, etc.) and eventually tumour removal/treatment should take place. Different tumour risks are associated with the various types of antineuronal antibodies. A strong tumour association is especially true for antibodies directed against intracellular neuronal antigens (Hu, Ri, Yo, CV2/CRMP5, Ma1, Ma2/Ta, amphiphysin, Tr, PCA-2, ANNA-3 and SOX1), most of which are paraneoplastic (Lancaster 2016; Dalmau et al. 2017; Prüss 2017a; Varley et al. 2017). However, as summarised in [Table 1](#), the risk of various tumours is also increased in patients with certain neuronal surface/synaptic autoantibodies, depending on the exactly identified molecular target structure. This information should be used for the choice of the most appropriate supplementary diagnostics (e.g., risk of ovarian teratoma in female patients with NMDA receptor encephalitis $\Rightarrow$ gynaecological examination and pelvic MRI with contrast enhancement). Notably, repeated tumour screening is indicated, such as repeat pelvic MRIs in women with non-remitting NMDA receptor encephalitis where no tumour is found on initial screening in order not to overlook any tumour.

Electroconvulsive therapy (ECT) may be applied as last resort if patients with autoimmune encephalitis do not respond sufficiently to the above immunosuppressive and pharmacological treatments. A beneficial effect of ECT has been described particularly in anti-NMDA receptor encephalitis patients with catatonia (Coffey and Cooper 2016; Gough et al. 2016). The

mechanism of action remains largely unclear, but in animal models ECT has been shown to upregulate the expression of NMDA receptors (Watkins et al. 1998).

Prognosis

Consideration of the above-mentioned recommendations for a step-by-step diagnostic procedure guided by clinical warning signs may shorten the time between symptom onset and correct diagnosis (Herken and Prüss 2017; Steiner et al. 2018). This is very relevant for patients with autoimmune encephalitis and antibodies against synaptic and neuronal cell surface proteins, as early and sufficiently intense immunotherapy often leads to a good prognosis despite severe illness, so that the vast majority of patients returns with relatively low neuropsychiatric deficits to school, work and family (Lancaster 2016; Dalmau et al. 2017; Prüss 2017a). On the contrary, a sole symptomatic antipsychotic therapy in cases with definite autoimmune encephalitis (criteria according to (Graus et al. 2016) can lead to the development of severe defect states (residual symptoms).

Need for optimisation in the measurement methodology and clinical trials

Finally, it should be noted that uncertainties exist regarding the optimal test method for the detection of antineuronal surface antibodies (Jezequel et al. 2017). Commercially available assays, using indirect immunofluorescence on fixed cells expressing synaptic or neuronal cell surface proteins (e.g., EUROIMMUN biochip assays, Lübeck, Germany), are sensitive but may be less specific than live cell assays which are available only in specialised laboratories (Jezequel et al. 2017). An important complementary procedure is an immunofluorescence screening test on rodent brain slices, which can detect even previously unknown antibodies and whose wider application is likely to reduce the number of 'seronegative' cases. The determination of anti-neuronal antibodies is less standardised than other quantitative measurements of laboratory medicine. There is still a need for optimisation. An important limitation in the diagnosis of autoimmune encephalitis is that commercial tests do not yet exist for some newly identified entities. Thus, in suspected cases of autoimmune encephalitis, we recommend the referral to a research laboratory so as not to overlook previously uncharacterised antibodies.

Notably, most treatment recommendations are based on the experience of experts in the field.

However, there is a need for clinical trials to identify clinically meaningful cut-off values of autoantibody titres which provide a clear indication for immunotherapy and to compare the efficacy of different immunotherapeutic strategies more objectively.

Conclusion for clinical practice in psychiatry

The drafted step-by-step diagnostic procedure aims to quickly identify and adequately treat patients with autoimmune encephalitis and psychotic symptoms:

1. Clinical warning signs: rapid progression, consciousness/orientation/memory impairment, catatonia, speech dysfunction, neurological deficits, epileptic seizures, autonomic dysfunction, hyponatremia ⇒ mandatory cMRI, EEG and routine CSF diagnostics.
2. If one of the following cMRI, EEG and CSF findings is present: mesiotemporal/multifocal hyperintense MRI signal, epileptic/slow-wave activity/'extreme delta brush'/lymphocytic pleocytosis/specific oligoclonal bands/blood-CSF-barrier impairment ⇒ *quick obligatory*³ testing of anti-neuronal autoantibodies in serum and CSF and microbiological-virological diagnostics.
3. In the case of a positive autoantibody test result (in combination with the above-mentioned typical clinical signs or diagnostic findings) ⇒ autoimmune encephalitis ⇒ immunotherapy and tumour search.

Notes

1. Recently, a study in mice with blood-brain barrier impairment showed that systemic endogenous formation of NMDA receptor antibodies alone did not cause brain tissue lymphocyte infiltration or microglia activation, although the antibodies broke into the brain and caused behavioral changes (disruption of social interaction (Pan et al. 2018). This implies that additional factors such as viral infection may cause the previously described neuropathological findings in patients with NMDA receptor encephalitis.
2. The characteristic EEG finding of NMDA receptor encephalitis was called 'extreme delta brush' (Schmitt et al., 2012), because of its resemblance to the delta brush EEG pattern seen in premature infants, also known as beta-delta complexes (transient patterns characterised by a slow delta wave with superimposed fast activity).
3. Notably, e.g., NMDA receptor encephalitis cannot be entirely excluded by the lack of the above-mentioned typical findings on EEG, by normal MRI or by a normal basic CSF profile. Thus, in a more cautious approach, antineuronal autoantibodies may be determined in all patients with clinical warning symptoms of

encephalitis, regardless of unremarkable MRI, EEG and CSF cell count/oligoclonal bands.

Contributions

Concept and design: all authors. First manuscript draft: JS. Critical revision and amendment of the manuscript: HP, SK, TF, AH, PF. Creation of Figure 1: AH, JS. Creation of Table 1: HP, JS. Creation of Figure 2 and Tables 2 and 3: JS, revised by HP, SK, TF, AH and PF. Supervision: JS, PF.

Acknowledgements

None.

Statement of interest

This work has been done without extra funding.

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