

# Autoimmune encephalitis in psychiatric institutions: current perspectives

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**Abstract:** Autoimmune encephalitis is a rare and newly described group of diseases involving autoantibodies directed against synaptic and neuronal cell surface antigens. It comprises a wide range of neuropsychiatric symptoms. Sensitive and specific diagnostic tests such as cell-based assay are primordial for the detection of neuronal cell surface antibodies in patients' cerebrospinal fluid or serum and determine the treatment and follow-up of the patients. As neurological symptoms are fairly well described in the literature, this review focuses on the nature of psychiatric symptoms occurring at the onset or during the course of the diseases. In order to help the diagnosis, the main neurological symptoms of the most representative synaptic and neuronal cell surface autoantibodies were detailed. Finally, the exploration of these autoantibodies for almost a decade allowed us to present an overview of autoimmune encephalitis incidence in psychiatric disease and the general guidelines for the management of psychiatric manifestations. For the majority of autoimmune encephalitis, the prognosis depends on the rapidity of the detection, identification, and the management of the disease. Because the presence of pronounced psychiatric symptoms drives patients to psychiatric institutions and can hinder the diagnosis, the aim of this work is to provide clues to help earlier detection by physicians and thus provide better medical care to patients.

**Keywords:** neuroimmunology, autoantibodies, organic psychosis, dementia, schizophrenia

## Introduction

Autoimmune encephalitis is a new and rare disease, characterized by brain inflammation and circulating autoantibodies. Various autoimmune encephalitis have been described, and each of them linked to the presence of specific autoantibodies directed against synaptic and neuronal cell surface antigens. The main targets appear to be *N*-methyl-D-aspartate receptor (NMDAR),  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropion acid receptor (AMPA), leucine-rich glioma inactivated 1 (Lgi1), contactin-associated protein-like 2 (Caspr2), glutamate decarboxylase (GAD) or gamma-aminobutyric acid type B receptor (GABA<sub>B</sub>R),<sup>1,2</sup> but a significant number of autoimmune encephalitis are due to rarer or unidentified targets. Clinical symptoms usually correlate with the associated antibody subtype. Removal of these antibodies by plasma exchanges or immunotherapy generally induces clinical improvement.<sup>3,4</sup> Neurological symptoms drastically vary according to epitope targeted by the autoantibody produced by the patients (Table 1). It is thus very important to know clinical symptoms and to recognize them in order to properly diagnose the patients and to give them adapted treatments.

Owing to the variety of antigens targeted by autoantibodies, autoimmune encephalitis is clinically heterogeneous, affecting both men and women, ranging from those with early age to those with older than 80 years. The common symptoms include a

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**Table 1** List of identified antibodies in autoimmune encephalitis

Antigen	Approximate number of cases reported	Syndrome/clinical presentation	Tumor association	Brain MRI	CSF abnormalities	Outcome	References
Antibodies against synaptic receptors							
NMDA receptor	>800	Psychiatric features, seizures, cognitive impairment, movement disorder, dysautonomia, fluctuation in the consciousness level	Type and frequency of tumor vary with age and sex. Tumor found in 50% of young women cases (mostly ovarian teratoma)	Normal (>50% of patients) or little inflammation (cortical or subcortical)	Lymphocytosis (70%) in early stages and OCBs after (52%)	75%–80% improvement or full recovery. Amnesia for the entire illness for almost all patients. Possible relapses	Dalmau et al <sup>17</sup> Irani et al <sup>13</sup> Titulaer et al <sup>3</sup> Florance et al <sup>14</sup> Schmitt et al <sup>14</sup> Dalmau et al <sup>29</sup>
AMPA receptor	~58	Limbic encephalitis, possible psychiatric features	Lung, breast, and thymoma (in 50% cases)	Abnormal: medial temporal lobe with increase in the FLAIR signal (90%)	Lymphocytosis, OCBs	Variable: influenced by the presence of associated autoantibodies and tumor	Lai et al <sup>43</sup> Battaller et al <sup>48</sup> Girau et al <sup>46</sup> Höftberger et al <sup>45</sup> Joubert et al <sup>44</sup>
GABA <sub>A</sub> receptor	~35	Encephalitis with high antibodies titers, Stiff-person syndrome, seizures with low titers	Thymoma, lung, and breast (in 70% cases)	Abnormal in all cases with increase in the FLAIR signal and rapid progression to atrophy	OCBs	Majority of the patients have a favorable response (>80%)	Petit-Pedrol et al <sup>15</sup> Ohkawa et al <sup>116</sup> Pettingill et al <sup>117</sup>
GABA <sub>B</sub> receptor	~67	Limbic encephalitis associated with seizures	Lung and neuroendocrine (in 50% cases)	Medial temporal lobe with increase in the FLAIR signal (60%–70%)	Usually cellular lymphocytosis, OCBs	50% improved	Lancaster et al <sup>118</sup> Boronat et al <sup>119</sup> Höftberger et al <sup>20</sup>
mGluR5	4	Ophelia syndrome, encephalitis	Hodgkin's lymphoma (in 70% cases)	Abnormal in 3/4 patients with variable increase in the T2/FLAIR signal	OCBs in half cases and lymphocytosis in 1/4 cases	Full recovery after oncologic treatment	Lancaster et al <sup>121</sup> Mat et al <sup>122</sup> Prüss et al <sup>123</sup>
Dopamine 2 receptor	26	Basal ganglia encephalitis with movement disorder, psychosis	Not yet reported	Abnormal with FLAIR signal increase in caudate, putamen, globus pallidus, and substantia nigra in 50% cases	Not reported	Variable. Full recovery in 50% or less cases	Dale et al <sup>24</sup> Pathmanandavel et al <sup>108</sup>
Glycine receptor	~77	Stiff-person syndrome, progressive encephalomyelitis with rigidity and myoclonus, limbic encephalitis	Thymoma (in <10% cases)	Abnormal with white matter lesions, increase of FLAIR signal or atrophy (30%)	Pleocytosis in half of the cases, OCBs (20%)	>90% improved. Relapses in ~10% cases	Hutchinson et al <sup>25</sup> Piotrowicz et al <sup>26</sup> McKeon et al <sup>27</sup> Carvajal-Gonzalez et al <sup>28</sup>
Antibodies against synaptic proteins or other cell surface proteins							
Lgi1 receptor	~200	Limbic encephalitis with tonic-dystonic seizures and hyponatremia, Creutzfeldt–Jacob-like syndrome	Variable (in <10% cases)	Abnormal: medial temporal lobe with increase in the FLAIR signal (60%)	Rare	80% full recovery or mild deficits	Lai et al <sup>52</sup> Irani et al <sup>58</sup> Irani et al <sup>46</sup> Ohkawa et al <sup>60</sup>

Caspr2	~95	Neuromyotonia and Morvan's syndrome with possible psychiatric features, Guillain-Barré-like syndrome	Thymoma (in 30% of cases)	Abnormal: medial temporal lobe with increase of FLAIR signal (40%)	Rare	80% substantial improvement	Irani et al <sup>58</sup> Lancaster et al <sup>60</sup> Vincent and Irani <sup>129</sup>
DPPX (DPP6)	21	Encephalitis associated with severe gastrointestinal symptoms	Not yet reported	Normal in majority of patients. Abnormal with no specificities in 30% of cases	Pleocytosis, OCBs (4/4 in Boron et al, <sup>130</sup> 7/10 normal in Tobin et al <sup>131</sup> )	50% full recovery or partial response	Boronat et al <sup>130</sup> Tobin et al <sup>131</sup>
Antibodies against intracellular antigen GAD65	> 100	Stiff-person syndrome, cerebellar ataxia, encephalitis, other neurological disorder	Variable frequency according to age and sex. Present in 25% of cases in men older than 50; mostly thymoma and small-lung carcinoma	Abnormal: characteristic medial temporal lobe increase of FLAIR signal	OCBs (30%–100%)	Not known	Honnorat et al <sup>132</sup> Saiz et al <sup>137</sup> Malter et al <sup>132</sup> Ali et al <sup>133</sup> Arino et al <sup>138</sup> Foulka et al <sup>139</sup>

**Abbreviations:** MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; NMDA, N-methyl-D-aspartate; AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropion acid; FLAIR, fluid-attenuated inversion recovery; GABA<sub>A</sub>R, gamma-aminobutyric acid type A; GABA<sub>B</sub>R, gamma-aminobutyric acid type B; mGluR, metabotropic glutamate receptor; Lgi1, leucine-rich glioma inactivated 1; Caspr2, contactin-associated protein-like 2; DPP6, dipeptidyl-peptidase-like protein 6; GAD65, glutamate decarboxylase 65 kDa isoform; OCB, oligoclonal bands.

wide range of psychiatric and neurological symptoms.<sup>5,6</sup> While most of the literature focuses on the neurological manifestations of these disorders, the initial presentation is often psychiatric.<sup>7</sup> Psychiatric symptoms occur generally early in the progress of the disease but may also appear during the course of the disease.<sup>3,8</sup> These psychiatric symptoms often slow down the diagnosis of the disease and alter the handling of the patient. This is a critical aspect as it is now clear that a rapid diagnosis is both necessary and limiting for a good outcome of the patients. In this regard, psychiatrists have a key role in the diagnosis process and orientation of the patients since they encounter many of them in their daily practice and often establish the first clinical diagnosis. This task is difficult as studies giving the specific symptomatology that would allow psychiatrists to establish their diagnosis and appropriate care are lacking.

Data are substantial for anti-NMDAR, anti-AMPA, and anti-Lgi1 encephalitis but sparse for other cell surface antibody encephalitis such as anti-Caspr2 and anti-GAD encephalitis. This article reviews the psychiatric and behavioral manifestations of these various subtypes of autoimmune encephalitis.

## Search strategy

Literature for this review was obtained by performing PubMed searches for each specific published neuronal surface antigen in the central nervous system (NMDA receptor, AMPA receptor, glycine receptor (GlyR), metabotropic glutamate receptors 1 and 5, gamma-aminobutyric acid type A receptor (GABA<sub>A</sub>R) and GABA<sub>B</sub>R, dopamine receptor, Lgi1, Caspr2, dipeptidyl-peptidase-like protein 6 (DPP6; also named DPPX), voltage-gated calcium channels and Tr/Delta/Notch-like epidermal growth factor-related receptor (Tr/DNER). These terms were combined with the terms of “antibodies”, “autoimmune”, “autoimmunity”, or “encephalitis”, and/or “psychiatric”, “psychiatry”, “psychosis”, “schizophrenia”, and “dementia”. Non-English publications were excluded. Bibliographies of included studies were also hand searched. The search strategy included articles starting from the date of the first publication on antibodies to each specific antigen till June 30, 2016.

## Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is the most common autoimmune encephalitis described so far,<sup>9</sup> with >900 cases identified worldwide since its first description in 2007.<sup>10,11</sup> Even if it is still considered as a rare disease, the relatively high occurrence for this subtype of autoimmune encephalitis

explains the focus of the literature on these antibodies in epidemiologic studies. Anti-NMDAR encephalitis represents 20% of immune-mediated encephalitis.<sup>12</sup> It predominantly affects young women (60%), children (35%), and more rarely men and elderly patients.<sup>3,13–16</sup>

## Psychiatric presentation

A Dutch retrospective study reported that 80% of patients diagnosed with anti-NMDAR encephalitis had initial psychiatric presentation<sup>8</sup> and >60% were first admitted in a psychiatric unit. Other retrospective studies found similar results: psychiatric symptoms at the first presentation were reported for 80%–100% patients and the patients initially seen by psychiatrists represented 70%–80% of the cases.<sup>13,17</sup> Most patients described did not have any psychiatric history;<sup>18</sup> therefore, a first psychiatric episode should be considered as an argument to test the presence of anti-NMDAR antibodies in patient's cerebrospinal fluid (CSF).

Psychiatric presentation is heterogeneous with grandiose and paranoid delusions, hallucinations (visual and auditory), bizarre behavior, agitation, fear, insomnia, confusion, and short-term memory loss.<sup>19</sup> These manifestations are generally considered as acute psychosis, mania (with psychotic features), or onset of schizophrenia (Table 2).<sup>20</sup> This period of the disease can be associated or not with major or discreet neurological signs, leading to an initial consultation in psychiatric institutions.<sup>18,21</sup> If neurological signs, such as dystonia,

oro-lingual-facial dyskinesias,<sup>17</sup> or seizures are present, they should lead to a search for autoantibodies.<sup>21</sup> Lejoste et al<sup>22</sup> found that half of the patients with psychiatric presentation were patients with prior discrete neurologic symptoms that did not lead to further investigations (magnetic resonance imaging [MRI], CSF analysis) and were thus misdiagnosed. Autonomic manifestations such as hyperthermia and/or tachycardia are also frequent. Even if it is rare, some patients will not present any neurological symptoms during the disease (first episode and possible relapses).<sup>22,23</sup> These patients present no particularities (fulfilled criteria for schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition) and respond to classical immunomodulatory treatment but are difficult to diagnose.<sup>24,25</sup>

A study focusing on the presentation in pediatric population described more manic than psychotic symptoms in this population, including temper tantrums, behavioral change, agitation, aggression, and progressive speech deterioration, as well as hyperactivity and hypersexuality.<sup>14</sup> Differential diagnosis generally arises between early onset schizophrenia, late onset autism, and childhood disintegrative disorder.<sup>26–28</sup>

Usual psychiatric drugs, including neuroleptics, benzodiazepines, and valproic acid, could occasionally help, but their effect is incomplete and transitory. Neuroleptics must be cautiously used because ~50% of patients with anti-NMDAR encephalitis treated by neuroleptics may develop intolerance characterized by high temperature, muscle rigidity, mutism or

**Table 2** Main psychiatric presentations of patients with autoimmune encephalitis

Antigen targeted	Psychiatric symptoms at onset	Psychiatric symptoms during course	References
NMDAR	All symptoms can be observed, but behavioral change (frequently bizarre), anxiety, agitation, and hallucinations are the most frequent	Psychiatric symptoms are first symptoms in >40% of patients, and during evolution, >80% of patients present psychiatric symptoms	Dalmau et al <sup>17</sup> Maat et al <sup>8</sup> Irani et al <sup>13</sup> Titular et al <sup>3</sup> Lejoste et al <sup>22</sup> Graus et al <sup>16</sup>
AMPA	Abnormal behavior (combative, aggressiveness), confabulation, hallucinations, sleep disturbances resembling acute psychosis	Reported in two patients	
Lgi1	Behavioral changes (apathy, irritability), confusion, disorientation, depression, delusions, hallucinations, sleep disorders		Vincent et al <sup>68</sup> Merchut <sup>69</sup>
Caspr2	Severe insomnia, hallucinations, personality changes, delusion	Mainly in patients with Morvan's syndrome	Vincent et al <sup>68</sup> Irani et al <sup>58</sup> Lancaster et al <sup>80</sup> Joubert et al <sup>59</sup>
GAD65	Disorientation, confusion, bipolar disease	Rarely reported. Relationship with GAD65-antibodies unclear	Padmos et al <sup>94</sup> Saiz et al <sup>87</sup> Çoban et al <sup>93</sup>
GABA <sub>B</sub>	Confusion, disorientation, behavioral changes, psychosis, hallucinations, paranoia, sleep disturbances		Lancaster et al <sup>118</sup> Höftberger et al <sup>120</sup>

**Abbreviations:** NMDAR, N-methyl-D-aspartate receptor; AMPAR,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropion acid receptor; Lgi1, leucine-rich glioma inactivated 1; Caspr2, contactin-associated protein-like 2; GAD65, glutamate decarboxylase 65 kDa isoform; GABA<sub>B</sub>, gamma-aminobutyric acid type B.

coma, and rhabdomyolysis biomarkers suggesting neuroleptic malignant syndrome.<sup>22</sup>

## Neurological signs and symptoms

In anti-NMDAR encephalitis, a set of nonspecific symptoms comprises a characteristic syndrome.<sup>7,21,29</sup> Presentation is variable depending on sex and age.<sup>29</sup> However, in 70% of patients,<sup>18</sup> clinical course begins with viral-like prodromes (fever, nausea, diarrhea) occurring ~1 or 2 weeks before psychiatric and/or neurologic symptoms leading to hospitalization. Acute psychiatric symptoms and cognitive impairments progress rapidly to severe neurological features (seizures, dyskinesias, dysautonomic symptoms) until a comatose phase.<sup>3,29</sup> Fatal outcomes due to respiratory complications were frequent in the past. Autoimmune encephalitis is now well characterized with an easier clinical and biological diagnosis. The latter is based on the detection of polyclonal immunoglobulin G (IgG) directed against GluN1 subunit of the NMDAR in CSF. Although the presence of IgG is found in most cases, other immunoglobulin subtypes can also be found.<sup>30</sup> The distinction between IgG, IgA and IgM immunoglobulin subtypes is essential as the prevalence,<sup>24,31</sup> the physiopathology,<sup>32</sup> and the clinical presentation<sup>33</sup> are different. Anti-NMDAR encephalitis is a primary antibody-mediated disease, and the treatment is based on immunotherapy and tumor removal (if present). The frequency of an underlying teratoma, which is in 94% of cases of an ovarian teratoma,<sup>3</sup> is dependent on age, sex, and ethnicity<sup>3,14,16,29</sup> and occurs more frequently in young adult women (~50% in this subgroup).

## Treatment and outcome

Guidelines have been published for the treatment of autoimmune encephalitis after antibody detection.<sup>29,34,35</sup>

Initially categorized in paraneoplastic disease, autoimmune encephalitis is also found in patients without tumors. Treatment is first based on tumor resection, when present, and first-line immunotherapy: corticosteroids associated with intravenous immunoglobulins (IVIg). Plasma exchanges are possible and showed efficacies but are more difficult to carry out in the context of autonomic instability or in poorly cooperative patients.<sup>29</sup> If a tumor is not detected, tumor screening should be initiated, taking into consideration the frequency of underlying tumor with this antibody and patient's age and sex.

Most patients respond within weeks to first-line treatments, but anti-NMDAR encephalitis patients are the slowest among autoimmune encephalitis. Early treatment

allows good outcome in 80% of patients,<sup>16</sup> but recovery is slow, >2 years.<sup>3</sup>

For the 47% of patients who do not respond to first-line treatments,<sup>3</sup> a second-line immunotherapy was started with rituximab or cyclophosphamide or both. The outcome of the second-line immunotherapy in patients is improved in 65% of cases.<sup>3,29</sup> Generally, the frequency of improvement is better for patients with tumor (80%) when compared to patients without tumor (48%). Patients without tumors consequently require more often a second-line immunotherapy.<sup>29</sup>

Despite this second-line treatment, relapse can occur in 20%–25% of the case.<sup>13,14,36</sup> To prevent relapses, immunosuppressive treatment can be continued with mycophenolate mofetil or azathioprine during 1 year.<sup>3</sup>

## Mechanisms

Antibodies found in patients are immunoglobulins G, classes IgG1 and IgG3.<sup>37</sup> They target an ionotropic glutamate receptor, the NMDAR and more precisely GluN1, the obligatory subunit of the receptor.<sup>17,38</sup> Syndromes observed in autoimmune encephalitis generally resemble those described in pharmacologic or genetic models of antigens' disruption (eg, with ketamine<sup>39</sup> and memory impairment and depressive-like behavior in mice models<sup>40</sup>). Detection of anti-NMDAR antibodies by immunohistochemistry on rodent brain slices indicates a high hippocampal staining, a moderate cortical staining and a limited cerebellar staining,<sup>10</sup> correlating well with the symptomatology. Various studies performed using animal models and in vitro suggest that the antibody decreases the surface expression and total density<sup>17,41</sup> of NMDARs, leading to an alteration in synaptic plasticity and synaptic transmission.<sup>41,42</sup> These data point toward a direct pathogenic role of antibodies on the NMDAR itself.

## Anti-AMPA encephalitis

Anti-AMPA encephalitis also belongs to autoimmune encephalitis with antibodies targeting ionotropic glutamate receptor. Initially described in a series of 10 patients 6 years ago,<sup>43</sup> its frequency is lower than anti-NMDAR encephalitis but patients who have already been described bring relevant information. New cohorts were recently published, giving further details on the first description that has been made.<sup>44,45</sup>

## Psychiatric presentation

Even if AMPAR and NMDAR are both ionotropic glutamate receptors and thereby are functionally related, clinical phenotypes are different. Patients who were described mostly

presented limbic dysfunction and prominent psychiatric symptoms such as confusion, disorientation, confabulation, agitation, combativeness, and perseveration. In 2010, Graus et al<sup>46</sup> found in an antibody screening study four patients (n=30 patients tested in total, including 17 with limbic encephalitis) with anti-AMPA antibodies, including two with acute psychosis. These two women presented confusion and aggressive behavior. Confusion was in 70% of the cases, the first sign reported at the onset of the disease;<sup>44,45,47</sup> this initial confusion can be associated with limbic encephalitis symptoms and seizures.

## Neurological signs and symptoms

Anti-AMPA encephalitis patients in addition to psychiatric symptoms frequently present classical limbic encephalitis features such as acute amnesia, confusion, and abnormal behavior. The variable presence of tumor<sup>44,45</sup> did not seem to cause any differences in the clinical presentation, but had implications for treatment. Seizures are frequently present and may guide to set the diagnosis. Insomnia, lethargy, and decreased level of consciousness have also been described.<sup>45,46</sup> Fulminant forms were also described<sup>44,43,44</sup> with fever, coma, and hypertonia. Brain MRI is often abnormal. Severity of lesions, when they are present, appears to correlate with clinical outcome.<sup>9,43</sup> Anti-AMPA encephalitis should be considered in elderly patients, mainly women, with a median age of ~60 years (range 23–81 years).<sup>43,45</sup>

## Treatment and evolution

Treatment consists of aggressive immunotherapy associated with tumor removal when present. IVIg treatment is generally followed by chemotherapy with cyclophosphamide or doxorubicin. Anti-AMPA encephalitis is a treatable disorder but with poorer recovery rate when compared to Lgi1 or NMDAR autoimmune encephalitis. It is important to note that among patients who responded to the treatment, 48% remain with residual effects.<sup>45</sup> Follow-up is crucial due to a propensity for relapse in these patients.<sup>43,46–48</sup> Long-term outcomes hang on the appropriate management of relapses.<sup>43</sup> Thus, chronic immunomodulatory treatment should be considered.

Special attention should be paid to possible associated autoantibodies (GAD, Sox1, amphiphysin) that correlate with a poorer prognosis.<sup>45</sup> In these cases, symptoms and tumor can be more characteristic of the additional immune response. Detection of anti-AMPA antibodies in patient's CSF must lead to the administration of an aggressive and rapid therapy and to the search for a possible associated tumor or classical paraneoplastic antibodies.

Anti-AMPA encephalitis diagnosis is based on the detection of polyclonal IgG against GluA1/2 subunits of AMPA receptor (formerly known as GluR1/R2) in patient's CSF. Titer is generally correlated with clinical evolution.

## Mechanisms

In AMPA encephalitis, symptoms such as memory deficits, movement disorders, and cerebellar signs suggest the dysfunction of structures such as the hippocampus, the cerebellum, and the basal ganglia. The binding of patient's anti-AMPA autoantibodies with a high affinity to these structures in brain rat sections is another argument in agreement with the alteration in the limbic system and the cerebellum.<sup>43</sup> Intrathecal synthesis of antibodies is strongly probable due to higher antibody titers in CSF than in serum<sup>43</sup> and the finding of CSF positive but serum negative in some patients.<sup>45</sup> Peng et al recently highlighted a rapid internalization of AMPA receptors *in vitro*, on cells treated with patient's antibodies. While this mechanism is not clearly identified yet, internalization seems to be followed by degradation of the receptor.<sup>49</sup>

*In vitro*, cultured neurons recorded using whole-cell patch clamp and treated with patient's CSF had reduced amplitude and frequency of miniature excitatory postsynaptic currents, demonstrating an impairment of AMPAR-dependant synaptic transmission in the presence of patient's antibodies.<sup>49,50</sup> There are few *in vitro* data, and most of them need to be reproduced in order to get enough credit. There is also a lack of *in vivo* studies allowing a better understanding of the mechanisms involved in the disease. Furthermore, differences in clinical presentation, from pure memory disturbances to fulminant encephalitis, suggest different mechanisms according to the patients.<sup>44</sup>

## Anti-Lgi1 encephalitis

Lgi1 is a protein secreted by hippocampal neurons largely associated with epilepsy.<sup>51</sup> In some cases of encephalitis, patients produce autoantibodies directed against Lgi1. There is still not a lot of data concerning Lgi1 autoantibodies as it was first assimilated to antibodies raised against the voltage-gated potassium channel.<sup>52</sup> Indeed antibodies against voltage-gated potassium channels were first described in neuromyotonia,<sup>53</sup> then in Morvan's syndrome<sup>54,55</sup> and finally in limbic encephalitis.<sup>56,57</sup> More recently, studies demonstrated that this entity gathered various encephalitis due to distinct antibodies targeting Lgi1, Caspr2, and contactin 2.<sup>52,58</sup> Identification of these antigens helped to clarify the apparent diversity of symptoms attributed to voltage-gated potassium channels antibodies. While anti-Lgi1 antibodies are

preferentially associated with classical limbic encephalitis, anti-Capsr2 antibodies are associated with Morvan's syndrome, neuromyotonia, and sometimes with neuropathies or limbic encephalitis.<sup>52,58,59</sup>

## Psychiatric presentation

Patients with anti-Lgi1 encephalitis are predominantly men (sex ratio 4:3)<sup>60,61</sup> with a median age of 54 years (range 32–67 years) at the onset.<sup>62</sup> In recent years, case reports described heterogeneous psychiatric signs at the onset of the disease such as confusion, depression, paranoia, behavior disturbances, visual hallucinations, and dementia.<sup>63–65</sup>

Early onset of the disease is most often characterized by confusion and dementia without family history. These psychiatric signs are generally associated with neurological symptoms from the onset of the disease.

## Neurological signs and symptoms

Patients with anti-Lgi1 antibodies mostly exhibit seizures and limbic encephalitis. Insomnia and paradoxical sleep disorders are typical features of the disease. Faciobrachial dystonic seizures (FDBS) are characteristics of anti-Lgi1 encephalitis and generally precede the limbic encephalitis.<sup>61,66</sup> The term tonic–dystonic seizures is now preferred because the dystonic seizures can be located throughout the body.<sup>61,67</sup> A recent study explored the anatomical origin of these tonic–dystonic seizures to help the diagnosis and found the motor cortex and the hippocampus as starting points.<sup>61</sup> Complementary signs can help to confirm the diagnosis: hyponatremia is reported in 60%–80% cases<sup>58,68,69</sup> and MRI is abnormal in 70%–80% of the cases with abnormalities in the temporal lobes.<sup>68–70</sup> The frequency of associated cancers is low, <20%.<sup>9</sup> As McQuillan and Bargman<sup>71</sup> summed up, it should always be kept in mind that for a patient presenting confusion and hyponatremia, the confusion may not be secondary to hyponatremia and that an anti-Lgi1 autoantibody may be present.<sup>71</sup>

## Treatment and evolution

In the literature, anti-Lgi1 encephalitis is described as responsive to immunotherapy.<sup>66,68,72–75</sup> Guidelines suggest using high doses of corticosteroid, IVIg and plasmapheresis as the first-line therapy. In refractory cases, rituximab and cyclophosphamide should be used as second-line therapies.<sup>76</sup> Anti-Lgi1 antibody encephalitis seems to be associated with poor cognitive outcome and evolves frequently with hippocampal atrophy. Relapses are reported in 10%–20% patients.<sup>57,76</sup> Introduction of immunotherapy

allows resolution of FDBS. The quickness to start immunotherapy is significantly correlated with the time to recover basal functions.<sup>77</sup> Management of antibody titers seems to be the easiest way to manage clinical improvement.<sup>70</sup> Residual symptoms after treatment consist of verbal memory impairment, and antibody titer at presentation seems to predict verbal memory index after treatment.

## Mechanisms

The precise function of Lgi1 is still a matter of debate. Lgi1 is a neuronal secreted protein.<sup>78</sup> Some reports indicate that Lgi1 prevents the inactivation of the Kv1 voltage-gated potassium channels through the cytoplasmic regulatory protein Kv.<sup>7,79,80</sup> It has also been shown that by interacting with pre- and postsynaptic proteins, Lgi1 may also have a role in the regulation of neurotransmitter release<sup>81,82</sup> and could control the function of AMPA receptors likely through its interaction with ADAM22.<sup>82</sup> Anti-Lgi1 antibodies are mainly IgG4 subtype and IgG1 in a lesser extent.<sup>83</sup>

The pathogenic role of anti-Lgi1 antibodies was rapidly suggested by *in vitro* and *in vivo* evidences. First, antibody titers seem to be well correlated with clinical presentation as immunotherapy induces prompt improvement in patients.<sup>62</sup> In the same order of idea, antibody titers seem to be linked with hippocampal atrophy. Indeed, in a prospective study, the two patients who developed hippocampal atrophy had the highest titers of antibodies. Anti-Lgi1 antibodies binded the N-terminal domain and the distal epitope domain. This binding was found to disrupt the Lgi1–ADM22 protein interaction in an *in vitro* model.<sup>60</sup> In mice models, symptoms induced by patient's IgG infusion were similar to those obtained after potassium channel blockers' administration (increase nerve excitability)<sup>84</sup> but, to date, there is no other *in vivo* studies. Finally, anti-Lgi1 antibodies seem to be pathogenic, but pathophysiological mechanisms remain to be determined.

## Others

Data concerning other antibodies involved in limbic encephalitis are partial and incomplete due to the low occurrence of these specific limbic encephalitis and the small amount of case reports. Here are the various psychiatric presentations concerning some known antibodies found in patients presenting limbic encephalitis.

## Anti-Capsr2 encephalitis

Caspr2 is a protein of the neurexin family that is found in the brain and peripheral nerves. