Biological Psychiatry

Review

The Neuropsychiatric Checklist for Autoimmune Psychosis: A Narrative Review

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ABSTRACT

Autoimmune encephalitis (AE) is a rapidly evolving topic in both neurology and psychiatry. A recent international consensus article defined criteria for possible, probable, and definite autoimmune psychosis (AP) inspired by the principles established in neurology for the definition of AE. This has stimulated much clinical research on AP but also criticism of the validity of the criteria for possible AP, justifying additional clinical investigations such as lumbar puncture. In clinical practice, it is often difficult to decide how far diagnostic procedures such as lumbar punctures and immunotherapies should go in unclear cases. Against this background, we have 3 aims in this review. First, we summarize and compare the available concepts for the diagnosis of AP in a systematic literature review. Second, we present an overview of typical specific and nonspecific findings that can be obtained in laboratory, electroencephalography, magnetic resonance imaging, cerebrospinal fluid, and [^{18}F]fluorodeoxyglucose positron emission tomography studies in the context of AP. Thirdly, we summarize these findings and present the Neuropsychiatric Checklist for Autoimmune Psychosis as a tool for clinical assessment of the likelihood of AP, with reference to the typical red-flag symptoms and the specific and many unspecific findings that can be identified in additional investigations. We suggest that this instrument may be a useful tool for a comprehensive, possibly uniform, and standardized case assessment in the context of possible AP.

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It has been known for several decades that paraneoplastic limbic encephalitis (LE), as with anti-Yo, Hu, or Ri autoantibodies, causes psychotic syndromes (1). Furthermore, ever since the description of steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT) by Lord Brain in 1966, other variants of presumed autoimmune diseases have been known to produce schizophrenia-like psychiatric syndromes (2). However, it was not until the discovery of anti-NMDA receptor antibody autoimmune encephalitis (NMDAR AE) at the beginning of the new century (3,4) that the topic of possible autoimmune psychosis (AP) became a major issue in psychiatric research. Since then, research in neurology (5,6) and psychiatry has developed dynamically (7–16) and identified a number of other antibodies (abs) that are associated with different neuropsychiatric syndromes (16–20). The terms AE and AP are often only vaguely defined, operationalized, and distinguished from each other. They may refer to specific underlying causes (etiologies) or to specific or general pathomechanisms; the term AP is used here in the sense of a broad pathogenetic concept (see Box S2).

In a seminal paper, Graus *et al.* (5) published criteria for different forms of AE including criteria for seronegative AE (Table S1). Following this concept and other proposals (19,21,22), international consensus criteria for AP were published (11). This triggered discussions (16,23,24) and stimulated further research (13,25–27). Following the basic principles for AE in neurology (5), red-flag symptoms for psychiatric patients that should trigger additional clinical investigations were specified (11,19,21,22) (Table 1). However, the validity of these criteria for possible AP (11) has been questioned (26,28). Other authors have advocated more caution and questioned the concept of AP in principle (16,25). In clinical practice, neurologists who are asked for a second opinion often believe that psychiatric cases do not meet their usual thresholds. A failure to define and demarcate the relevant terms was also criticized. Finally, investigations such as [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) have not yet been considered in the consensus approach (11).

While in some patients with possible AP, clear pathological findings can be obtained in magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), or PET, in most cases, there is multiple but nonspecific evidence of possible autoimmune pathophysiology (13,27,29). A recent case of catatonia illustrates this challenging constellation (Box S1). Other factors add to the complexity. Because schizophrenia is stigmatized, many patients and relatives hope for a diagnosis of AP to escape this stigma (30–32).

All this leads to the clinical problem of deciding how far diagnostic and therapeutic measures should go. As shown in case 3 in Box S2, immunotherapy can also be harmful. Therefore, it is important to develop more clarity about diagnostic and therapeutic algorithms.

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Rationale for This Review

Against this background, this review answers 3 research questions (RQs 1–3).

First, we summarize available recommendations to guide diagnostic and therapeutic decisions in first-episode psychosis (FEP) regarding possible autoimmune pathophysiology. (RQ 1: Are there guidelines for the diagnosis and treatment of AP?)

Secondly, we present an overview of findings that may be obtained in laboratory, electroencephalography (EEG), MRI, CSF, FDG-PET, and neuropsychological studies. (RQ 2: What are typical diagnostic findings in AP?)

Third, we present the Neuropsychiatric Checklist for Autoimmune Psychosis (NEPCAP) as a tool for assessing the likelihood of AP. (RQ 3: How can we objectively assess the likelihood of AP?)

The relevant terms for this review are explained and defined in Box S2.

METHODS

This work was funded by the KKS Foundation and is based on systematic literature reviews for RQ 1 and RQ 2 and a description of institutional approaches at our specialized center for RQ 3.

All methodological aspects are summarized in Box S3.

RESULTS

RQ 1: Guidelines for the Diagnosis and Treatment of AP

The results of our systematic literature review are summarized in Table S2.

Three of the 4 evidence-based guidelines included did not address the topic of AP to a relevant degree (33–35). Most guidelines avoided specific recommendations and suggested MRI, EEG, and CSF testing in cases of high clinical suspicion. However, the exact nature of this suspicion was left open. Only one guideline specifically addressed the issue of AP (36) (Table S2).

In all articles, the authors agreed that the typical presentation of AP is neuropsychiatric, i.e., syndromes with an acute or subacute onset of diverse psychotic symptoms with many atypical features (such as optical hallucinations, affective symptoms such as mania or mood swings) and additional neurological signs (such as seizures, disturbance of consciousness, focal signs such as aphasia) or neurological soft signs and less specific signs (such as motor symptoms, catatonia, dyskinesia, ataxia, dysmetria, dysautonomia) (Tables 1 and 2; Table S2). Following the Graus criteria for AE (5), most articles defined possible AP according to a critical-symptom approach (yellow or red flags) (Table 1). While the approaches of Pollak *et al.* (11) and the German S3 guideline (36) focus on acute or subacute psychotic syndromes, other algorithms define the clinical inclusion syndrome more broadly as acute or subacute psychiatric syndromes or symptoms (18,19,22) (see Tables 1 and 2; Table S1). This is related to the approach in neurology in which the clinical core syndrome for possible AE is defined as "rapid progression (<3 months) of working-memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms" (5) (Table S1). It also relates well to other studies that showed that not only psychotic but also depressive, manic, neurocognitive, delirious, and personality change syndromes were seen with autoimmune causality (27,37) or with guidelines for the diagnosis and treatment of AE in neurology, such as the Canadian consensus guidelines (38). All these findings illustrate that although the typical presentation of AP is neuropsychiatric, a phenotype of classical idiopathic psychosis does not exclude AP (27,37,39,40). Thus, different primary psychiatric presentations may be caused by autoimmune mechanisms (37,39–45). Table 1 shows that there is a general consensus regarding the typical AP symptoms.

