Neuropsychiatric symptoms in autoimmune encephalopathies: a clinician’s guide

Fátima Carvalho¹, João Massano¹,², and Rui Coelho¹,³

Abstract

Background: The spectrum of central nervous system autoimmune disorders has recently expanded with the discovery of disorders associated with antibodies directed against the neuronal membrane surface. Although many of these disorders have an underlying malignancy and present with signs of dysfunction of the limbic system (paraneoplastic limbic encephalitis, PLE), a high proportion of cases is non-paraneoplastic. They may occur with milder symptoms, and present no abnormalities in the exams usually used in the investigation of PLE. A striking number of cases may be misdiagnosed as primary psychiatric or other neurological disorders. This paper aims to review the current knowledge on this topic, and provide physicians with an updated text on the neuropsychiatric presentation, diagnostic approach and current management of autoimmune encephalopathies.

Methods: We searched PubMed for articles published in English until December 2013, using the terms: “Autoimmune limbic encephalitis”; “Limbic encephalitis”; “Psychiatry”; “Psychotic Disorders”; “Anti-N-Methyl-D-Aspartate Receptor Encephalitis”; “Gamma-aminobutyric-acid receptor”; “Leucine-rich-glioma-inactivated 1”; “Voltage-gated-potassium channel”; “ω-amino-3-hydroxy-5-methyl-4-isoxazolepropionic-acid receptor”; “RI”; “Ma2”; and “Hu”. We restricted the search to human studies, and selected articles for further analysis. Article reference lists were also reviewed and relevant articles retrieved for consultation.

Results: 109 articles were reviewed, and data summarized. The authors propose diagnostic and treatment algorithms.

Conclusions: Autoimmune encephalitis is not a rare disorder. It often has a psychiatric presentation, and should be considered whenever a non-psychiatric etiology is contemplated. Diagnosis is often challenging, but certain clinical features should raise suspicion about an underlying autoimmune or paraneoplastic disorder, thus guiding the physician to structured investigations, including tumor screening, and adequate therapeutic interventions, namely immunotherapy.

Keywords: Clinical medicine, Paraneoplastic syndromes, Limbic encephalitis, Psychotic disorders, Autoantibodies, Immunotherapy.
Neuropsychiatric symptoms in autoimmune encephalopathies

Introduction

The association between antibodies and encephalopathies has been known for several decades, as paraneoplastic limbic encephalitis (PLE) was first described, back in the 1960’s. Since then, the clinical spectrum of central nervous system autoimmune disorders has expanded astonishingly. In the past decade, several new antibodies against proteins and receptors involved in synaptic transmission and neuronal plasticity have been discovered in patients presenting with encephalitis. When compared to PLE, these disorders differ in their pathophysiology, cancer association, and clinical response, since not all cases are paraneoplastic, they occur frequently in young individuals and children, and can show an impressive response to immunotherapy [1-6].

Furthermore, while PLE is uncommon, recent data suggests a much higher prevalence of non-paraneoplastic autoimmune encephalitis (AE) than previously imagined. In one study, autoimmune etiology was reported in 7% of patients in a sample of 203 individuals with encephalitis. This percentage might even be higher since in cases associated with unknown causes only anti-VGKC and NMDAR antibodies were searched for [7]. Also, in the last few years, several cases describing milder or atypical presentations have been published. This indicates that AE can present predominantly or solely with psychiatric symptoms, frequently mimicking schizophreniform or mood disorders [8-30]. Hence, this diagnostic entity might present as a clinical challenge to any physician, especially neurologists and psychiatrists, whom the majority of patients seek for help first.

This paper aims to review the current knowledge on this topic, and to clarify physicians about the neuropsychiatric presentation of the most common autoimmune encephalopathies, their diagnostic approach and current management.

Clinical presentation, with emphasis on neuropsychiatric features

Antinuclear/cytoplasmatic autoimmune encephalitis

Antinuclear antibodies usually occur in PLE. As the name suggests, symptoms related to limbic system involvement predominate, as individuals present with the classic triad of memory impairment, temporal lobe seizures, and psychiatric symptoms. It occurs predominantly in the elderly and, like most paraneoplastic syndromes, a higher incidence is noted in women [31]. Seizures can be subtle, and even follow an unrecognized course. Cognitive impairment, such as confusion or short-term memory dysfunction, occurs within days to weeks, and progression to dementia may be noted over time. Overall, depression, psychosis, and behavioral changes are the most usual psychiatric manifestations, sometimes accompanied by delusions and hallucinations. Patients can also experience sleep disturbances and obsessive-compulsive behavior (OCB)[31, 32].

Data suggest that classical onconeural antibodies have no pathological role, and central nervous system (CNS) damage is mediated by T cells. Nevertheless, these antibodies underlie different tumor associations, disorder-predominant neuropsychiatric features, and response to treatment (Table 1) [5, 33].

PLE associated with anti-Hu, also called anti-neuronal nuclear antibodies 1 (ANNA-1), occurs in older patients, usually with a long history of smoking, as 74% of patients with underlying malignancy have small cell lung carcinoma (SCLC). More frequently than limbic encephalitis (LE), individuals present with sensory neuropathy (54%), cerebellar ataxia (10%), or multisystem disease (11%). More commonly they have depression or hallucinations, but confusion, sleep disturbances, agitation, and anxiety can occur. Patients with these symptoms respond poorly to antipsychotics and sedatives, and are followed by the onset of seizures, ataxia, and depressed alertness [34].

On the contrary, anti-Ma2 is more often seen in younger men, and there is a strong association with testicular cancer. Besides LE, they can also develop diencephalic or brainstem encephalitis, or a disorder with mixed features. Individuals usually display severe short-term memory deficits, gait disturbances, and hypokinesia. Signs of hypothalamic dysfunction (i.e. diurnal hypersomnia, cataplexy, hyperphagia, hormonal changes, hyperthermia, weight gain, or sexual dysfunction) occur in up to one third of patients. Signs of brainstem dysfunction include cranial neuropathy, nuclear or supranuclear opthalmoparesis, dysarthria, and dysphagia. Parkinsonism might also ensue. Anxiety, OCB, and personality changes are the most frequently reported psychopathological manifestations. Contrarily to anti-Hu, mood disorders and hallucinations are rare. Anti-Ma1 antibodies can also be present and are associated with female gender, older patients, cerebellar dysfunction and malignancies other than testicular, thus predicting poorer prognosis [35].

Another common antibody in PLE is anti-crossveinless-2/collapsing response mediated protein 5 (anti-CV2/CRMP5). It has a strong association with thymoma and SCLC (in this particular case, it may co-exist with anti-Hu), but can also occur with other malignancies, such as uterine sarcoma. It associates with a wide range of neurological and psychiatric symptoms, being subacute dementia and peripheral neuropathy the most common. Ocular abnormalities (optic neuritis, posterior uveitis), olfactory or taste loss are more frequent than in other forms of PLE, and the presence of chorea, particularly facial, is highly suggestive. Patients may also display personality changes, depression, confusion, psychosis, manic mood, OCB, memory deficits, and disorientation to space and time [36-38].

Anti-Ri antibody, also called ANNA-2, is a rare onconeural antibody associated with breast, lung, or cervical cancer. It is more frequent in the female gender and has been associated with several neurological paraneoplastic syndromes, most frequently brainstem symptoms, but cerebellar syndrome, peripheral neuropathy, cranial neuropathy, Lam-
burt–Eaton myasthenic syndrome (LEMS), and limbic encephalitis can also coexist. Patients can present with subacute behavioral and neuropsychiatric changes, [39, 40] although gait instability is the commonest symptom at presentation. Most individuals develop multifocal neurological impairment, including ataxia, opsoclonus, myoclonus, jaw-opening dystonia, visual blurring, laryngospasm, sphincter incontinence, cranial nerve impairment, peripheral neuropathy, or myelopathy. Neurological impairment can be severe, and 60% of the patients will require the use of a wheelchair. Contrarily to ANNA-1, gastrointestinal motility disorders are not common. Most patients show concomitant antibodies in serum (Hu, CRMP5, GAD65, but also thyroid peroxidase or thyroglobulin), suggesting predisposition to autoimmunity, and the majority will respond to immunotherapy [40-42].

Other oncoantibodies associated with paraneoplastic neurological syndromes include anti-amphiphysin, anti-Yo/anti-Purkinje cell 1 (PCA-1), and, less commonly, anti-neuronal nuclear antibodies 3 (ANNA-3), anti-Purkinje cell 2 (PCA2), anti-Zic4, and anti-mGluR1, found in several syndromes, especially paraneoplastic cerebellar degeneration or stiff person syndrome (SPS) [33].

In most patients, PLE will present before cancer is diagnosed, so tumor screening in the presence of onconeural antibodies is mandatory. Coexistence with anti-surface antibodies can occur, most commonly anti-VGKC, as does the development of onconeural-antibodies-associated LE without an underlying malignancy, although less frequently [33, 34].

More recently, anti-Glutamic Acid Decarboxylase (GAD), already associated with diabetes mellitus type 1, SPS, cerebellar ataxia, and epilepsy, has been associated with non-paraneoplastic LE. These patients are more frequently young adults (median age: 23 years old), with female predominance. Seizures are universal at presentation and cognitive impairment or psychiatric disturbances are rare. This disorder usually responds to immunotherapy, but to a much less extent than in anti-surface disorders, and patients rarely become seizure-free [43]. Another recent study also reported the presence of GAD antibodies in idiopathic limbic encephalitis in children. All had fever and acute clinical deterioration, followed by refractory seizures and a wide spectrum of neuropsychiatric disturbances, even after immunomodulatory therapy [44].

### Anti-neuronal surface autoimmune encephalitis

#### Anti-VGKC complex

These antibodies are associated with a wide range of clinical manifestations such as LE, cramp fasciculation syndrome, Isaac’s syndrome, LEMS, or Morvan syndrome (Table 2).

Previously thought to be a disorder associated with antibodies to the voltage-gated potassium channels (VGKC), recent studies revealed that in fact, the targets are the associated proteins, rather than the channel itself [45]. Most cases are associated with antibodies against leucine-rich glioma inactivated 1 (LG1) or contactin-associated protein relates 2 (Casp2), but evidence suggest that other still unrecognized antibodies to VGKC-associated proteins might be involved, explaining such diversity [46]. Although cell-based assays can differentiate them, radioimmunoassay (RIA, still considered the diagnostic gold-standard exam), cannot, and they are still commonly called VGKC-complex antibodies.

Anti-LGI1 is by far the most common, afflicting middle-aged to older patients. It is almost exclusive of patients exhibiting the classic LE clinical presentation triad. Tumor association is infrequent, occurring in 11% of

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Patient Features</th>
<th>Associated malignancies</th>
<th>Common psychiatric symptoms</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu</td>
<td>Older patients Smoking history</td>
<td>SCLC</td>
<td>Depression, Hallucinations, Sleep disturbances, Anxiety disorders</td>
<td>Seizures, Ataxia, Impairment of consciousness, Painful sensitive neuropathy, Gastrointestinal motility disorders</td>
</tr>
<tr>
<td>Ma2</td>
<td>Young males, Older women</td>
<td>Testicular germ cell tumor SCLC</td>
<td>Sleep disturbances, Anxiety disorders, OCB, Mood disturbances</td>
<td>Supranuclear gaze palsy, Cranial neuropathy, Parkinsonism, Hypothalamic dysfunction</td>
</tr>
<tr>
<td>CV2/CRMP5</td>
<td>SCLC, Thymoma, Uterine sarcoma</td>
<td></td>
<td>OCB, Personality changes, Mood disturbances, Psychosis, Subacute dementia</td>
<td>Chorea, Ocular disturbances (uveitis, optic neuritis), Olfactory/taste loss, Cerebellar ataxia, Peripheral neuropathy, Anti-Hu Abs can coexist</td>
</tr>
<tr>
<td>Ri</td>
<td>Older women Smoking history</td>
<td>Lung cancer Breast cancer Cervical cancer Bladder cancer</td>
<td>Behavioral changes</td>
<td>Ataxia, Opsoclonus-myoclonus, Laryngospasm, Jaw-opening dystonia, Visual blurring</td>
</tr>
</tbody>
</table>

Abs = Antibodies; CV2/CRMP5 = Crossveinless-2/collapsing response mediated protein 5; OCB = Obsessive-compulsive behavior; SCLC = Small cell lung cancer.

### Table 1. Clinical features of the different oncoantibody associated disorders.
the patients [45]. Concerning Caspr2, the spectrum of associated disturbances is wider (LE, Morvan syndrome, neuromyotonia, painful neuropathy) and has a stronger association with cancer, notably thymoma [47, 48].

Signs of autonomic dysfunction such as sialorrhea and hyperhydrosis are common features. Hyponatremia, often resistant to treatment [49], and faciobrachial dystonic seizures (FBDS), are other peculiar associations. FBDS are almost exclusive of patients with anti-LGI1 antibodies and present as frequent, sudden, brief myoclonic-like movements, with facial grimacing accompanied by ipsilateral arm posturing, often preceding the onset of other symptoms. They are often resistant to antiepileptic drugs but show a good response to immunotherapy. Verbal and visual memory deficits may also be present [50]. Organ specific autoimmunity is seen in one third of these patients, often with a family history of autoimmune disorder [51, 52].

Common disturbances include behavioral changes, depression, hallucinations and delusions, as well as REM sleep disorders [52]. Seizures occur in the majority of patients, usually of the temporal lobe type but the frontal lobe can also be involved, without EEG abnormalities even during the seizure, thus can be mistaken for psychogenic non-epileptic seizures [53].

**Anti-NMDAR**

This is probably the most common form of autoimmune encephalitis (AE). Since it was first reported in 2006, the number of cases dramatically increased, surpassing 500, with the California encephalitis project reporting an incidence almost as high as viral encephalitis [54]. It is more common in young females (median age: 21 years; age range: 8 months and 85 years), and nearly half are paraneoplastic. Ovarian teratoma is by far the most frequent underlying malignancy, particularly between 12 and 45 years old, especially in females of African or Asian descent. SCLC, neuroblastoma, breast carcinoma, thymoma, testicular cancer, and non-gonadal teratomas may also underlie this disorder, especially in older patients [55-57].

