Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin

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There is increasing recognition in the neurological and psychiatric literature of patients with so-called isolated psychotic presentations (ie, with no, or minimal, neurological features) who have tested positive for neuronal autoantibodies (principally N-methyl-D-aspartate receptor antibodies) and who have responded to immunotherapies. Although these individuals are sometimes described as having atypical, mild, or attenuated forms of autoimmune encephalitis, some authors feel that that these cases are sufficiently different from typical autoimmune encephalitis to establish a new category of so-called autoimmune psychosis. We briefly review the background, discuss the existing evidence for a form of autoimmune psychosis, and propose a novel, conservative approach to the recognition of possible, probable, and definite autoimmune psychoses for use in psychiatric practice. We also outline the investigations required and the appropriate therapeutic approaches, both psychiatric and immunological, for probable and definite cases of autoimmune psychoses, and discuss the ethical issues posed by this challenging diagnostic category.

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Introduction

Human and experimental data indicate the presence of diverse immunological and inflammatory abnormalities in subgroups of individuals who have been diagnosed with a broad range of severe psychiatric disorders, including new-onset psychosis and schizophrenia,[1–5] as defined by existing DSM and ICD criteria. These aberrant inflammatory and immunological responses might contribute not only to psychiatric and behavioural problems, but also to accompanying cognitive impairment, soft neurological signs, and autonomic abnormalities.[3,6] These responses might contribute to disease severity, and could help to explain the substantial proportion of patients whose condition does not respond adequately to conventional antipsychotics or psychotherapies.[3,7] Moreover, the discovery of neuronal surface protein antibodies in autoimmune encephalitis has generated a great deal of interest in the possibility that some psychiatric patients, in particular those with both affective and non-affective psychoses, have a specific autoantibody-mediated disease, or so-called autoimmune psychosis.[8–10]

Complementary to previously published criteria and guidelines that provide a clinical approach to the diagnosis of autoimmune encephalitis,[11] in this Position Paper we aim to develop an approach to identify psychoses of possible, probable, and definite autoimmune origin. The full aims of this Position Paper are: (1) to summarise the reasons for the hypothesis that some forms of psychosis are autoimmune; (2) to briefly describe autoimmune encephalitis and discuss whether studies of autoimmune encephalitis support the hypothesis of autoimmune psychosis; (3) to propose a future approach for the investigation of possible autoimmune psychoses; (4) to summarise the possible immunotherapies that will help to define autoimmune psychosis; (5) overall, to ensure that psychiatrists think about autoimmune psychosis or autoimmune encephalitis in clinical practice so that neurological referral and appropriate immunotherapies are considered; and (6) to ensure that systematic studies are undertaken on autoimmune psychosis for future validation and to assist the design of clinical trials.

Methods

An initial working draft of this Position Paper was developed by KB and subsequently discussed at two round table sessions held on March 22 and March 25, 2018, at the 14th Psychoimmunology Expert Meeting in Günzburg, Germany. All co-authors contributed to the working draft, the three circulations of the subsequent drafts, and agreed the final submission and revision (appendix).

Evidence linking inflammation, immune dysregulation, and autoimmunity to psychosis neurobiology

There is growing evidence from studies of genetics, inflammatory markers, infections, and neuropathology (table 1) that links low-grade neuroinflammation (ie, cellular-infiltrative or humoral inflammation below the threshold observed in established CNS inflammatory disease) and immune dysfunction to the pathophysiology of psychosis in a subset of individuals who have been diagnosed with acute psychosis or schizophrenia-spectrum disorders.[7,12–15] These findings include the identification of multiple immune-related loci of the MHC (including the complement system, which is also implicated in the process of synaptic pruning during neurodevelopment),[16–18] an increased frequency of autoimmunity in the patient or their family members,[19–22] and the existence of serum and cerebrospinal fluid (CSF) biomarkers of inflammation.[1,23]

	Schizophrenia and psychotic disorders	Autoimmune encephalitis
Immunogenetic associations	A strong and diffuse association has been found at the MHC locus;[16] causal HLA variants have proved elusive; the association could arise in part because of structurally diverse alleles of the complement component 4 genes.[17] Genetic associations are also strongly enriched in genes that are expressed in tissues with important immune functions, particularly B-lymphocyte lineages (CD19 and CD20).[16]	LGI1 antibody associated encephalitis is most strongly associated with HLA-DRB1*07:01;[111,112] is it also associated with HLA-DR7 and HLA-DRB4.[113] CASPR2 antibodies are less strongly associated with HLA-DRB1*11:01.[111] NMDAR antibody encephalitis is weakly associated with HLA-I allele B*07:02.[112]
Autoimmunity in patients with psychosis or first degree relatives	The presence of autoimmune disease increases the risk of psychosis and vice versa.[20–22,114,115] A family history of autoimmunity increases the risk of psychoses by 10% and a family history of psychosis increases the risk of autoimmune diseases by 6%.[19]	Autoimmunity in the patient and their family is variable.
Serum biomarkers	Raised CRP, IL-6, IL-1β, and TGF-α are increased in patients with acute psychosis compared with healthy controls;[23] raised IL-12, IFN-γ, TNF-α, and sIL-2R could be trait markers.[23] An increased prevalence of multiple neuronal or non-neuronal antibodies versus controls has been reported in a systematic review[116] (although this review conflated multiple assay methods and positivity thresholds, often with small sample sizes in the studies included). The prevalence of NMDAR antibodies could be dependent on the assay used.[37,38]	Antibodies to neuronal surface antigens, particularly NMDAR have been identified in patients with autoimmune encephalitis.[28] There are no consistent cytokine or chemokine abnormalities in peripheral blood;[117] increased Th17 pathway markers could help differentiate autoimmune encephalitis with antibodies to neuronal surface antigens from other autoimmune CNS conditions and healthy controls.[118]
CSF biomarkers	The ratio of CSF to serum albumin, CSF to serum IgG, CSF protein, IL-6, and IL-8 is increased in patients with psychosis compared with healthy controls.[1] Pleocytosis is 3–10%[50,51,119], the proportion of oligoclonal bands restricted to the CSF is 7–15%,[50,51] and neopterin is increased (34%).[119]	Pleocytosis is frequent, specific antibodies are usually present, and intrathecal antibody synthesis occurs in most cases.[28,57,120] NMDAR encephalitis is characterised by few but frequent NR1-specific intrathecal B cells.[49] Levels of CSF TNF-α, IL-6, IL-10, IFN-γ, IL-17A, and CXCL13 are increased in NMDAR encephalitis.[117,121,122] Increased neopterin is common in NMDAR encephalitis.[121]
Infectious antecedents	The risk of psychosis is increased by specific viral and protozoal infections during pregnancy,[123] childhood,[124] or adulthood.[125,126] The effect of multiple infections on psychosis risk is cumulative (ie, the quantitative risk of a subsequent psychosis diagnosis increases with successive infections). A diagnosis of psychosis shows a temporal relationship with preceding infectious episodes, indicating that risk of psychosis is increased nearer the time of infection.[127]	There is a strong association between NMDAR encephalitis and preceding or concurrent HSV encephalitis in a proportion of patients.[71,128] Also associated with non-encephalitic HSV-1 infection.[129] Other viral organisms (mainly herpesviruses) also implicated in multiple subtypes of autoimmune encephalitis.[130] HSV encephalitis is also associated with the production of NMDAR antibodies without resulting secondary encephalitis.[131]
Immunopathology	There is marked variability in studies but there is evidence of increased microglial activation[4] and density,[5] and *SERPINA3*[4] and *IFITM* expression.[4] Evidence from meta-analyses shows increased expression of pro-inflammatory genes at the protein and transcript level.[5] In two studies,[26,27] lymphocyte infiltration occurs in approximately 20% of brains of individuals who had schizophrenia, particularly in the hippocampus.	High concentrations of CD8 and CD3 T-cell infiltrates in patients with paraneoplastic or GAD antibody related conditions.[132] There is neuronal loss and complement activation in patients with LGI1 antibody encephalitis.[133] There is minimal neuronal loss or complement deposits and variable cellular infiltrates in patients with NMDAR antibody encephalitis.[133–135]