Recommendations regarding the question of what precise combination of symptoms and findings should trigger further investigations such as lumbar puncture are heterogeneous. Table 2 summarizes the recommendations of the 7 most elaborated algorithms. For example, Al-Diwani *et al.* (19) and Pollak *et al.* (11) recommend MRI, EEG, and CSF investigations when a subacute severe mental illness is associated with 1 red-flag symptom. Herken and Prüss (22) point out that their algorithm would significantly shorten the time to correct diagnosis without formulating specific recommendations. Following German S3 guidelines, patients with FEP should undergo MRI investigations, while EEG and CSF are recommended in specific constellations (36). Hansen *et al.* (18) called for CSF, MRI, and EEG analysis in all possible autoimmune psychiatric syndromes based on their variant of critical signals. Steiner *et al.* (46) recommended baseline EEG and MRI and CSF analysis only in cases of suspicious findings in the former. Our group offers baseline EEG, MRI, and CSF studies in a tertiary referral setting (47). Guasp *et al.* (26) recommended baseline MRI, EEG, and serum autoantibody tests and CSF examination in FEP patients with additional neurological symptoms or signs. Abnormal findings on EEG or MRI, detectable serum autoantibodies, specific comorbid conditions, and resistance/adverse effects to antipsychotics should also trigger CSF investigations (26).

In most approaches, specific recommendations are not made. The proposed decision trees are similar in principle, but they are often somewhat complicated and sometimes contradictory in detail. The diagnostic pathways are not supported by sufficient empirical evidence but rather follow expert opinion.

In defining probable AP, specific CSF findings such as increased white blood cell (WBC) counts and oligoclonal bands (OCBs) are of paramount importance in all systems. Specific MRI findings such as bilateral temporolimbic abnormalities or EEG patterns (extreme delta brush) are also highlighted. Some systems, such as that of Al-Diwani *et al.* (19), require the exclusion of LE for a diagnosis of AP, thus creating conceptually disjunctive definitions of AE and AP. However, they do allow for overlap between AE and AP, which they refer to as synaptic and neuronal autoantibody-associated psychiatric syndrome. Others consider the presence of CSF NMDAR IgG as a criterion for definite AP, implying an overlapping ontology (11). The exclusion of other secondary causes is implicitly required in all systems but is explicitly required only in some (19,36).

In summary, the overarching concept is similar in all algorithms, with minor differences in detail. All rely on EEG, MRI,

Table 1. Comparison of Published Red-Flag Approaches to Identify Clinical Cases With Possible Autoimmune Psychosis or Psychiatric Symptoms

Author	Type
Oldham, 2017—Autoimmune Encephalopathy for Psychiatrists: When to Suspect Autoimmunity and What to Do Next (21)	Psychiatric symptoms • Personality change • Multisymptom presentations • Nonauditory hallucinations History • Viral prodrome • Severe diarrhea • Fever • Personal/family history of autoimmunity • Personal/family history of neoplasm • Associated with paraneoplastic syndromes • Current or significant history of tobacco use Natural history • Abnormal age of symptom onset • Abrupt or florid symptom onset • Rapid symptom progression • Changing neuropsychiatric symptoms • Treatment resistance Neuropsychiatric symptoms • Unexplained delirium • Premature cognitive impairment • Subacute anterograde amnesia • Catatonic features • REM sleep behavior disorder Neurological features • Seizures • Unexplained stroke-like events, particularly multifocal • Headache • Localizing neurological signs • Cranial nerve palsies • Sensorimotor findings • Movement disorder Medical features • Hyponatremia • Central sleep apnea • Dysphagia • Dysautonomia
Al-Diwani *et al.,* 2017—Synaptic and Neuronal Autoantibody-Associated Psychiatric Syndromes: Controversies and Hypotheses (19)	Yellow flags • Subacute onset <3 months • First-episode severe mental illness Red flags • Speech dysfunction • Seizures • Catatonia/movement disorder, dyskinesias, or rigidity/abnormal postures • Decreased consciousness level • Autonomic dysfunction or central hypoventilation • Neuroleptic sensitivity
Herken and Prüss, 2017—Red Flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients (22)	Yellow flags • Decreased levels of consciousness • Abnormal postures or movements (orofacial, limb dyskinesia) • Autonomic instability • Focal neurological deficits • Aphasia or dysarthria • Rapid progression of psychosis (despite therapy)

Table 1. Continued

Author	Type
	• Hyponatremia • Catatonia • Headache • Other autoimmune diseases (e.g., thyroiditis) Red flags • CSF lymphocytic pleocytosis or CSF-specific oligoclonal bands without evidence of infection • Epileptic seizures • Faciobrachial dystonic seizures • Suspected malignant neuroleptic syndrome • MRI abnormalities (mesiotemporal hyperintensities, atrophy pattern) • EEG abnormalities (slowing, epileptic activity, or extreme delta brush)
DGPPN e.V., 2019—S3 Guideline for Schizophrenia (36)	Soft signs • Quantitative disturbances of consciousness • Motor disorder or unsteadiness when standing or unsteady gait • Autonomic instability • Focal neurological deficits, including aphasia or dysarthria • Rapid progression of psychotic symptoms despite treatment • Hyponatremia • Catatonia • Headache of unclear etiology • Other comorbid autoimmune diseases Hard signs • Lymphocytic pleocytosis in CSF with no indication of an infectious cause • Epileptic seizures • Faciobrachial dystonic seizures • MRI abnormalities (medial temporal hyperintensities, atrophy in this region) • EEG abnormalities (slowing of basic rhythm, pattern typical for epilepsy, holocephalic extreme delta brush [beta-delta complexes, consisting of bilateral delta activity with 1–3 Hz and overlaid beta activity with 20–30 Hz]) (4) for which there is no other explanation. The extreme delta brush seems to be a common feature of NMDAR autoimmune encephalitis in people other than newborns, although its specificity is unclear (4,5).
Pollak *et al.,* 2020—Autoimmune Psychosis: an International Consensus on an Approach to the Diagnosis and Management of Psychosis of Suspected Autoimmune Origin (11)	Red flags for suspicion of autoimmune encephalitis in patients with psychosis • Infectious prodrome • New-onset severe headache or clinically significant change in headache pattern • Rapid progression • Adverse response to antipsychotics or presence of neuroleptic malignant syndrome