Unlike most AEs, symptoms are not mainly limited to the limbic system. Clinical manifestations can be subdivided into eight categories: behavior, cognition, memory deficits, seizures, movement disorders, decreased alertness, autonomic dysfunction, and central hypoventilation. Although initially monosymptomatic, the majority of patients will exhibit symptoms in at least 4 categories within 4 weeks after presentation, with monosymptomatic disease occurring in only 5% of individuals [56]. The initial clinical presentation differs among age groups: while adults tend...
to manifest behavioral changes, movement disorders and seizures are more common in children, although psychopathological manifestations can also dominate the clinical picture [29, 58-61], as well as developmental regression [13]. In older adults (>45 years) predominant symptoms also diverge, as these patients are more prone to exhibit behavioral changes, and cognitive impairment, and less commonly movement disorders, decreased level of consciousness, or prodromal symptoms [57]. In the extremes of age, no gender preference is observed, with tumors or need for ventilatory support being less frequent.

In young adults, this disorder evolves according to a pattern that often starts with a flu-like prodromal phase, characterized by fever, headache, gastrointestinal, or upper respiratory symptoms. Subsequently, psychiatric symptoms arise, isolated or along with cognitive decline and/or seizures. Two to three weeks after presentation, movement disorders and autonomic instability surface, followed by impaired consciousness and central respiratory dysfunction, often warranting admission to the intensive care unit, with the need of ventilatory support [62].

Psychiatric manifestations include anxiety, agitation, mania, depression, bizarre behavior, delusional and/or paranoid thoughts, and visual or auditory hallucinations, frequently refractory to antipsychotic therapy. In a retrospective study of 100 patients diagnosed with anti-NMDAR encephalitis, all presented psychiatric symptoms, and 77% were first seen by a psychiatrist [63]. Patients are often misdiagnosed with a primary psychiatric disorder, usually psychotic illness. Data from 571 patients showed that purely psychiatric presentation could occur in up to 4%, and in up to 28% in relapsing disease [62]. More commonly these individuals have delusional thinking (74%), half will show aggressive behavior, and hallucinations is noted in 43%. Mood disorders occur in 70%, more often mania. Emotional lability or impulsivity is also common [64].

Movement disorders include jaw-opening dystonia, facial grimacing, atethosis/dystonia or orolingual-facial dyskinetic movements, opisthotonic postures, and limb or trunk choreoathetosis. Autonomic dysfunction manifests as tachycardia/bradycardia, hyperhidrosis, persistent pyrexia, central hypoventilation, blood pressure fluctuation, hypersalivation, intestinal pseudo-obstruction, and cardiac arrest [55, 62].

Relapses occur in 24% of patients, with higher incidence in those who did not receive immunotherapy [65], and in non-paraneoplastic cases [56], sometimes several years after discharge [66], thus suggesting that long follow-up periods and probably long-term immunosuppression should be considered.

**Anti-AMPA**

Almost all patients are older females (median age: 60 years), with relapsing LE. Most cases are paraneoplastic, usually coexisting with breast cancer, lung carcinoma, or thymus cancer [67]. Although only a few cases have been reported, the clinical presentation is variable, since more insidious disease, with progressive memory loss and behavioral changes suggesting dementia has been described [68], as well as fulminant disease with acute confusion, hypersomnia, visual hallucinations, and combativeness accompanied by severe memory loss and brain atrophy [69]. Psychopathological manifestations in these patients include confusion, sleep disturbances, aggressiveness, confabulation, lethargy, combativeness and perseveration. Other reported features are seizures, nystagmus, decreased level of consciousness, and gait unsteadiness [67]. These data are based in a small number of reported patients and further studies are necessary to better clarify the clinical presentation, progression and prognosis.

**Other anti-neuropil antibodies**

Anti-GABAB AE is an apparently rare and recently described anti-surface LE. Almost all cases are older men (median age: 60 years). It is thought to be the most frequent antibody in autoimmune limbic encephalitis associated with SCLC previously considered "seronegative" [70]. Idiopathic forms have also been reported, more commonly in younger patients (median age: 30 years). Seizures, often unresponsive to treatment, are the predominant symptom at presentation, along with confusion, disorientation, striking memory impairment and behavioral changes, suggesting LE. Psychiatric symptoms reported include psychosis, paranoia, confabulation, delusions, sleep abnormalities, and visual/gustatory hallucinations.

These antibodies can coexist with anti-Hu, SOX-1, TPO, anti-VGKC complex and anti-GAD antibodies, the latter more frequently in paraneoplastic cases. Besides SCLC, neuroendocrine lung cancer and thymus carcinoma can also occur. The outcome is worse as compared to other disorders with anti-neuronal surface antibodies, since response to treatment is frequent, but full recovery is rare and death due to the underlying malignancy is common [71, 72].

More recently, basal ganglia encephalitis, associated with antibodies against dopamine receptor 2 (DR2) has been described in children previously diagnosed with encephalitis lethargica, similar to what has been observed with anti-NMDAR AE [73]. In these patients there is a predominance of movement disorders but psychiatric symptoms are also quite common, as are sleep disturbances. None were paraneoplastic, there was no gender or ethnic preference, and in most there was a history of recent infection or immunization [74].

**Diagnostic approach**

In cases with highly suggestive clinical presentation, a definitive diagnosis of anti-neuronal/cytoplasmatic encephalitis can be achieved in most cases using the Graus criteria [33]. However, many cases of anti-surface antibodies associated encephalitis do not fulfill these criteria. Thus, Zuliani et al. proposed further diagnostic criteria in sus-
Neuropsychiatric symptoms in autoimmune encephalopathies

Figure 1

Features that should raise the suspicion of autoimmune etiology in case of atypical psychiatric presentation, particularly in first episode of psychosis or mania.

Box 2

Recent flu-like syndrome
No past psychiatric illness
Rapid onset of psychosis and/or catatonia
Seizures/neurological dysfunction
Known history of malignancy, especially if SCLC, teratoma or thymus cancer
Signs of autonomic dysfunction
Worsening of symptoms after antipsychotic therapy
Refractory hyponatremia
Long history of smoking
Personal/family history of auto-immune disease

ECT = Electroconvulsive therapy; SCLC = Small cell lung cancer

Some possible differential diagnoses are listed in Box 1. Seizures, movement disorders, language dysfunction, and psychiatric manifestations are commoner in AE when compared to viral encephalitis, while autonomic dysfunction is very suggestive of the former [54]. When suspecting a paraneoplastic syndrome associated with anti-CV2/CRMP5, it is wise to exclude Huntington’s and Wilson’s disease, due to the coexistence of chorea or dystonia and psychiatric symptoms. Another common presentation can be acute dementia [76], and other causes of rapidly progressive dementia should also be excluded. As previously noted, most of them, particularly the early stage of NMDAR AE, can mimic primary psychiatric disease, most frequently schizophreniform illness with acutely disorganized behavior or catatonia. Certain features should raise the suspicion of autoimmune encephalitis, particularly in a first psychotic episode (Box 2).

Neurological examination is often unremarkable, besides any cognitive or behavioral features. Full blood count, evaluation of renal, hepatic and thyroid function, prolactin, cortisol, serum protein electrophoresis, cobalamin and folic acid level, serum ions, serological screen for autoimmune disorders, toxicological tests (when appropriate) and viral screening tests should be performed.

The standard clinical investigation includes also brain MRI, EEG, CSF analysis, autoantibody screening, and eventually positron emission tomography (PET). The findings may vary among the different subtypes of AE, as well as their prevalence (Table 3).

Typical MRI findings in PLE are increased temporomesial signal intensity on T2/FLAIR weighted sequences, with swollen anterior structures, unilaterally or bilaterally (asymmetry is common) (Figure 1). Later, it evolves to hippocampal atrophy, with persistent swelling remaining after six months mainly in patients with poor response to treatment [77]. Such findings are rarer in anti-neuronal membrane AE. In NMDAR AE normal imaging is the rule, and lesions outside the limbic system are commoner [78, 79]. The same findings can also be seen, although to a lesser extent, in anti-VGKC complex and anti-AMPA AE [49, 67].