CRP=C-reactive protein. CSF=cerebrospinal fluid. CXCL13=C-X-C motif chemokine ligand 13. GAD=glutamic acid decarboxylase. HSV=herpes simplex virus. IFN-γ=interferon gamma. IL=interleukin. LGI1=leucine-rich glioma inactivated 1. NMDAR=N-Methyl-D-aspartic acid receptor. NR1=nuclear receptor 1. sIL-2R=soluble IL-2 receptor. Th17=T-helper cell 17. TGF-α=transforming growth factor α. TNF-α=tumour necrosis factor α.

Table 1: **Evidence linking inflammation, immune dysregulation, and autoimmunity to psychotic disorders and autoimmune encephalitis**

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These biomarkers of inflammation are consistent with increased permeability of the blood–brain barrier with neurovascular unit abnormalities that could initiate brain infiltration of immune cells or other inflammatory mediators.[24,25]

Although some studies on post-mortem brains of individuals who had schizophrenia document upregulated inflammatory mediators and microglial activation,[2] studies looking for lymphocytic infiltration and IgG deposition are rare.[4,5,26,27] The possibility of an adaptive immune response to specific neuronal receptors has, however, become a major interest since autoimmune forms of encephalitis associated with neuronal surface antibodies have been identified.

Autoimmune encephalitis and associated findings in patients with psychosis

Typically, in addition to psychiatric disturbance, patients with autoimmune encephalitis develop clear neurological features, including seizures, cognitive dysfunction, and movement disorders.[28] These patients have pathogenic antibodies that target surface epitopes on synaptic and related proteins, principally the N-methyl-D-aspartate receptor (NMDAR, specifically the NR1 subunit), and the voltage-gated potassium channel (VGKC)-complex proteins, leucine-rich-glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2).[28–30] The clinical associations of these and other antibodies are described in table 2. These antibodies are measured in clinical laboratories by testing serum or CSF antibodies that bind to cells that express the specific antigen but the cells need to be fixed onto slides for commercial distribution.

These IgG neuronal surface antibodies also bind to the target membrane proteins on live neurons, which often leads to divalent cross-linking of the protein, resulting in internalisation and loss of surface expression;[31,32] some antibodies directly inhibit function of the protein.[33] Most studies have not addressed complement-activation or possible cell-mediated immune mechanisms, and the neuropathological studies in patients with autoimmune encephalitis are scarce (table 1).

In some individuals, behavioural and psychiatric disturbance dominate the course of autoimmune encephalitis,[34,35] stimulating the search for these antibodies in patients with primary psychiatric disorders such as schizophrenia and first-episode psychosis.

Neuronal autoantibodies in psychotic disorders

Most studies have concentrated on NMDAR antibodies because NMDAR antibody-associated encephalitis has the strongest association with psychiatric features, an incidence that mirrors the age-related incidence of

	Antigen description or epitope	Main encephalopathy syndrome and psychiatric features	Other associated neurological disorders	Main psychiatric features
Commonly targeted antigens				
NMDAR	Ligand-gated ion channel	Encephalopathy (frequently extralimbic manifestation)	Post-herpes simplex encephalitis relapse with chorea; paediatric dyskinetic encephalitis lethargica; idiopathic epilepsy; immunotherapy-responsive dementia[71,128,136–138]	Anxiety, agitation, bizarre behaviour, catatonia, delusional or paranoid thoughts, and visual or auditory hallucinations; also movement disorder, seizures, autonomic instability[34,57,103]
LGI1*	VGKC-associated and AMPAR-associated secreted molecule	Limbic encephalitis with or without faciobrachial dystonic seizures; prominent hyponatraemia	Morvan's syndrome, neuromyotonia, epilepsy, REM sleep behaviour disorder;[120] rarely isolated movement disorder (parkinsonism, dystonia, chorea)[139,140]	Confusion, hallucinations, depression[120]
CASPR2*	VGKC-associated adhesion molecule	Morvan's syndrome: peripheral nerve hyperexcitability, autonomic instability, encephalopathy	Limbic encephalitis, neuromyotonia, epilepsy;[120] rarely isolated movement disorder (chorea, myoclonus)[141,142]	Confusion, hallucinations, agitation, delusions[143]
AMPAR	Ligand-gated ion channel	Limbic encephalitis	NA	Personality change, psychosis, apathy, agitation, confabulation[144–146]
$GABA_AR$	Ligand-gated ion channel	Limbic encephalitis with refractory seizures	Varied presentations[147]	Confusion, anxiety, affective changes (including depression), hallucinations, catatonia[147–49]
$GABA_BR$	Ligand-gated ion channel	Limbic encephalitis with refractory status epilepticus	Opsoclonus-myoclonus; cerebellar ataxia; PERM[150,151]	Psychosis, agitation, catatonia[144,150]
Hu	Intracellular RNA-binding protein	Limbic encephalitis or limbic encephalomyelitis occurring with small cell lung cancer	Painful sensory neuropathy; cerebellar ataxia[152,153]	Confusion, depression, less commonly hallucinations[152,153]
Ma2	Intracellular protein involved in mRNA processing or biogenesis	Limbic encephalitis occurring with testicular germ cell tumours; REM sleep disorder is common; frequent short-term memory problems	Visual dysfunction, gait disturbance, hypokinesia[154,155]	Confusion and anxiety, including obsessions and compulsions[154,155]
CRMP5 (CV2)	Intracellular protein involved in axon guidance	Limbic encephalitis occurring with small cell lung cancer or thymoma	Chorea; sensory neuropathy[156]	Subacute dementia; also personality change, depression, confusion and psychosis[156]
Amphiphysin	Intracellular protein involved in synaptic vesicle endocytosi	Stiff person syndrome	NA	Rarely can present with depression and anxiety, psychosis[157,158]
Less commonly targeted antigens or those more recently described				
D2R	Metabotropic receptor	So-called basal ganglia encephalitis with prominent movement disorder (ie, dystonia, parkinsonism, chorea, tics)[159]	Sydenham's chorea, PANDAS[160]	Agitation, depression, psychosis, emotional lability[160]
DPPX	Auxiliary subunit of Kv4.2 potassium channels	Limbic encephalitis with enteropathy	PERM[161]	Amnesia, delirium, psychosis, depression[162,163]
MGluR5	Metabotropic glutamate receptor	So-called Ophelia syndrome: Limbic encephalitis in association with Hodgkin lymphoma	Paraneoplastic Limbic encephalitis without lymphoma, or non-paraneoplastic Limbic encephalitis;[164] immunotherapy-responsive prosopagnosia[165]	Depression, anxiety, delusions, visual and auditory hallucinations, personality change, anterograde amnesia[164,166]
IgLON5	Neural cell adhesion molecule of unclear function	Characteristic sleep disorder preceded or accompanied by bulbar symptoms, gait abnormalities, oculomotor problems, and cognitive decline; a tauopathy, strongly associated with HLA-DRB1*10:01[167,168]	NA	Usually chronic cognitive decline, sometimes frank dementia[167,168]