Table 1. Continued

Author	Type
	• Insufficient response to antipsychotics • Movement disorder (e.g., catatonia or dyskinesia) • Focal neurological disease • Decreased consciousness • Autonomic disturbance • Aphasia, mutism, or dysarthria • Seizures • Presence of a tumor history of a recent tumor • Hyponatremia (not explained by side effects of medication, e.g., SSRIs, carbamazepine, and others) • Other autoimmune disorders (e.g., systemic lupus erythematosus, autoimmune thyroid disease) • Paresthesia
Steiner *et al.,* 2020—Autoimmune Encephalitis With Psychosis: Warning Signs, Step-by-Step Diagnostics and Treatment (46)	Yellow flags • Subacute onset (rapid progression within <3 months despite psychopharmacotherapy) • Decreased consciousness level • Memory deficits (amnesia)/disorientation (deficits go beyond typical deficits of ICD-10/DSM-5 F20–F29) • Catatonia • Speech dysfunction • Abnormal postures or movements (dystonia or dyskinesia) • Focal neurological deficits • Autonomic dysfunction (hyperthermia, tachy-/bradycardia, hyper-/hypotension, hypersalivation, urinary incontinence) • Hyponatremia • Other autoimmune diseases (e.g., thyroiditis) Red flags • Epileptic seizures/faciobrachial dystonic seizures • Suspected malignant neuroleptic syndrome (neuroleptic sensitivity)
Hansen *et al.,* 2020—Autoantibody-Associated Psychiatric Symptoms and Syndromes in Adults: A Narrative Review and Proposed Diagnostic Approach (18)	Red flags • Aphasia, mutism, or dysarthria • Autonomic disturbance • Central hypoventilation • Decreased level of consciousness • Epileptic seizures • Faciobrachial dystonic seizures • Focal neurological disease • Hyponatremia (not explained by medication) • Infectious prodrome with fever • Movement disorder (e.g., catatonia, hypo- or hyperkinetic movements) • New-onset severe headache or clinically significant change in headache pattern • Adverse response to antipsychotics or antidepressants or other psychopharmacologic drugs • Optic hallucinations • Other autoimmune disorders • Paresthesia

Table 1. Continued

Author	Type
	• Presence of a tumor or history of a recent tumor • Presence of neuroleptic malignant syndrome • Severe otherwise not explained cognitive dysfunction Yellow flags • Confusion • Dynamic course • Early resistance to therapy • Fluctuating psychopathology • Psychomotor symptoms
Wang *et al.,* 2022—Autoimmune Antibodies in First-Episode Psychosis With Red Flags: A Hospital-Based Case-Control Study Protocol (84)	Red flags Clinical characteristics • Tumor • Catatonia or dyskinesia • Adverse response to antipsychotics with rigidity, hyperthermia, or raised creatine kinase • Severe or disproportionate cognitive dysfunction • Decreased level of consciousness • Seizures • Abnormal blood pressure, temperature, or heart rate Test results • CSF pleocytosis of >5 white blood cells per μL, or CSF oligoclonal bands or increased IgG index • MRI abnormalities on bilateral medial temporal lobes • EEG encephalopathic changes

CNS, central nervous system; CSF, cerebrospinal fluid; DGPPN, German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology; EEG, electroencephalogram; MRI, magnetic resonance imaging; NMDAR, NMDA receptor; REM, rapid eye movement; SSRI, selective serotonin reuptake inhibitor.

and CSF studies, with a focus on CSF analysis and antineuronal antibody detection. None discuss the diagnostic potential of FDG-PET.

Only Herken and Prüss (22) attempted to ground their algorithm in empirical data. All algorithms are based on expert opinion or consensus (18,19,46).

RQ 2: Typical Instrumental Findings in Diagnosing AP

High-quality empirical evidence was not available for any method. Controlled trials could not be identified. The different publications generally did not clearly operationalize the concept of AP or used different and inconsistent operationalizations. This carries a considerable risk of circularity. It illustrates the need to further systematize this research (Table S2).

Laboratory Blood Findings in AP. No specific laboratory blood findings were reported. High levels of serum antineuronal abs against CASPR2 and LGI1 antigens may point to autoimmunity but can also be found in healthy individuals (48). All authors suggested that CSF testing is superior to serum testing alone, with a few abs (e.g., CASPR2 and LGI1) having a higher sensitivity in serum than in CSF, while the reverse is true

Table 2. Diagnostic and Operationalization Concepts of AE, AP, and Autoimmune Psychiatric Symptoms in Psychiatry

	Al-Diwani *et al.* 2017 (19)	Herken and Prüss 2017 (22)	DGPPN e.V. 2019—S3 Guideline for Schizophrenia (36)	Hansen *et al.* 2020 (18)	Pollak *et al.* (11)	Steiner *et al.* 2020 (46)	Guasp *et al.* 2021 (26)
Disorders of Interest	Antibody-associated psychiatric syndromes	AE in psychiatry	Schizophrenia/ secondary psychotic syndromes	Autoantibody-associated psychiatric syndromes	Autoimmune psychosis	Autoimmune psychosis	Autoimmune psychosis
Red/Yellow Flags	See Table 1 (Guasp *et al.* refer to Pollak *et al.* and Herken and Prüss)						
Basic Diagnostic Recommendations for FEP and Primary Psychiatric Phenotypes	Serum antibody testing should be done in all cases with subacute onset <3 mo and first-episode severe mental illness and should be considered in cases of severe mental illness with 1) an onset of longer than 3 mo, 2) in relapse, or 3) in a chronic phase	Not mentioned	For all patients with FEP: • Physical and neurological evaluation • Blood tests (differential blood count, glucose, GPT, γ-GT, creatinine, GFR, sodium, potassium, calcium, ESR, CRP, TSH) • Urine drug screening • cMRI (if abnormal, contrast MRI); CCT if MRI not possible	Not mentioned	Not mentioned	Elective diagnostics for all patients with FEP • Physical examination • Laboratory chemical examination (including, e.g., electrolytes, thyroid, liver and kidney parameters) • Drug screening • cMRI • EEG • Neuropsychological testing	All FEP (<6 mo) patients • Serum antibody testing • EEG • Brain MRI
Advanced Investigations	If 1 red flag (see Table 1) or serum antibody testing positive • Brain MRI • EEG • Paired serum-CSF neural surface antibody testing	Implicit recommendation of MRI, EEG, and CSF, if at least 1 yellow flag is present	• CSF (if indicators of organic disease; see Table 1) • Psychological testing • EEG (if clinical indications) • Dementia diagnostics (if dementia is suspected) • Optional laboratory tests (if indicated by medical history and/or clinical findings and/or other sources): • Creatinine kinase • Rheumatic laboratory tests • Iron and copper metabolism • Vitamins B1, B6, B12 • Serology for infectious diseases	All patients with subacute (≤3 mo) or subchronic (>3 mo) psychiatric syndrome with a suspected diagnosis and one symptom cluster listed in a) from the possible autoimmune psychiatric syndrome criteria (see below) • CSF analysis including serum and CSF autoantibodies • EEG • MRI For subchronic psychiatric syndrome including prior to diagnostic tests, additional red or yellow flags should be present to warrant a serum autoantibody investigation	If possible autoimmune psychosis criteria fulfilled, diagnostics should include EEG, MRI, serum autoantibodies, and CSF analysis (including CSF autoantibodies)	• Rheumatologic laboratory (if indicated) • CSF if conspicuous findings in EEG, cMRI, rheumatology laboratory or physical examination (autoantibodies in individual cases) • If certain clinical symptoms: Treponema pallidum/HIV, copper/cerulo-plasmin, rare causes If clinical warning signs (Table 1) obligatory: • cMRI • EEG • CSF including autoantibodies in serum and CSF	All patients with FEP of unclear etiology with • Accompanying neurologic symptoms or • Abnormal paraclinical tests (EEG, MRI) or • Comorbid conditions including recent (<3 mo) history of herpes or other viral encephalitis or presence of an active tumor or • Resistance/ adverse effects of antipsychotics Should have CSF testing (NMDAR-abs, cell count, oligoclonal bands)
Further Subclassification	1) SNAps 2) Patients with	No specific diagnostic criteria	Subacute onset (rapid progression within <3 mo) of memory loss, qualitative or	1) Possible autoimmune psychiatric syndrome: Subacute (≤3 mo) or subchronic (>3 mo)	1) Possible autoimmune psychosis-Psychotic symptoms of abrupt	No specific diagnostic criteria	No specific diagnostic criteria