Fluorodeoxyglucose-PET (FDG-PET) often detects changes in the brain when other imaging tests reveal no abnormalities, including MRI [6, 28, 79-82]. There is correlation between the type of antibodies and FGD-PET findings: while classical PLE presents mesiotemporal hypermetabolism, accompanied by hypometabolism in the associative cortices [80], anti-surface antibodies associate
Table 3. Correlation between associated antibody frequency of findings in auxiliary exams and prognosis.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>EEG changes</th>
<th>MRI</th>
<th>CSF abnormalities</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onco-AB</td>
<td>Common, non specific</td>
<td>Temporomesial hyperintensities Ma2: lesions outside the limbic system are common</td>
<td>Common Lymphocytic pleocytosis Mild elevation of protein levels</td>
<td>Hu: Poor, median survival 12 months Ma2: 50-70% clinical stabilization/ improvement CV2/CRMP5: poor, median survival 48 months; 18 months if anti-HU antibodies coexist Ri: good response to treatment; better than CV2 or Hu</td>
</tr>
<tr>
<td>LGI1</td>
<td>Common, non specific</td>
<td>Temporomesial hyperintensities Cortical atrophy Mesiotemporal and basal ganglia hypermetabolism</td>
<td>Rare Slight increase in proteins level Seldom OCB</td>
<td>Excellent response to immunotherapy Improvement: 80% Full recovery: 24% Mortality: 6%</td>
</tr>
<tr>
<td>Caspr2</td>
<td>Common, non specific</td>
<td>Same as LGI1</td>
<td>Same as LGI1</td>
<td>Poor prognosis, although good response to therapy</td>
</tr>
<tr>
<td>NMDAR</td>
<td>Common, non specific or &quot;extreme delta brush&quot; pattern</td>
<td>Rare Abnormalities outside the medial temporal lobe Fronto-temparo-parietal gradient on FDG-PET</td>
<td>Very common Mild pleocytosis Raised protein level Oligoclonal bands</td>
<td>Good Full recovery: 70-80% Mortality: 10%</td>
</tr>
<tr>
<td>AMPAR</td>
<td>Common, non specific</td>
<td>Temporomesial hyperintensities Lesions outside the limbic system (i.e., anterior septal nuclei, cerebellum)</td>
<td>Common Lymphocytic pleocytosis</td>
<td>Poor, although good response to therapy Relapses are common</td>
</tr>
<tr>
<td>GABA B R</td>
<td>Common, non specific</td>
<td>Temporomesial hyperintensities</td>
<td>Abnormal in half of the cases</td>
<td>Poor Full recovery: 18% Partial response: 36%</td>
</tr>
</tbody>
</table>

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2 = Contactin-associated protein relates 2; CV2/CRMP5 = Crossveinless-2/collapsing response mediated protein 5; GABA B R = Gamma-aminobutyric acid receptor; LGI1 = Leucine-rich glioma inactivated 1; NMDAR = N-methyl-D-aspartate receptor; FDG-PET = fluorodeoxyglucose positron emission tomography; OCB = Oligoclonal bands; VGKC = Voltage-gated potassium channel.

Figure 1. Brain MRI (FLAIR weighted, left picture on axial plane, right picture is coronal) of a patient with typical anti-VGKC associated autoimmune encephalitis. There is high intensity signal in the medial temporal lobes involving the hippocampus, especially on the left side of the brain. Apparent brain asymmetry is attributed to slight rotation of the patient’s head during image acquisition.
more frequently with normal scans or findings elsewhere in the brain. Common locations include the cerebellum, thalamus, parietal or occipital cortices [79]. In NMDAR AE, findings have been further divided into two major patterns. The first one is more often seen in younger patients, and consists of increased metabolism in the temporal and orbitofrontal cortex, with hypometabolism in the occipital cortex and diffuse borderline hypermetabolism in the cerebellum, usually referred to as fronto-temporo-occipital gradient [83]. The second pattern is seen in older patients, with less striking symptoms and without seizures. In this group, FDG-PET shows diffuse decreased metabolism, predominantly in the temporal lobes, with normal uptake in subcortical structures [84]. It is still not clear whether these findings represent different stages of disease evolution.

EEG abnormalities are almost universal, usually non-specific, including diffuse or focal slowing, frontal or temporal intermittent rhythmic delta activity (FIRDA or TIRDA), or temporal epileptiform activity [85, 86]. In anti-NMDAR AE, a specific pattern, called “extreme delta brush” (EDB) has been observed in 30% of patients in small series. This pattern has not been described in any other disorder, and these patients show more frequently a normal MRI, longer hospitalization, and worse prognosis, suggesting that it might be a marker of more severe disease [84, 87]. In the pediatric group, EEG findings also seem to have prognostic value: while patients with normal physiological background activity (PBA), with unilateral or focal abnormalities, presented with milder neurological impairment and better outcome, those patients who had more diffuse abnormalities without PBA showed more severe neurological symptoms and a poorer outcome [88].

CSF analysis often reveals lymphocytic pleocytosis, increased protein concentration or presence of oligoclonal bands (OCB) [32, 89]. In anti-NMDAR AE, over 80% of patients have an abnormal CSF at presentation; progression of findings is usually characterized by an early phase with lymphocytic pleocytosis, with or without elevated protein levels, followed by the decrease of white blood cells in CSF and the appearance of OCB. On the other hand, only half of the individuals with anti-VGKC AE show abnormal CSF screen and rarely present OCB [90, 91].

Antibody titers can be determined in both serum and CSF. Gold-standard tests differ among the different antibodies, since onconeural antigens are linear, and can be detected either by immunoblotting, ELISA or immunohistochemistry using mammalian brain; anti-surface antibodies are directed against conformational epitopes, losing their reactivity when the antigen is denatured. So, they require either an adapted immunohistochemistry protocol, the use of live neurons, or cell-based assays [92].