(Table 2 continues on next page)

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See Online for appendix

	Antigen description or epitope	Main encephalopathy syndrome and psychiatric features	Other associated neurological disorders	Main psychiatric features
(Continued from previous page)				
Neurexin 3α	Synaptic molecule involved in formation and maturation of synapses	Infectious-like prodrome followed by cognitive dysfunction, seizures, reduced consciousness, and orofacial dyskinesias; sometimes severe clinical course; mimic of NMDARE but with less prominent psychiatric symptoms[169]	NA	Agitation, emotional lability, and confusion[169,170]
ARHGAP26	Multidomain protein involved in regulation of endocytosis	Autoimmune cerebellar ataxia with dizziness and dysarthria; also memory dysfunction and depression[171,172]	NA	One patient reported with immunotherapy-responsive psychosis with suicidality, aggression, and mutism[173]
Synapsin	Synaptic vesicle-associated protein involved in regulation of neurotransmitter release	69-year-old man with confusion, disorientation, seizures, and left hippocampal hyperintensities on MRI[174]	Synapsin antibody also detected in patients with neurological disorders, including clinically isolated syndrome, longitudinally extensive transverse myelitis, NMDAR antibody associated encephalitis, and anti-Hu antibody associated encephalitis[175]	Synapsin antibody also detected in patients with psychiatric disorders including psychosis, depression, and bipolar disorder, with unclear pathogenic significance[175]
AK5	Intracellular (cytosolic) nucleoside monophosphate kinase, expressed exclusively in the brain	>50 y; subacute pure anterograde amnesia, occurring in most cases after a prodromal phase of asthenia, anorexia, and depression; hippocampal atrophy on MRI scan. Seizures not reported[176]	NA	Prodromal depression, prominent anxiety; rarely delusions[176,177]
GFAP	Intracellular (cytosolic) glial intermediate filament protein	Corticosteroid-responsive meningoencephalitis or encephalitis, with or without myelitis; presents with subacute onset of memory loss and confusion[178-180]	NA	Occured in 29% in one study but not described in detail;[178] psychosis and behavioural changes reported[181]

Note that screening for all these antibodies in patients with an isolated psychotic presentation is not recommended. Adapted from Pollak and colleagues.[29] AK5=adenylate kinase 5. AMPAR=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. ARHGAP26=Rho GTPase activating protein 26. CASPR2=contactin-associated protein-like 2. CRMP5=collapsin response mediator protein 5. DPPX=dipeptidyl-peptidase-like protein-6. D2R=dopamine receptor D2. $GABA_AR$=γ-aminobutyric acid type A receptor. $GABA_BR$=GABA type B receptor. GFAP=glial fibrillary acidic protein. LGI1=leucine-rich glioma-inactivated 1. MGluR5=metabotropic glutamate receptor 5. NA=not applicable. NMDAR=N-methyl-D-aspartate receptor. NMDARE= anti-N-methyl-d-aspartate receptor encephalitis. PANDAS=paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. PERM=progressive encephalomyelitis with rigidity and myoclonus. REM=rapid eye movement. VGKC=voltage-gated potassium channel.
*Note that VGKC antibodies measured by radioimmunoprecipitation are not recommended because the LGI1 and CASPR2 cell-based assays are more reliable.

Table 2: **Summary of the main antigenic targets in autoimmune encephalitis, with associated psychiatric features***

psychotic disorders, and a pathophysiology compatible with the glutamate hypothesis of schizophrenia.[36] Studies focusing on antibodies in patients with psychiatric disorders have largely been restricted to serum samples. In one meta-analysis,[38] the prevalence of positive IgG NMDAR antibodies in serum in individuals with first-episode psychosis varied from 0% to 12% and in some reports the frequencies and titres of positive antibodies were not different from controls. However, studies varied in duration of psychiatric disease, age of the patients, and particularly the antibody tests used.[37,38] Moreover, some using the commercial fixed cell assays found higher numbers of IgA or IgM antibodies (in both patients and controls) that are of unclear clinical relevance. Other researchers tested IgG binding to live, unfixed cells expressing the NMDAR subunit or subunits, binding of IgG to the hippocampal region on rodent brain tissue sections, and binding of IgG to neuronal cultures. These approaches are useful for confirming the specificity and potential clinical relevance of serum IgG autoantibodies in autoimmune encephalitis when confirmatory CSF studies are not available.[39]

CSF studies are indeed very rare in patients with psychosis and the clinical significance of serum antibodies is not always clear. This uncertainty is exemplified by several studies that have shown serum neuronal autoantibodies to be found between 1 and 5% of various patient groups and healthy individuals, when they are unlikely to be clinically relevant.[40] In the following sections we use the term seropositive psychosis to refer to any case of psychosis that is positive for neuronal surface autoantibodies in serum only; this definition should not assume causation or exclude the possibility that there could be alternative mechanisms.

Clinical psychiatric presentation and history of patients with autoimmune encephalitis or possible autoimmune psychoses

In NMDAR antibody-associated encephalitis, patients present with a polymorphic psychosis with prominent

affective symptoms and cognitive impairment, but negative psychotic symptoms might also feature, with depression and suicidality relatively common.[41–43] Importantly, the presentation of patients with NMDAR antibody-associated encephalitis, according to existing diagnostic criteria,[11] rarely maps easily onto existing diagnostic constructs for schizophrenia-spectrum disorders.[41,43–45] Moreover, most studies have not found clinically meaningful differences in severity across multiple symptom domains between seropositive and seronegative patients with psychosis.[46–48]

CSF examinations in autoimmune encephalitis and autoimmune psychoses

In autoimmune encephalitis, CSF positivity, which usually indicates substantial intrathecal synthesis of NMDAR antibodies, is considered necessary and sufficient for a definitive diagnosis; indeed pathogenic NR1-antibodies have been cloned from CSF B cells.[49] However, in psychosis, CSF studies are rare[50,51] and, in most undifferentiated psychosis cohorts, the proportion of seropositive patients who are also CSF positive is highly variable (0–75%).[52–54] These results might be confounded by low titres and the use of different tests between centres, increasing the difficulties in interpreting the clinical significance,[55] but might also reflect an absence of intrathecal synthesis in some cases. An additional possibility, not widely considered, is that CSF antibodies might not be detectable because of their absorption by the relevant antigen in the brain.[56]

Other CSF investigations can be very helpful. CSF lymphocytes are, typically, moderately increased (above 5 white blood cells per µL but typically less than the high values observed in viral encephalitis) in NMDAR antibody- associated encephalitis and some other forms of autoimmune encephalitis, mainly during the early stages, with oligoclonal bands appearing later.[57] Lymphocytosis (>5 white blood cells per µL) generally occurs in less than 5% of patients within undifferentiated psychosis cohorts,[50,51] without comparison with control groups. Only two studies[52,54] have reported CSF abnormalities (including pleocytosis, raised protein, or the presence of oligoclonal bands) in patients with NMDAR antibody seropositive psychosis, and these findings need to be extended to paired serum and CSF samples in large cohorts of patients (as is being done in the Danish PSYCH-FLAME study).

Neuroimaging findings

Limbic encephalitis is the classical form of autoimmune encephalitis and is associated with unilateral or bilateral hippocampal MRI FLAIR-T2 hyperintensities, with or without transient contrast enhancement, in the medial temporal lobes.[11,58,59] By contrast, MRI features are neither sensitive (only 40%), specific (mainly non-specific white matter changes), nor necessary for the diagnosis of NMDAR antibody-associated encephalitis,[60] and structural abnormalities are rare (figure 1).[59] MRI findings in individuals with seropositive psychosis have not been helpful to date.[52,53] Cortical fluorodeoxyglucose (FDG) hypometabolism (figure 1) or hypermetabolism, both found in autoimmune encephalitis, could be indicative of active and persistent neuroinflammatory processes,[2,61] but FDG-PET studies have not been done in patients with seropositive psychosis.

Similarly, pathological electroencephalogram (EEG) findings, such as diffuse slowing, intermittent rhythmic delta or theta activity, or clear epileptiform discharges, are neither very sensitive nor specific for autoimmune encephalitis;[62] they have also been reported in small subgroups of patients with schizophrenia, depression, or schizoaffective disorders.[63] Moreover, the interpretation of such abnormalities is confounded by the effects of psychiatric (particularly antipsychotic) drugs on the EEG. By contrast, a very typical EEG pattern—extreme delta brush (ie, δ waves with superimposed beta waves [brush])[64]—was observed in 30 (6·7%) of 446 patients with NMDAR antibodies.[65] This typical EEG pattern, or a less widespread so-called extreme delta brush-like pattern characterised by fast waves superimposed on δ waves (figure 2),[53,66,67] could be an important sign of NMDAR antibody-associated pathology.

Potential association with infections and systemic autoimmunity

Infections are a risk factor for autoimmunity, and prodromal infections are evident in autoimmune encephalitis and psychotic disorders.[68,69] Most striking is the history of a preceding herpes simplex viral encephalitis in a proportion of patients with NMDAR antibody-associated encephalitis.[70–72] CNS infection might therefore be an initiator of autoimmune psychosis,[73] a hypothesis that is consistent with a considerable body of evidence that implicates infections as a cause of psychotic disorders (table 1).

Although associations between psychosis and several classical autoimmune disorders exist, including neuropsychiatric lupus, the frequency of anti-nuclear antibodies (ANA) and thyroid antibodies in the general population precludes their relevance in defining possible autoimmune psychosis. Equally, psychotic features are not infrequent in patients with classical paraneoplastic syndromes, but they are seldom isolated and the utility of antibody testing in individuals with isolated psychiatric presentations or definite risk factors for cancer, remains unclear.[74,75]

For more on the **PSYCH-FLAME study** see https://www.psykiatri-regionh.dk/psych-flame/Sider/default.aspx

Consensus multimodal approach to the systematic investigation of patients with suspected autoimmune psychosis

Collectively, the observations summarised in this Position Paper point to a potential overlap between autoimmune encephalitis-associated psychosis and psychotic disorders,[76,77] prompting some authors to adopt the term mild encephalitis[78] or autoimmune psychosis[10] as a possible incomplete or forme fruste of autoimmune

encephalitis with dominant psychotic features.[2] Acknowledging that debate exists regarding appropriate terminology,[79] here we use the term autoimmune psychosis and propose a clinical approach to the identification of patients with possible, probable, or definite autoimmune psychosis within psychiatric