Table 2. Continued

Al-Diwani *et al.* 2017 (19)	Herken and Prüss 2017 (22)	DGPPN e.V. 2019—S3 Guideline for Schizophrenia (36)	Hansen *et al.* 2020 (18)	Pollak *et al.* (11)	Steiner *et al.* 2020 (46)	Guasp *et al.* 2021 (26)
• Isolated psychiatric symptoms and • Detectable neural surface antibodies 3) AE according to Graus *et al.* 2016 (5) 4) SNAps-AE: Patients with isolated psychiatric symptoms who fulfill criteria for AE		quantitative disorders of consciousness, lethargy, changes in temperament/ personality or other psychological symptoms AND At least 1 of the following: • New focal neurological deficits • New-onset epileptic seizures • Lymphocytic pleocytosis in the CSF (>5 cells/μL) • MRI features suggestive of encephalitis: hyperintense MRI signal on T2 or FLAIR sequences, mesiotemporally emphasized (limbic encephalitis) or in multifocal areas involving gray matter, white matter, or both AND • Exclusion of other causes of illness such as infectious encephalitis or sepsis, rheumatic diseases, metabolic and toxic encephalopathies, mitochondrial diseases, cerebrovascular diseases, tumors, and Creutzfeldt-Jakob disease	autoimmune based psychiatric syndrome or symptoms (details see Table S2) 2) Probable autoimmune psychiatric syndrome a) Subacute or subchronic psychiatric syndrome with one of the following nine items: • Actual or recent diagnosis of a tumor • Movement disorder (catatonia, hypo- or hyperkinetic movements) • Adverse response to antipsychotics or antidepressants, DD neuroleptic malignant syndrome • Severe cognitive dysfunction • Altered consciousness • Seizures • Optic hallucinations • Infectious prodrome with fever • Aphasia, dysarthria, mutism b) Subacute or subchronic psychiatric syndrome with one of the following items: • CSF pleocytosis of >5 white blood cells per μL, or intrathecal IgG synthesis • Uni- or bilateral brain abnormalities/unilateral brain abnormalities	onset (<3 mo) with at least one of the following: • Currently or recently diagnosed with a tumor • Movement disorder (catatonia or dyskinesia) • Adverse response to antipsychotics, raising suspicion of neuroleptic malignant syndrome (rigidity, hyperthermia, or raised creatine kinase) • Severe or disproportionate cognitive dysfunction • Decreased level of consciousness • Occurrence of seizures that are not explained by a previously known seizure disorder • Clinically significant autonomic dysfunction (abnormal or unexpectedly fluctuant blood pressure, temperature, or heart rate) 2) Probable autoimmune psychosis: Criteria for possible autoimmune fulfilled and at least one of the following: • CSF pleocytosis of >5 white blood cells per μL		

Table 2. Continued

	Al-Diwani *et al.* 2017 (19)	Herken and Prüss 2017 (22)	DGPPN e.V. 2019—S3 Guideline for Schizophrenia (36)	Hansen *et al.* 2020 (18)	Pollak *et al.* (11)	Steiner *et al.* 2020 (46)	Guasp *et al.* 2021 (26)
				on T2-weighted FLAIR MRI highly restricted to temporal lobe/ hyperintense lesions outside the limbic system Or subacute or subchronic psychiatric syndrome with two of the following items: • EEG changes (spike, spike wave, rhythmic slowing changes, extreme delta brush, FIRDA or TIRDA) • Presence of serum autoantibodies • High tau or Nfl changes related to acute phase 3) Definitive autoimmune psychiatric syndrome a) Probable subacute or subchronic auto-immune based psy-chiatric syndrome with IgG class auto-antibodies in CSF b) These criteria do not exclude an episode if a previous psychi-atric episode has already terminated	• Bilateral brain abnormalities on T2-weighted FLAIR MRI highly restricted to the medial temporal lobes Or two of the following: • EEG encephalo-pathic changes (i.e., spikes, spike-wave activity, or rhythmic slowing [intermittent rhythmic delta or theta activity] focal changes, or extreme delta brush) • CSF oligoclonal bands or increased IgG index • Presence of a serum anti-neuronal anti-body detected by cell-based assay after exclusion of alternative diagnoses 3) Definite autoim-mune psychosis: The patient must meet the criteria for probable autoim-mune psychosis with IgG class anti-neuronal antibodies in CSF		

The concepts are simplified for better comparability; detailed diagnostic procedures can be found in Table S2 and the corresponding articles.

AE, autoimmune encephalitis; AP, autoimmune psychosis; CCT, cranial computed tomography; cMRI, cranial magnetic resonance imaging; CRP, C-reactive protein; CSF, cerebrospinal fluid; DGPPN e.V., Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde e.V. (German Society of Psychiatry, Psychotherapy and Psychosomatics); EEG, electroencephalography; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; FEP, first-episode psychosis; FIRDA/TIRDA, frontal/temporal irregular delta activity; FLAIR, fluid-attenuated inversion recovery; GGT, gamma-glutamyl transferase; GPT, glutamate pyruvate transaminase; Nfl, neurofilament light; NMDAR-abs, NMDA receptor antibodies; SNAps, synaptic and neuronal autoantibody-associated psychiatric syndromes; TSH, thyroid-stimulating hormone.

for most of the most relevant abs (e.g., NMDAR and GFAP) (38) (Table S3).

Serum antithyroid abs may indicate Hashimoto's encephalopathy (HE) or SREAT (17). Like AP, HE may present with a neuropsychiatric phenotype (49) and may mimic schizophrenia (39). The concepts of HE and SREAT are highly controversial, and some authors have suggested that they are not valid entities but rather harbingers of another unidentified autoimmune pathomechanism (50). Serum antiphospholipid abs or antinuclear abs (ANA) with or without specificity against double-stranded DNA or extractable nuclear antigens may indicate neuropsychiatric variants of systemic lupus erythematosus or other autoimmune diseases, but none of these were discussed in detail. A possible diagnostic role of total tau protein or neurofilament was discussed in one article (18). Otherwise, no specific laboratory blood findings were reported for AP.

EEG Findings in AP. EEG abnormalities are very common in AP, with a prevalence of around 60% in several cohorts (28,37,51). Encephalopathic features such as slow wave activity, generalized slowing, or intermittent rhythmic slowing are more sensitive and clear epileptic discharges, focal abnormalities, and status epilepticus more specific, at least for secondary catatonia (52). Comparative figures for AP have not been reported but are likely (Table S4).

The extreme delta brush in severe courses of NMDAR AE is an EEG phenomenon with some specificity that tends to disappear with clinical improvement (53,54). Overall, EEG appears to be a useful tool for detecting general secondary causality (encephalopathy) with low specificity for AE/AP.

MRI Findings in AP. In NMDAR AE with psychotic features, bitemporal MRI abnormalities typical for LE were reported in only 14% of patients, with 70% having normal MRIs (55). In another study, 5 of 6 patients with AP had nonspecific abnormalities but no typical bitemporal or temporolimbic patterns of LE (28). In a case series of 145 individuals with acute or subacute psychiatric syndromes or symptoms (37), 49% showed normal MRIs. Abnormalities were most common in cases with intracellular (86%) and cell surface (54%) abs and less common in SREAT (36%). Only 25% had limbic pathologies (intracellular abs 64%, cell surface abs 32%, SREAT 2%). Other abnormalities included extralimbic lesions (16%), generalized cortical atrophy (5%), localized cortical atrophy (3%), and postischemic defects (2%) (37). Thus, the pattern of findings in AP appears to be quite variable and may not represent a single entity (Table S5).

CSF Findings in AP. CSF abnormalities are common in AP; however, unremarkable findings do not rule it out. Normal findings in basic investigations were reported in ~20% (37,56) or >35% (55) of cases. The most common abnormalities were increased protein/albumin quotient, elevated WBCs, and CSF-specific OCBs (type 2 or 3) (25,26,28,51,37,56). One study found pleocytosis to be more frequent in AP patients with NMDAR-abs in CSF compared with serum only (57) (Table S6).

Psychosis is very common in classic AE (up to 80%), reflecting the classic neuropsychiatric phenotype (58). AP with a primary psychiatric phenotype with well-characterized abs is rare, occurring in 0% to 2% of patients with FEP (13,26,29,37,47,57,59–61). However, novel abs with still-unspecified antigens may play a role in such cases (13,62). This constellation is similar to that of autoantibody-negative but probable AE (5). Following the Canadian guidelines, other parameters such as neopterin, cytokines, or CSF cytometry may also be helpful as research targets (38). All articles in neurology and psychiatry that have addressed the diagnosis of possible AE/AP have stressed the outstanding importance of CSF investigations (38).

FDG-PET Findings in AP. In a seminal study, all patients with LE with and without psychosis yielded regional hypo- and hypermetabolism (6/6) complementary to MRI abnormalities but less restricted to the medial temporal lobes than in paraneoplastic or voltage-gated potassium channel abs AE/AP (63). Leypoldt *et al.* demonstrated a characteristic pattern of frontotemporal hypermetabolism and occipital hypometabolism (fronto-occipital gradient) in NMDAR AE (64), the extent of which correlated with disease severity and course (63,64). This was confirmed by Ge *et al.* (65), stressing that the metabolic abnormality was usually asymmetrical in cryptogenic, symmetrical in paraneoplastic, and more diverse in viral encephalitis–related NMDAR AE. Two recent retrospective analyses confirmed the diversity of findings in 9 of 15 patients with abs to intracellular or cell-surface antigens who underwent FDG-PET (29). Furthermore, variable regional hypometabolism was significantly linked to antithyroid abs (66) (Table S7).

In contrast to the sparse results in AP, much more evidence has been generated in AE. In a recent meta-analysis (N = 444), the sensitivity of FDG-PET for AE was 87% and was fairly stable across different abs (NMDAR: 88%, LGI1: 87%). This compared favorably with MRI at 56% (46–66%) (67). Typical metabolic patterns for the more common types (e.g., anteroposterior metabolic gradient in NMDAR AE, mesial temporal/striatal hypermetabolism with cortical hypometabolism in LGI1 AE, similar to a limbic encephalitis–like pattern in onconeuronal abs) were contrasted with more variable findings in less prevalent AE types or autoantibody-negative AE (67–69). However, most studies have had methodological issues such as low numbers; ill-defined time points of examination in relation to disease duration, severity, and treatment; and technical factors, highlighting the need for more research.

Whole-body FDG-PET/computed tomography (CT) is also an essential tool for tumor screening in suspected paraneoplastic syndromes [sensitivity/specificity 89%/83% (70)], which may occur in both AE and AP. This is important because the detection of a tumor on whole-body FDG-PET/CT may also support the suspicion of AE and AP.

In conclusion, FDG-PET is a promising diagnostic tool in AP. While some patients show typical findings, many others are likely to show different patterns of cerebral hypo- and hypermetabolism depending on various, partly undefined factors (e.g., antibody type, disease state, treatment, methodology). These findings are in contrast to the typically normal FDG-PET findings seen in patients with FEP and drug-free schizophrenia, whereas in chronic and medicated schizophrenia

there is on average significant frontal hypometabolism, but only in the grand mean of group studies and not on an individual basis (71). But even in established AP, a normal FDG-PET does not rule out an autoimmune etiology, as has been shown on a case-based level.

Potential Neuropsychological Findings in AP. There were no articles that reported specific neuropsychological deficit profiles indicative of AP, but 21 studies analyzed neuropsychological aspects of AE (25,72,73), none of which yielded a specific diagnostic deficit profile. Thus, although cognitive deficits have been widely described as a prominent feature early in the presentation of AE and AP, no concrete neuropsychological deficit profile has been reported that specifically indicates AP.