In anti-neurit associated AE, unlike antinuclear disorders, antibody titers often correlate with symptomatic improvement [4, 93], but they can also decrease with time, even without therapy and irrespectively of clinical outcome [90, 94], their levels fluctuate due to immunosuppressants (particularly in serum), and they can remain elevated for years after recovery [66, 92, 95].

Finally, further investigation to exclude an underlying neoplasm should be considered in all cases, since the neurological presentation often precedes the diagnosis of cancer. Tumor screening should be focused on most commonly associated malignancies. In children at least an ultrasound and MRI of the abdomen is advised [60]. Other advised screening tests are listed in Table 4. Imaging might not be sensitive enough to detect micrometastasis; thus, in highly suspicious paraneoplastic cases (due to the associated antibodies or patient characteristics, i.e., heavy smoking, unintended weight loss), repeat exams should be carried out every 3 to 6 months for up to 4 years if no malignancy is found in the meantime [96]. In cases of relapsing disease, the possibility of an undetected or recurrent tumor should be considered in the appropriate setting.

### Management and follow-up

Once other relevant causes have been ruled out, immunotherapy should be considered in all cases. Since most disorders are rare and/or were recently classified, there are no robust randomized clinical trials providing evidence-based data. Current treatment options are based on case reports and uncontrolled case series. Cancer treatment should always be carried out, when applicable [56, 62], since combined treatment typically results in more favorable outcome than immunotherapy alone [97].

Treatment includes high-dose corticosteroids (CSTs), intravenous immunoglobulin (iv-Ig) and plasma exchange as first line immunotherapy. Rituximab, azathioprine, and cyclophosphamide are considered second line therapeutic interventions, thus prescribed when individuals fail to respond to first line drugs. Due to the high occurrence of relapsing disease, chronic immunosuppressant therapy with mycophenolate mofetil or azathioprine can also be considered. It has been suggested that the response to treatment could be evaluated with the modified Rankin Scale (mRS);

<table>
<thead>
<tr>
<th>Suspected malignancy</th>
<th>Suggested diagnostic exams</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC</td>
<td>Chest CT; if negative FDG-PET</td>
</tr>
<tr>
<td>Non-SCLC</td>
<td>Chest CT; if negative FDG-PET</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Chest CT</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>Ultrasonography; if negative pelvic CT</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Pelvic ultrasonography; if negative CT/MRI of pelvis/abdomen; if negative chest CT</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Mammography; if negative MRI; if negative FDG-PET</td>
</tr>
</tbody>
</table>

CT = Computed tomography; FDG-PET = Fluorodeoxyglucose positron emission tomography; MRI = Magnetic resonance imaging; SCLC = Small cell lung cancer.
treatment has been considered successful if the score lowers at least one point on mRS [56].

Classic anti-nuclear PLE usually follows a monophasic course, even with combined treatment, and prognosis is poor, with extremely rare cases of spontaneous recovery without treatment [98]. The exception is anti-Ma2, with one third of patients having a complete recovery, and clinical stabilization seen in one fifth. Some features associate with better outcome, including male gender, younger age (<45 years), with complete response to treatment with underlying testicular tumor, absence of anti-Ma1 antibodies, and limited involvement of the CNS [35]. These severity hallmarks differ for anti-Hu, with older patients (>60 years), mRS >3, involvement of more than one area of the CNS, and absence or delayed treatment being considered mortality predictors [31, 34].

In anti-VGKC-complex AE, immunotherapy has been tried with intravenous methylprednisolone 1 gram or 30-50 mg/kg for 5 days, or iv-Ig 0.4 g/kg for 3-5 days, or 5 to 7 cycles of plasmapheresis (on alternate days). If patients respond to this treatment within 6 weeks, then a corticosparring agent can be initiated. If not, or in case of relapsing disease, second line therapy should be promptly considered [51]. In these patients, good outcome is correlated with early treatment, and the initial therapy regimen (with CSTs and iv-Ig apparently better than CSTs alone) [91]. In cases of presentation with FBDS, immunotherapy should also be administered, since many patients are resistant to antiepileptic drugs (AED). Furthermore, evidence suggests than immunotherapy at this early stage might prevent the emergence of cognitive impairment [91, 99].

In anti-NMDAR AE, the most commonly used strategy is iv-Ig 0.4 g/kg/day for 5 days, plus methylprednisolone 1 g/day for 5 days; plasma exchange is postponed for treatment failure cases [100]. If no improvement occurs after 4 weeks of first therapy, second line drugs should be considered [56]. Once again, early treatment, younger age, no need for intensive care, and longer follow up are associated with better prognosis [56, 94].