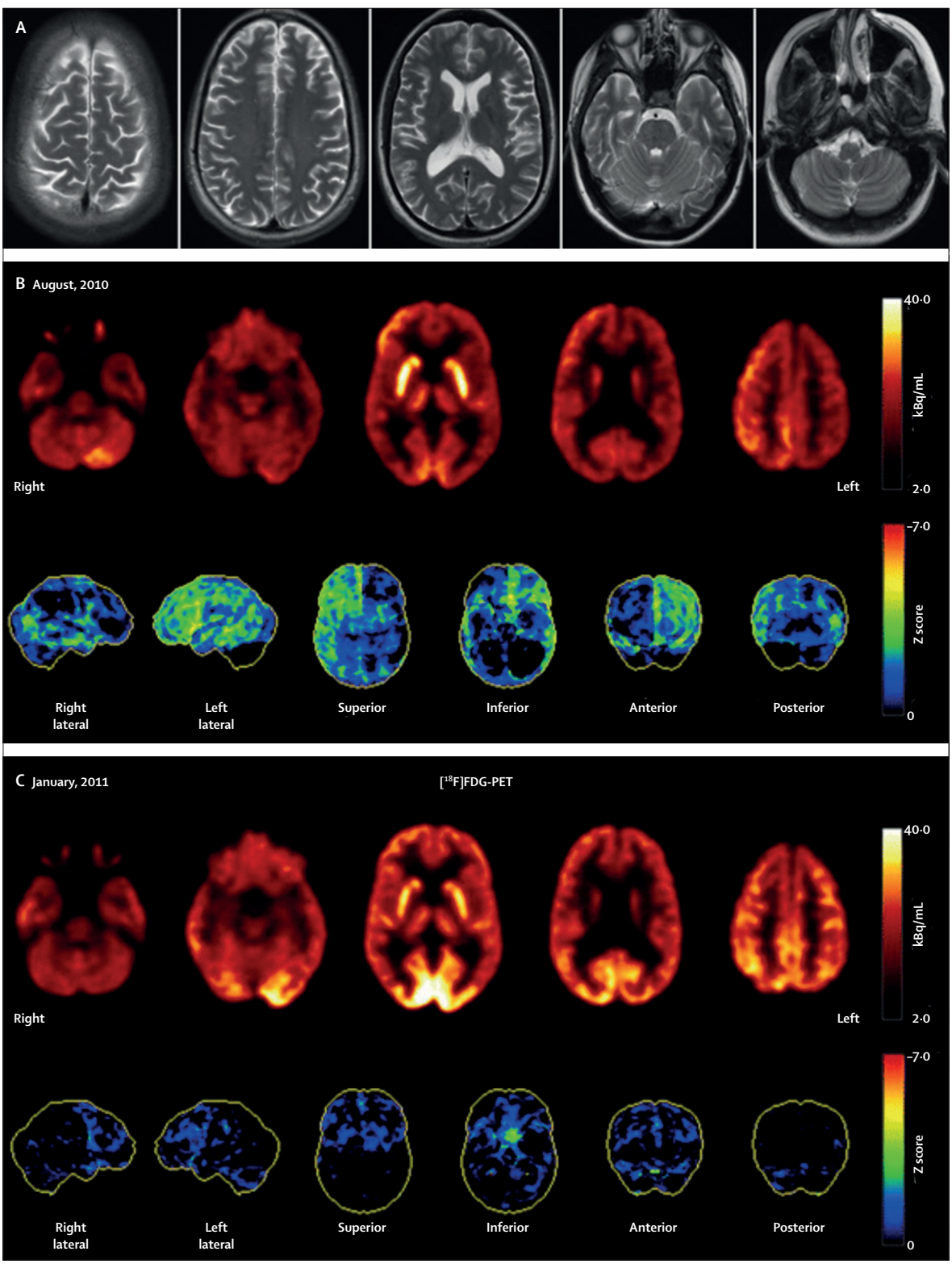

Figure 1: **MRI and FDG-PET findings of a 31-year-old female patient with a catatonic syndrome**
The patient initially presented with affective changes, delusions, agitation, and delirium-like episodes. Initial cerebrospinal fluid (CSF) analysis showed increased CSF white blood cells and protein concentration. Following non-response to anti-infective agents for presumed viral encephalitis, the patient received a diagnosis of catatonic schizophrenia. After 21 months, the diagnosis of N-methyl-D-aspartate receptor antibody encephalitis was made following a screening for neuronal autoantibodies, and both MRI and FDG-PET scans were done. The MRI is largely unremarkable, except for a moderate perisylvic and temporal brain atrophy. Both hippocampi are normal (A). The FDG-PET showed a cortical hypometabolism pronounced on the left hemisphere. Cerebellar hypometabolism was particularly prominent on the right side, probably due to crossed cerebellar diaschisis (B). Following successful immunotherapy, the FDG-PET appearances had normalised (C). Reproduced from Endres and colleagues.[182] FDG-PET=fluorodeoxyglucose PET.

practice. In panel 1, we propose diagnostic criteria for autoimmune psychosis. These criteria are necessarily conservative in terms of the support required from clinical and paraclinical investigations. These diagnostic criteria demarcate a group of patients who we agree have a possible, probable, or definite autoimmune cause to their psychotic disorder. As such, there is overlap with existing consensus criteria for autoimmune encephalitis,[11] but the autoimmune psychosis clinical criteria are less stringent, mainly by including patients with an isolated psychotic presentation. Consequently, the requirements for paraclinical evidence are more stringent for autoimmune psychosis to minimise the possibility of a misdiagnosis (and inappropriate treatment).

The existing criteria for definite NMDAR antibody-associated encephalitis would allow a clinician to make the diagnosis in a patient with evidence of acute psychosis who also has serum NMDAR antibodies, provided these antibodies show binding to live neurons or brain slices.[11] However, because there are occasional healthy individuals with serum NMDAR antibodies that bind to cultured hippocampal neurons (Pollak TA, Vincent A, unpublished), we consider that, for autoimmune psychosis, additional paraclinical evidence is required in the case of a positive serum antibody test without confirmatory CSF positivity.

The criteria for autoimmune psychosis (given in Panel 1) might be too conservative and exclude potential patients with autoimmune psychosis who present with one or more of the following: a more chronic psychotic picture (ie, >3 months); none of the symptomatic criteria of possible autoimmune psychosis (ie, no so-called red flags); or normal EEG, MRI, and CSF findings. Establishing that these patients exist and whether they respond to immunotherapies must await future developments. Nevertheless, if such cases raise clinical concerns, they should be individually discussed with clinicians with appropriate expertise. For the present, we propose these criteria as a first step and consider their validation to be a research priority.

Note that the criteria do not exclude a diagnosis being made in a patient with an acute onset (<3 months) of psychosis, even if that patient has had a previous psychotic, other psychiatric or encephalopathic episode that has now resolved. This aspect of the criteria is consistent with case reports of patients with previous (single or multiple) episodes of psychiatric symptoms, the most recent of which was diagnosed as autoimmune encephalitis,[80–84] as well as evidence that relapses of NMDAR antibody-associated encephalitis (which can occur up to 13 years later)[85] are more likely to present with isolated psychiatric symptoms.[34]

Several authors have proposed lists of clinical red flags (and some have proposed so-called yellow flags) that should raise suspicion of CNS autoimmunity in patients presenting with psychosis.[9,62] These red flag elements, similar to those in autoimmune encephalitis, are summarised in panel 2, with those that we consider necessary for raising suspicion of possible autoimmune psychosis listed in panel 1. This list, although based on all