Summary. In summary, all the diagnostic tools discussed here appear to be useful in a complementary way in the diagnostic workup of AP. However, none of the 6 diagnostic dimensions (laboratory blood tests, EEG, MRI, CSF, FDG-PET, neuropsychological assessment) can be considered the sole diagnostic gold standard. There is general agreement that CSF testing is of paramount importance in detecting established specific markers of autoimmune pathophysiology (such as specific antineuronal abs), but also in detecting more unspecific signals that increase the likelihood of AP without allowing a clear diagnosis (such as increased cells, detection of as-yet-unknown abs, or other signals such as neopterin or cytokines). The detection of relevant titers of well-characterized antineuronal IgG-abs in the CSF supports AP. However, this is rare. Patchworks of nonspecific but suspicious findings are much more common (e.g., Hashimoto's abs, ANA in serum, rhythmic slowing in EEG, nonspecific or postinflammatory white matter changes in MRI, OCBs in CSF, borderline abnormalities in FDG-PET).

At this point, it should be emphasized once again that the construct of AP chosen here represents a broad pathogenetic concept that includes specific pathomechanisms, such as in NMDAR AE with a psychotic phenotype, as well as psychotic syndromes in HE, the pathophysiology of which is still completely unclear (see Box S2). The reason for this conceptual decision is that in clinical practice, classification as at least a possible case of AP is, among other things, a mandatory requirement under medical law for autoimmune therapy trials to be justified at all.

RQ 3: Assessment of the Likelihood of AP in Clinical Practice

The literature review for RQ 1 showed that there are a few international expert and consensus guidelines that recommend an advanced diagnostic procedure in subacute psychotic syndromes or FEP, either based on a red-flag approach (11,22) or in principle (18,19,26,36,37,47). Other investigators have pointed out that the red-flag approach is not sensitive enough to detect definite AP and therefore recommended EEG, MRI, and CSF studies for all patients with FEP, at least in cases of treatment resistance (26,28,74). While these authors call for generous implementation of broad diagnostic measures including CSF examination for psychiatry (75), others have pointed out that this does not correspond to the clinical reality of many psychiatric centers in most countries of the world and that pragmatic red-flag criteria are needed to optimize the organization of the diagnosis of FEP (76). The authors of a recent empirical study concluded that the criteria for probable but not possible AP discriminated between the AP group and the reference group (28). Consistent with this, it was pointed out in an earlier report that relevant subgroups of patients with AP identified in other contexts did not meet these consensus criteria for possible AP (26), an assertion that was, however, contradicted by the authors of the consensus guidelines (75,76). In any case, this is an important proposition because according to this concept, possible AP is a prerequisite for scheduling CSF investigations.

Some of the findings in additional investigations (well-characterized antineuronal IgG-abs in serum like CASPR2 or CSF like NMDAR), increased WBC count, CSF-specific OCBs, local IgG synthesis in CSF, bitemporolimbic abnormalities on MRI as in LE, or epileptic temporal discharges in EEG are considered pathologically relevant. However, no article has addressed the relevance of less clear findings such as encephalopathic EEG signals, disseminated nonspecific or postinflammatory white matter changes on MRI, or novel anti-CNS abs findings on native mouse brain slices, all of which can be obtained in a comprehensive diagnostic workup with EEG, MRI, and CSF. Clinical experience has shown that the latter constellations are more common than that of clear pathological findings. In addition, very few articles have addressed the potential value of FDG-PET, known to be very useful in AE even in otherwise inconclusive constellations (29,67).

With this in mind, we developed the NEPCAP (see Table 3) to systematize respective clinical work. This instrument aims to summarize the different clinical and paraclinical features (Table 1) and the possible findings that can be obtained in the different investigations (Tables S2–S7). In contrast to the algorithms summarized in Table 1 and the approach in neurology (5) (Table S1), we have refrained from a clear, criteria-based operationalization of a case of possible, probable, or definite AP. The reason for this methodological decision is that we believe that the empirical basis for such an approach is still too weak. The evidence points to a constellation in which the pathophysiological background of AP is much more heterogeneous than that of the clinical syndromes that have been operationalized in neurology by Graus *et al.* (5). Several conceivable pathomechanisms that could lead to AP include variants of cytotoxic T-cell activity, direct agonistic or antagonistic antibody activity at neuronal receptors, receptor depletion by antibody-receptor internalization, complement activation by abs, immunodeficiencies associated with autoimmunity, small-vessel vasculitis, and many other currently unknown mechanisms.

For the time being, and taking into account the pragmatic realities of clinical psychiatry in many centers around the world, we believe that the approach adopted in most major guidelines (33,35,77) of recommending MRI, EEG, CSF (and FDG-PET on the basis of clinical suspicion, without specifying it) may well be pragmatically feasible. At the same time, we believe that the NEPCAP could be a tool to raise awareness of possible AP, helping clinicians and researchers who are unfamiliar with the topic to understand, in a relatively simple and clear way, what to look for and expect from the different

Table 3. Systematic Assessment of Evidence For and Against the Likelihood of AP: The NEPCAP

Clinical and Paraclinical Phenomena		Rating of Relevance					
		−	0	+	++	+++	Comment
Clinical Findings, Disease Course, and Clinical Context	Abrupt onset				X		
	Infectious syndrome temporary close to onset			X	X		
	Neoplastic disease known to be associated with paraneoplastic syndromes (small cell lung cancer, teratoma, thymoma, lymphoma, etc.)				X		
	Seizures (occurring outside the context of a diagnosis of an established seizure disorder)					X	
	Disturbance of consciousness				X		
	Severe headache (not previously known or otherwise explainable)			X			
	Unusual severe cognitive deficits, disorientation, strong word-finding difficulties, or memory deficits				X	X	
	Polymorphic psychotic symptoms			X			
	Catatonia, catatonic and other motor symptoms: akinesia, mutism, catalepsy, new tics, hyperkinesia, dyskinesia, dystonia, other new motor symptoms				X	X	
	Adverse response to antipsychotic medication or rare side effects to medication (e.g., dyskinesia, akathisia, twitching, motor instability)			X			
	Dysautonomia (unexplained and clinically relevant new autonomic symptoms such as tachycardia, bradycardia, hyper- or hypotension, new severe orthostatic dysregulation, central hypoventilation, sweating, anhidrosis, sicca syndrome, bladder problems, etc.)				X		
	Neurological symptoms and signs (e.g., aphasia, ataxia, paraethesia, dysarthria)					X	
	Neurological soft signs			X			
	Personality change atypical for psychosis			X			
	Atypical age of onset of symptoms (i.e., onset of psychosis <13 or >60 years; onset of tics in > third decade)			X			
	Treatment resistance or rapid progression despite guideline-based therapy			X			
	Rare side effects to medication (e.g., dyskinesia, akathisia, twitching, and motor instability)			X			
	Rheumatological/immunological comorbidity (connective tissue diseases like SLE, sarcoidosis, etc.)			X			
	Relevant psychiatric symptoms in history	X	X				
	Positive family history for primary psychosis	X					
	Positive family history for immunological disease			X			
	Substance abuse temporary close to onset	X					
	Others (specify)						
	Clinical summary assessment						

Table 3. Continued

Clinical and Paraclinical Phenomena		Rating of Relevance					Comment
		−	0	+	++	+++	
Laboratory Blood Findings	Presence of LGI1 or CASPR2 antineuronal IgG-abs (in validated and relevant titers)					X[a]	
	Presence of other well-characterized antineuronal IgG-abs (in validated and relevant titers)			X	X		
	Onconeuronal IgG-abs (in validated and relevant titers; i.e., amphiphysin, CV2, Ta/Ma2, Ri, Yo, Hu, recoverin, SOX1, titin, Zic4, others)			X	X		
	Specific antineuronal or antiglial binding patterns in tissue-based assays (with well-characterized negative antineuronal abs)			X			
	ANAs (using IIF on Hep2 cells)			X			
	Clearly positive ENA screening (e.g., anti-ds DNA abs)			X	X		
	Clearly positive antiphospholipid abs			X	X		
	Antithyroid abs (anti-TPO: anti-TG)			X	X[a]		
	Hyponatremia (unexplainable by other factors such as known side effects to medication)			X			
	Others (specify)						
EEG Findings	Normal EEG		X				
	Diffuse slowing			X			
	Clear focal slowing			X			
	Rhythmic generalized slowing (IRDA/IRTA)			X	X		
	Spike-wave complexes and clear epileptic activity				X	X	
	Extreme delta brush				X	X	
	Other (specify)						
MRI Findings	Normal MRI		X				
	Bilateral mesolimbic signal abnormalities typical for limbic encephalitis and any other clear MRI pattern of known limbic encephalitis (after exclusion of alternative explanations)					X[b]	
	Unspecific signal hyperintensities in mesiotemporal lobe regions			X	X		
	(Sub)cortical hyperintensities on T2/FLAIR sequences or (post)inflammatory white matter lesions			X			
	Focal atrophies			X			
	Otherwise unexplained hippocampal atrophy			X			
	Nonspecific white matter signal changes		X	X			
	Others (specify)						
CSF Findings	Presence of well-characterized antineuronal IgG-abs (e.g., NMDAR, DPPX, LGI1, CASPR2, mGluR5, $GABA_AR$)					X[b]	
	Specific novel antineuronal or antiglial binding patterns in tissue-based assays (with well-characterized negative antineuronal abs)			X	X		

Table 3. Continued

Clinical and Paraclinical Phenomena		Rating of Relevance					Comment
		−	0	+	++	+++	
	Nonspecific anti-CNS binding patterns in tissue-based assays (e.g., against vessels or ANAs)		X	X			
	Increased WBC count (≥5 cells) (after exclusion of infections or other established causes)				X	X[a]	
	CSF-specific oligoclonal bands or increased IgG index				X	X[a]	
	Increased albumin quotient			X			
	Increased protein levels alone		X	X			
	Intrathecal IgG, IgA, IgM synthesis			X			
	Others (specify) (e.g., neopterin, novel findings in cell cytometry, cytokines)						
FDG-PET Findings	Normal FDG-PET (general)		X				
	Normal FDG-PET in an acute, untreated state	X					
	Clear evidence on FDG-PET for an alternative diagnosis (e.g., FTD, early-onset AD, HD, herpes encephalitis, etc.)	X					
	NMDAR AE-like frontal/temporal-to-occipital metabolic gradient					X[b]	
	LGI1 AE-like mesiotemporal (and possibly striatal) hypermetabolism with variable degree of cortical hypometabolism; limbic encephalitis-like pattern					X[b]	
	Focal or multifocal regional hypermetabolism without alterative explanation (e.g., seizure, technical artifact; with or without accompanying regional hypometabolism)				X[a]		
	Regional or diffuse cerebral hypometabolism without alternative explanation (e.g., medication effect)			X			
	Evidence of malignancy/tumor on whole-body PET/CT			X	X		
	Others (specify)						
Neuropsychological Findings	Objective measures of concentration and attention deficits			X			
	Objective measures of impaired memory, language, orientation, etc.			X			
	Others (specify)						

− indicates that the findings speak against AP; 0 indicates a normal finding and does not exclude AP; + slightly supports AP; ++ supports AP; and +++ clearly supports AP.

abs, antibodies; AD, Alzheimer's disease; AE, autoimmune encephalitis; ANA, antinuclear antibody; anti-ds DNA, anti–double-stranded DNA; AP, autoimmune psychosis; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; ENA, extracted nuclear antigen; FDG-PET, [^{18}F]fluorodeoxyglucose positron emission tomography; FTD, frontotemporal dementia; $GABA_AR$, gamma-aminobutyric acid A receptor; HD, Huntington's disease; IRDA, intermittent rhythmic delta activity; IRTA, intermittent rhythmic theta activity; MRI, magnetic resonance imaging; NEPCAP, Neuropsychiatric Checklist for Autoimmune Psychosis; NMDAR, NMDA receptor; OCB, oligoclonal band; SLE, systemic lupus erythematodes; TG, thyroglobulin; TPO, thyroid peroxidase antibody; WBC, white blood cell.

[a]Finding may justify immune therapy in possible AP in certain settings of severe symptoms and therapy resistance.

[b]Finding may justify immune therapy in case of possible AP.

additional investigations. It also provides an initial assessment of the potential relevance of the findings that may be obtained. It may also help clinicians decide when to start an individual therapy trial with immune therapy. We emphasize that currently, the assessment of the relevance of specific findings is based on an expert consensus procedure, including experts from psychiatry, neurology, neuroradiology, nuclear medicine, and immunology/rheumatology. In the future, this expert consensus should be taken to the international level and eventually tested empirically on case collections.

The NEPCAP approach could also be used in future studies to identify diagnostic constellations in which immunotherapy may be indicated. Ideally, it could provide a basic structure for discussing cases in interdisciplinary AP committees. Finally, the NEPCAP (and any future scoring system derived from it) may also be an overdue tool to harmonize and facilitate communication between different institutions.

Possible, Probable, and Definite AP and Immunotherapy. The question of the categorical diagnosis of probable AP is linked to the justification of immunological therapy options. Following international consensus guidelines, a diagnosis of definite AP should lead to immunotherapy as first-line treatment (11), following the principles established in neurology (5), and immunotherapy could also be considered for probable AP (11). What to do in the case of only possible AP remains an open question, with immunotherapy being implicitly avoided. The analog problem in neurology regarding only possible AE has been thoroughly addressed in the recently published Canadian Consensus Guidelines for AE (38). Some authors have stressed that there are cases that do not fulfill the criteria for possible AP that turned out to have AE and responded well to immunotherapy, illustrating the practical problem of this approach (26,28). We think that it is likely that all the categorical approaches summarized in Table 2 will have similar problems when tested on a case-by-case basis. This is because the AP concept represents a collection of different immunological entities and not a unified etiology or pathomechanism, unlike most of the neurological diseases summarized by Graus *et al.* (5).

For this reason, the noncategorical approach of the NEPCAP may have advantages. All phenomena and findings are considered without defining critical inclusion or exclusion criteria for consideration of relevance and definition of specific subcategories.

However, it is important to note that some of the findings do have outstanding importance. For example, in Table 3, the findings marked with footnote *b* may warrant early immunotherapy in case of possible AP even in case of classic primary psychiatric presentation (such as FEP). Findings marked with footnote *a* could justify such consideration in case of severe symptoms resistant to classic guideline-based therapy. All other combinations of less specific findings may still justify individual treatment trials in the case of debilitating, treatment-resistant syndromes if requested by informed patients and decided on an individual basis in specialized centers. Interdisciplinary decision-making structures that involve neurological, neuroradiological, nuclear medicine, immunological, and rheumatological expertise should be established to ensure appropriate diagnostic and therapeutic competence in all cases.

All stakeholders should be aware that even the discussion of possible AP, and even more so trials of immunotherapy, could be associated with relevant risks and disadvantages for patients (see Box S4).

Limitations and Some Notes of Caution

Several authors have warned that the concept of AP/autoimmune psychiatric symptoms may lead to misdiagnoses and unnecessary treatments (16,78). We agree and see the further problem that the AP concept may give patients and relatives hope for a cure and escape from an unwanted diagnosis of schizophrenia, which may be frustrating if it turns out to be invalid. Therefore, we highlight a number of caveats.

First, the diagnosis of AP should always be made in a clinical context, taking all available evidence into account. The phenotype is of paramount importance, as has been emphasized in all articles in the field, and is neuropsychiatric with red- and yellow-flag symptoms and signs in the vast majority of cases. Nevertheless, up to 50% of patients with AE have been mistaken for cases of primary psychiatric disorders (16,25,26), which underlines the psychiatric relevance of this issue. A minority of perhaps 5% of patients with NMDAR AE may have a purely psychiatric phenotype (79). The data for AP are unclear. In such cases, only further investigation may lead to the correct diagnosis.

It must also be stressed that serum autoantibodies are not highly diagnostic in most cases and that CSF testing should be used instead (16,78). The results of autoantibody testing are highly method dependent (in the antigen presented, assay method, individual laboratory aspects), results vary from center to center, and autoantibody testing may produce false positive, false negative, or borderline and difficult-to-interpret results. Therefore, experts in CSF assessment in specialized centers should be involved, particularly in the interpretation of novel or atypical findings (38,80). White matter lesions in MRI investigations may not have any relevance, and the same is true for all the other unspecific findings. Pleocytosis may be artificially induced, for example by treatment with intravenous immunoglobulins (81). In many psychiatric settings, it will be practically difficult to obtain PET imaging, and the expertise, particularly for AP issues, will not yet be available. However, this will change as the potential of this method becomes increasingly recognized, not only for neurodegenerative diseases but also for AP. Thyroid abs are common in the general population (82), but their diagnostic value is low (83). To diagnose a possible case of AP in the presence of thyroid abs, the criteria for HE by Graus *et al.* (5) can be used (see Table S1). It is beyond the scope of this article to discuss the methodological details of the various additional investigations. For clinical psychiatry, it seems imperative to organize the relevant methodological competence for the various additional examinations through interdisciplinary cooperation. Unspecific findings should not be taken as clear evidence for secondary causation, and a thorough and comprehensive diagnostic evaluation is mandatory to rule out other causes of encephalopathy (5,78). The significance of findings such as tissue-based neuronal abs is unclear (13). However, in clinical practice, such unspecific findings must ultimately be evaluated

when deciding whether or not to offer immunotherapy as an individualized treatment option.

Some authors have claimed that there are no empirical data to support AP as a single diagnostic entity outside the well-defined disorders in neurology (16). We agree with this statement. However, accepting that AP does not represent a single and unified etiology or pathomechanism, but rather a group of different entities with different immunological pathologies, does not diminish its scientific and clinical importance. As with NMDAR AE, a small subset of cases may present clinically as primary psychiatric disorders, and the difficult question is how to identify these patients.

In agreement with the critics of the AP concept, we emphasize that the diagnosis should not be made lightly on the basis of unspecific findings in the additional examinations (see Box S4). Diagnostic and therapeutic measures should be carried out in specialized centers, taking multidisciplinary aspects into account. In this context, we believe that the NEPCAP can be a useful tool for possibly uniform and standardized case assessment. However, its usefulness should be tested in additional empirical clinical investigations, and it should not be used as a 1-dimensional diagnostic or, in particular, therapeutic tool. In any case, the future of psychiatric clinical research may lie in moving away from defining psychiatric diagnostic categories based solely on phenotype and trajectory information. Instead, the inclusion of results from additional assessments outlined in the NEPCAP or, for example, response to immunotherapy may help to define more etiopathogenetically valid study groups.

SUMMARY AND CONCLUSIONS

In this review, we searched the relevant literature on the identification and operationalization of AP. We compared the respective classification systems, all of which are based on a critical-symptom approach (yellow and red flags), and the results of additional investigations and reviewed the literature with respect to the likely findings. We summarized and systematized these findings using the NEPCAP tool, which provides a clear overview of possible clinical and diagnostic findings in AP and allows for assessment of the clinical likelihood of AP. Cutoffs or categorical decision pathways are not used, because we think that the empirical data do not currently allow for this. Nevertheless, there are some rare findings that are highly relevant to immunotherapy. A number of abnormal but nonspecific findings that may allow consideration of immunotherapy at least in cases of resistance to conventional therapy are more common in clinical practice. The significance of such nonspecific findings, both individually and in combination, should be systematically investigated in future research. In broad analogy to the history of research on AE, clinical research on AP is expected to be casuistic. The NEPCAP tool could be a useful instrument for standardizing and unifying research efforts in this area.

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