Electroconvulsive therapy (ECT) has been used to treat

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**Figure 2.** Algorithm for antibody testing in autoimmune encephalopathies.

Hypothalamic dysfunction includes hypersomnia, cataplexy, hyperphagia, hormonal changes, hyperthermia, weight gain, and sexual dysfunction. AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropanic acid receptor; CV2/CRMP5 = Crossveinless-2/collapsing response mediated protein 5; GABABR = Gamma-aminobutyric acid receptor B; GAD = Glutamic acid decarboxylase; NMDAR = N-methyl-D-aspartate receptor; VGKC = Voltage-gated potassium channel.
Neuropsychiatric symptoms in autoimmune encephalopathies

Suspected autoimmune Treatment algorithm of anti-VGKC associated encephalitis

<table>
<thead>
<tr>
<th>Clinical response within 6 weeks?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone* (iv, 1 gram or 30-50 mg/kg) - 5 days</td>
<td>OR</td>
<td>Immunoglobulin* (iv, 0.4 g/kg) - 3 to 5 days OR Plasmapheresis** (5 to 7 cycles on alternate days) OR CT + iv-ig combination ***</td>
</tr>
<tr>
<td>Relapse?</td>
<td></td>
<td>Consider second line treatment Rituximab OR Cyclophosphamide</td>
</tr>
</tbody>
</table>

Figure 3. Treatment algorithm of anti-VGKC associated encephalitis. iv = Intravenous. * If corticotherapy not advised; ** If neither corticotherapy nor immunoglobulin are advised; *** Associated with better clinical response.

Conclusion

Autoimmune encephalopathies, particularly those with antibodies directed against cell surface membrane and associated proteins, can present with psychiatric symptoms, and many of these individuals seek psychiatric help first. Hence the importance of including these disorders in the list of possible differential diagnoses in patients presenting with a new-onset or atypical psychotic or mood disturbance, especially if there is no history of mental illness, not only in elderly patients but also in young adults and children [103].

After excluding commoner or treatable causes, antibody testing should be performed, since no clinical symptom or finding is pathognomonic, but some are highly suggestive of a given disorder (Figure 2). Antibody screening may lead to the correct diagnosis, can help direct cancer screening, and also provides clues regarding prognosis and likely response to therapy.

Antibody screening with currently available tests may result negative in some patients, even when clinical presentation is archetypal [104-107]. These patients may also improve under immunotherapy, which is strongly advised in cases with highly suggestive clinical presentation, after alternative etiologies have been appropriately excluded; tumor screening should also be carried out in these cases [108]. Although complete recovery in the absence of immunotherapy has been reported, prompt prescription seems to associate with better prognosis in most instances. Patients who do not receive proper treatment usually suffer from slower recovery, longer hospitalization periods, and a higher risk of relapsing disease [65].

The startling number of cases of autoimmune encephalitis described in the last decade suggests that this is not a rare disorder and it is likely underdiagnosed, thus clinicians should keep a high suspicion index. As autoimmune encephalopathies become more widely recognized, additional autoantibodies, features, and atypical presentations are likely to be identified, as well as their actual prevalence. The prevalence of autoimmune in psychiatric disorders such as schizophrenia is the object of current research.

Figure 4. Treatment algorithm of anti-NMDAR associated encephalitis. iv = Intravenous. * *Consider plasma exchange if therapeutic failure.

Immunoglobulin* (iv, 0.4 g/kg/day) - 5 days AND Methylprednisolone* (iv, 1 g/day) - 5 days

Consider long-term immunosuppressant agent Mycophenolate mofetil OR Azathioprine
true contribution is yet to be assessed, and a role for immunotherapy remains to be
determined in these conditions. Also, further exploration is needed in order to
guarantee that the epidemiology of autoimmune ence
phalitis, the clinical course of its various subgroups, and
doctor to determine the most effective management strategies
during acute illness and thereafter.

Abbreviations

AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
receptor; ANNA-1: anti-neuronal nuclear antibodies 1; ANNA-2: anti-neuronal nuclear antibodies 2; ANNA-3: anti-neuronal nuclear antibodies 3; Caspr2: contactin-associated-protein relates 2; CV2/CRMP5: crosssiveness-2/collapsing response mediated protein 5; FDG-PET: fluorodeoxyglucose-position emission tomography; FLAIR: fluid-attenuated inversion recovery; GABABR: gamma-aminobutyric acid receptor B; GAD: glutamic acid decarboxylase; LE: limbic encepha
litis; LGI-1: leucine-rich glioma inactivated 1; NMDAR: N-methyl-D-aspartate receptor; SPS: stiff person syndrome; VGKC: voltage-gated potassium channel.

Competing interests

The authors declare no conflict on interest.

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