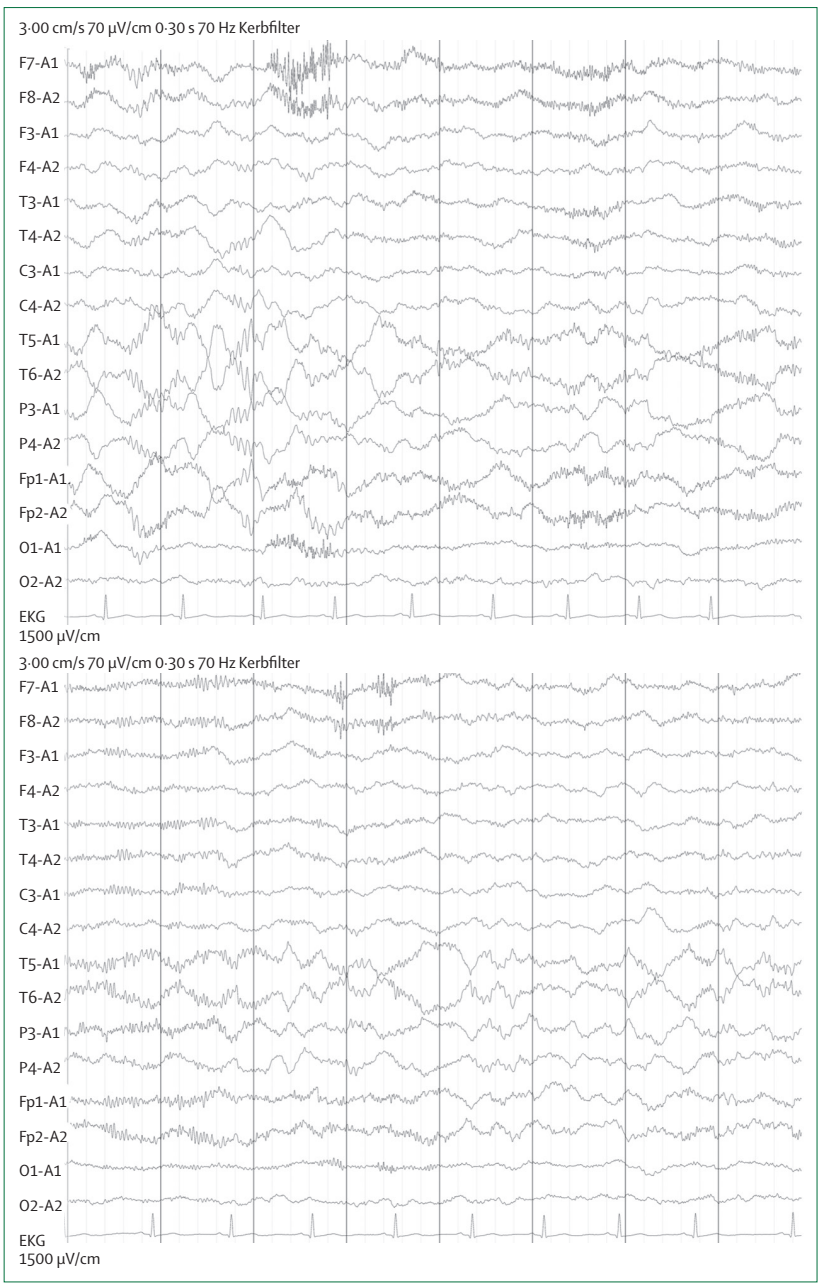

Figure 2: **Extreme delta brush-like electroencephalogram pattern in NMDAR antibody encephalitis.** The patient was a 27-year-old woman who had been diagnosed with schizophrenia 2 years previously following a first episode of psychosis. During the course of a research study using stored samples, N-methyl-D-aspartate receptor (NMDAR) IgG at titre 1:1000 were detected in the patient's serum, which was taken during this first episode as well as during a second episode 2 years later when the patient presented with catatonia. At this time, cerebrospinal fluid (CSF) NMDAR IgG was also detectable at titre 1:320 and the patient had a lymphocytic pleocytosis (21 cells/ µl) with unmatched oligoclonal bands. At this point, the patient's electroencephalogram (EEG) reading showed intermittent bilateral δ activity with superimposed fast activity, a pattern subsequently recognised as an extreme delta brush-like pattern (note the abnormality is less widespread than in classical descriptions of extreme delta brush). Despite the purely psychiatric presentation, the patient was rediagnosed post-hoc with NMDAR antibody-associated encephalitis. The case was originally described by Steiner.[53] EEG=electroencephalogram.

Panel 1: **Proposed diagnostic criteria for autoimmune psychosis**

For a diagnosis of possible autoimmune psychosis:

The patient must have current psychotic symptoms of abrupt onset (rapid progression of <3 months) with at least one of the following:

- Currently or recently diagnosed with a tumour
- 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
- A decreased level of consciousness
- The occurrence of seizures that are not explained by a previously known seizure disorder
- A clinically significant autonomic dysfunction (abnormal or unexpectedly fluctuant blood pressure, temperature, or heart rate)

If a patient has possible autoimmune psychosis, they should be investigated as per section 5 ("Consensus multimodal approach to the systematic investigation of patients with suspected autoimmune psychosis"), including electroencephalography , MRI, serum autoantibodies, and cerebrospinal fluid (CSF) analysis (including CSF autoantibodies). The results should lead to a diagnosis of non-autoimmune psychosis or probable/definite autoimmune psychosis.

For a diagnosis of probable autoimmune psychosis:

The patient must have current psychotic symptoms of abrupt onset (rapid progression of <3 months) with at least one of the seven clinical criteria listed above for possible autoimmune psychosis and at least one of the following:

- CSF pleocytosis of >5 white blood cells per µL
- Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes

Or two of the following:

- Electroencephalogram encephalopathic changes (ie, 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
- The presence of a serum anti-neuronal antibody detected by cell-based assay after exclusion of alternative diagnoses.

For a diagnosis of definite autoimmune psychosis:

The patient must meet the criteria for probable autoimmune psychosis with IgG class anti-neuronal antibodies in CSF.

Note that these criteria do not exclude a diagnosis being made in a patient with an acute onset (<3 months) of psychosis, even if that patient has had a previous psychotic, other psychiatric, or encephalopathic episode that resolved.

available evidence, should be understood as provisional and requires validation. Notably, not all these red flags are uncommon when looked at individually in psychotic disorders, although they could be mild in severity.[9] Clinically, recognition of these red flags could prompt early investigation for autoimmune encephalitis in patients presenting with psychosis, potentially avoiding morbidity associated with untreated active CNS autoimmune disease or disease progression. One of the authors of this Position Paper (HP) identified red and yellow flags from a clinical case series of 100 patients with autoimmune encephalitis and estimated that the use of red flags to prompt diagnostic consideration of autoimmune encephalitis in patients under psychiatric care would result in a 58% reduction in time (74 to 31 days) from symptom onset to diagnosis for all patients with autoimmune encephalitis, and a 75% reduction (from 40 to 10 days) in patients with NMDAR antibody-associated encephalitis.[62] However, patients with CNS autoimmunity can present with psychiatric symptoms and histories that are indistinguishable from so-called non-organic or functional psychoses, and therefore a red flag approach might miss cases of potentially immunotherapy-responsive autoimmune psychosis. Rather than all patients with acute psychosis being screened for neuronal autoantibodies or other evidence of CNS autoimmunity,[86] testing for antibodies should be clinically mandatory only in the presence of specific red flags. We suggest that testing in all other cases should happen at the clinician's discretion.

Detection of IgG antibodies in serum and CSF

If a patient meets the criteria for possible autoimmune psychosis, antibody tests should be done on both serum and CSF, and preferably include all neuronal surface autoantibodies and paraneoplastic antibodies as clinically indicated (table 2). To ensure a full investigation, all efforts to test a patient's CSF sample should be made. The commercial assays provide multiple testing for autoantibodies of NMDAR, LGI1, CASPR2, γ-aminobutyric acid type A receptor ($GABA_AR$), GABA type B receptor ($GABA_BR$), and the AMPA receptor (AMPAR). VGKC antibody tests by radioimmunoprecipitation should not be specifically requested because a positive result can be clinically irrelevant;[87,88] LGI1 and CASPR2 are the appropriate antigens. If not all tests are available, the choice of test will depend on the clinical presentation of the patient—eg, movement disorders (commonly NMDAR, rarely LGI1 and CASPR2), hyponatraemia (LGI1 and CASPR2), or a diarrhoeal prodrome (DPPX). If only serum is available, the conclusions drawn should be cautious and, in these cases, or if the patient does not have a CSF antibody, positive evidence from other steps are required to make a diagnosis of autoimmune psychosis (see panel 1).

If there is other paraclinical or laboratory evidence, such as encephalopathic EEG or CSF pleocytosis, confirmatory testing to show binding to live neurons or reactivity with brain tissue is not essential for a diagnosis of probable autoimmune psychosis.[11,61,89] However, positivity on the confirmatory immunoassays can be useful when other paraclinical findings are unavailable, or show only borderline abnormalities.

CSF biomarkers of inflammation or immune activation

Pleocytosis (>5 white blood cells per µL), presence of oligoclonal bands, and an increased IgG index should be investigated. If possible, accurate measurement of IgG concentrations and antibody titres on parallel CSF and serum will allow for the calculation of intrathecal production of specific antibodies. However, intrathecal

production and high levels of CSF antibodies, although common in some forms of autoimmune encephalitis (eg, with NMDAR, $GABA_BR$, and AMPAR antibodies), are less common in others (eg, with LGI1 and CASPR2 antibodies) and the requirement for intrathecal synthesis in autoimmune psychosis needs further investigation.

Other serum or neuroimaging biomarkers of inflammation and autoimmunity

ANA and anti-double-stranded DNA (dsDNA) antibodies are useful to screen for co-existing systemic lupus erythematosus and other systemic autoimmune disorders, particularly in patients with clinical evidence of systemic autoimmunity. Although ANA is frequently present in healthy individuals, dual positivity with anti-dsDNA antibodies is far more specific. The pathogenicity of thyroid antibodies is unknown, although their association with steroid responsiveness is more established. Thus, thyroid antibody seropositivity in isolation is not sufficient for autoimmune psychosis diagnosis but would provide further support for autoimmune psychosis in patients who satisfy probable autoimmune psychosis criteria.[90]

MRI

MRI is essential both to look for signs of inflammatory changes and to exclude other causes, such as infections, tumours, or other brain inflammatory disorders, particularly demyelinating diseases and vasculitis. The recommended MRI protocol overlaps with that used for infectious causes of encephalitis.[91] Crucially, a negative MRI does not preclude an autoantibody-mediated CNS disorder. In MRI-negative cases, ^{18}F-FDG-PET could show focal areas of hypometabolism or hypermetabolism that can support an autoimmune CNS process.[18]

EEG

EEG is essential to establish the presence of temporal neocortical or limbic epileptiform discharges, as well as slow-wave activity (focal or diffuse, rhythmic or polymorphic, symmetric or asymmetric, theta or delta), showing encephalopathy associated with the psychosis. Specific evidence of extreme delta brush (1–3 Hz slowing with superimposed 20–30 Hz activity) is highly indicative of NMDAR antibody-associated pathology, after reasonable exclusion of other causes.

Brain biopsy

A brain biopsy should only be considered in selected cases of severe, but potentially treatable, atypical forms of rapidly evolving encephalopathy that present with refractory psychosis and cognitive decline (that are not associated with known pathogenic neuronal surface autoantibodies). Further, brain biopsies should only be considered for patients for whom the diagnosis is elusive, despite exhaustive less invasive diagnostic testing (including CSF, EEG, and MRI).[92,93] Brain biopsy can confirm an inflammatory process that, after reasonable exclusion of known disorders, can indirectly implicate its immune-mediated pathogenicity and facilitate timely consideration of immunotherapy trials in individuals with suspected autoimmune psychosis. Biopsy targets are focal MRI lesions that are amenable to sampling, or areas within the non-dominant, cortico-subcortical, frontal region if no lesions are detected by MRI, to limit the functional impact of potential biopsy-related complications. However, the diagnostic value of brain biopsies can be limited by sampling error.[94]

Panel 2:* 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
- Insufficient response to antipsychotics
- Movement disorder (eg, catatonia or dyskinesia)
- Focal neurological disease
- Decreased consciousness
- Autonomic disturbance
- Aphasia, mutism, or dysarthria
- Seizures
- Presence of a tumour, or history of a recent tumour
- Hyponatraemia (not explained by side-effects of medication, eg, SSRIs, carbamazepine, and others)
- Other autoimmune disorders (eg, systemic lupus erythematosus, autoimmune thyroid disease)
- Paraesthesia

*Based on Al-Diwani and colleagues[9] and Herken and Prüss.[62] See panel 1 for the criteria required for a diagnosis of autoimmune psychosis.

Tumour screening

Serum or CSF positivity for any onconeural antibodies (including neuronal surface autoantibodies that are associated with tumours) warrants a CT scan or whole body PET to search for occult malignancy. When the relevant clinical syndrome is present or antibody is detected, abdominal contrast MRI or transvaginal ultrasound should be done in women to look for ovarian tumours and testicular ultrasound in men. Neuronal surface autoantibody serum positivity without concurrent autoimmune CNS disorder is not known to have paraneoplastic associations (eg, when neuronal surface antibodies are detected in healthy individuals).

Treatment strategies

Symptomatic approaches to psychiatric management

Treatment of autoimmune encephalitis and related psychiatric symptoms of confusion, psychosis, or agitation can prove difficult to manage, especially in a general hospital setting where staff might not have the appropriate

mental health expertise and where the physical environment presents many additional risks, potentially leading to serious incidents of assaults against staff or patient suicides on acute medical wards.[42] It is therefore crucial to establish an appropriate physical environment for treatment, ideally a secure neuropsychiatric unit staffed with individuals with both physical and mental health nursing expertise, that is equipped with MRI and EEG capability, and ability to provide infusion therapies or plasma exchange.

The pharmacological management of patients with psychosis in the acute phase typically involves the use of antipsychotics. However, their use in autoimmune encephalitis-related psychosis can precipitate autonomic instability, often recognised in the mental health setting as suspected neuroleptic malignant syndrome.[95,96] Antipsychotics should, therefore, be used with care in patients with suspected autoimmune psychosis; the general approach of starting low and going slow is recommended.

There is no clear evidence to support any particular antipsychotic. Antipsychotics that allow optimal symptom control with minimal risk for extrapyramidal symptoms should be preferentially used, mainly the atypical or second generation antipsychotics. Benzodiazepines are essential in the management of catatonia and in unclear cases of psychosis or aggression. Electroconvulsive therapy has been used in some cases for rapid symptom control, with significant efficacy reported.[97,98]

Indications for immune treatment

A clear indication for immunotherapy in patients with a psychiatric presentation requires a strength of evidence similar to that for diagnosis of NMDAR antibody-associated encephalitis or another form of autoimmune encephalitis.[11] Although the use of immunotherapies in autoimmune encephalitis is supported by considerable clinical experience,[99] no randomised placebo-controlled clinical trials have been reported. On the basis of our experience, we suggest that immunotherapy can be considered in cases of probable or definite autoimmune psychosis (panel 1). To provide a clear indication for immune treatment in autoimmune psychosis, there should be both the symptoms and paraclinical features supportive of a probable autoimmune psychosis diagnosis and the presence of IgG class anti-neuronal antibodies in CSF.

In some cases of autoimmune encephalitis, such as LGI1 antibody-associated disease, CSF antibodies might be undetectable. Because these antibodies are less frequently associated with psychosis, a case of autoimmune psychosis associated with LGI1 antibodies, for example, might achieve only so-called probable autoimmune psychosis status.

For patients with organic psychosis that does not satisfy the high threshold for a definite autoimmune psychosis diagnosis, the presence of clear diagnostic abnormalities (eg, inflammatory changes in CSF or characteristic EEG or MRI abnormalities as described in panel 1) can prompt careful consideration of immunotherapy after reasonable exclusion of alternative causes. Lumbar puncture should always be sought in seropositive cases, but is not always possible, particularly in patients with acute psychosis, and barriers to lumbar puncture might exist that reflect cultural differences between psychiatric and neurological practices. In these cases, IgG neuronal surface autoantibody seropositivity, coupled with one other item of positive paraclinical evidence, must be present to support a probable autoimmune psychosis diagnosis and to justify a trial of immunotherapy in this individual. In all cases, the potentially psychosis-exacerbating effects of high-dose steroid treatment, as one element of the considerable adverse effect profiles of most immunotherapies, must be carefully balanced against the possible immunotherapy benefits.

In cases in which supportive investigations are normal or unavailable, particularly if the neuronal autoantibody seropositivity is the sole abnormality, the question of whether immunotherapy has a role is far from clear. To extrapolate from the literature concerning the treatment of autoimmune encephalitis would be dangerous and is not recommended. There are only a few unblinded case series to suggest that patients with serum-only NMDAR antibodies and psychosis do respond to treatment with immunotherapy, rather than antipsychotics.[54,100] The number of immunotherapy-treated serum-only cases reported is considerably fewer than the number reported who have CSF antibodies. A phase 2, randomised controlled trial (SINAPPS-2; NCT03194815) is underway to compare intravenous immunoglobulins and rituximab with placebo in this group.[101,102] Presently, treatment for this group should be considered on a case by case basis following evaluation by an expert team of neurologists and psychiatrists, with specialist technical neuroimmunology input where appropriate: obtaining paraclinical supporting evidence is paramount. Rheumatologists, or others with specific experience in immunotherapies, can also be very helpful.

Panel of treatment options

The clinical consensus on autoimmune encephalitis treatment strategies involves the rapid initiation of treatment to remove circulating antibodies, including tumour removal (if relevant), plasma exchange, immunoadsorption, or intravenous immunoglobulins, followed by immunosuppression (with either steroids or steroid-sparing agents such as azathioprine, methotrexate, or mycophenolate mofetil) to suppress antibody synthesis.[99] The rapid progression to second-line treatments (eg, rituximab, which depletes CD20-positive B cells, or cyclophosphamide) is also common practice. In some centres, rituximab is used as first-line treatment. This treatment approach is reported to provide the best outcomes for autoimmune encephalitis when started within the first few weeks of symptom onset,[103–105] with

fewer relapses in patients with second-line immunotherapy.[103] However, none of these approaches has been evaluated in randomised controlled trials, even though they are now part of existing guidelines for treatment of autoimmune encephalitis.

Once a patient with definite autoimmune psychosis or autoimmune encephalitis has been treated effectively with immunotherapy, antipsychotics or any other symptomatic treatments can be cautiously tapered off, while remaining vigilant for potential re-emergence of psychotic symptoms (because post-encephalitic patients continue to be at risk of de novo psychotic disorder).[106] There is no evidence that ongoing treatment with antipsychotics can prevent autoimmune psychosis relapse.

Ethical issues and perspectives

The ethical issues regarding the treatment of patients with suspected autoimmune psychosis primarily revolve around the question of whether a trial of immunotherapy is warranted in patients for whom the diagnosis of autoimmune psychosis is uncertain, but considered likely. At present, there are no trials to address this issue and most data available are in the form of case reports and series. Clearly, well conducted trials are needed to inform treatment options, but these are somewhat hampered by inconsistencies in diagnostic approaches. Therefore, we recommend that trials with defined diagnostic categories (such as those outlined in Panel 1 or the SINAPPS-2 study[102] of seropositive patients with psychosis) that are designed to confirm or reject immunotherapeutic approaches, should be done.

Another important aspect to consider will be whether patients with a definite or probable autoimmune psychosis who refuse treatments should be treated coercively under country-specific mental health laws so that appropriate immunotherapies can be attempted. Whereas treatment of incapacitous patients with severe autoimmune encephalitis is commonplace, compulsory immunotherapy of patients with a possible or probable autoimmune psychosis might cause concern for many patients, relatives, and clinicians, and would require a comprehensive clinical and ethical analysis of the risks and possible benefits of both the immunotherapy and treatment as usual (antipsychotics or a so-called watch-and-wait approach). In doing so, the patient's advance health-care directive or, if such is not available or applicable, the presumed will of the patient must be observed.

Conclusion

In this Position Paper we have summarised an approach for the diagnosis and management of psychosis of probable autoimmune origin, highlighting its inherent diagnostic challenges. The proportion of patients with an acute-onset psychosis and red flag symptoms who have an autoimmune brain disease is unknown. This uncertainty arises because these patients are not routinely investigated. There is preliminary evidence that the epitopes targeted by NMDAR antibodies are different for patients with autoimmune psychosis and research to further characterise these antibodies could help to improve selection of those with a predominantly psychotic presentation.[52] More research is required to address the diagnostic and therapeutic pitfalls in evaluating autoimmune psychosis in clinical practice. We hope that the developments summarised in this Position Paper will be essential requirements for designing randomised, multicentre clinical trials that aim to assess the efficacy of targeted immunotherapies.

Further, we need to prioritise the implementation of current best practice in neuroimaging, neurophysiology, and neuroimmunological testing of CSF to identify the proportion of patients who require immunotherapy. A similar approach to the diagnosis of autoimmune encephalitis[11] has been validated[107,108] and an immunotherapy response score for patients who have suspected autoimmune epilepsy has been established.[105,109] We hope that the current criteria will stimulate similar efforts to validate the existence of autoimmune psychosis and begin to document the response to immunotherapy. Lastly, the outcome of treatment in patients with autoimmune psychosis must be shared with the clinical community—eg, for instance, through the GENERATE-psych database.[110]

Search strategy and selection criteria

Relevant papers were identified through PubMed searches of articles published in English from Jan 1, 1960, up to Oct 1, 2018, using the following search terms (alone or in combination): "autoimmune encephalitis", "limbic encephalitis", "anti-NMDA receptor encephalitis", "autoimmune psychosis", "antibody-mediated psychosis", "mild encephalitis", "neuronal surface antibodies", and "neuronal autoantibodies". Additional studies were identified from our own files. The final reference list was generated on the basis of their relevance to the topics covered in this Position Paper.

Contributors

KB developed the initial idea for this Position Paper, organised the meetings, and chaired the working groups. All co-authors contributed to the working draft, three circulations of the subsequent drafts, and agreed the final submission and revision. TAP, AV, SN, and KB oversaw the editing of the manuscript.

Declaration of interests

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Medicine, University of Freiburg. In addition, he was supported by the Berta-Ottenstein-Programme for Advanced Clinician Scientists, Faculty of Medicine, University of Freiburg. JHM reported receiving operating grant funds from Janssen, Sanofi, and Venessance in the past 2 years. He is also an inventor of several patents for biomarkers, including inflammation markers to predict brain inflammation and affective disorders. He is also an inventor of a dietary supplement to prevent postpartum depression. DAB has a patent for a GDF15 Assay with royalties paid to St Vincent's Hospital. AH received paid speakership by Janssen, Otsuka, Lundbeck, and Roche and was member of advisory boards of Janssen, Otsuka und Lunbeck. He is also the editor of the World Federation of Societies of Biological Psychiatry guidelines on schizophrenia and co-editor of the German Association of the Scientific Medical Societies-S3-guidelines schizophrenia. EH reports grants from US National Institutes of Mental Health (NIMH), during the conduct of the study. NIMH did not influence the content or preparation of this Review in any way. All other authors declare no competing interests.

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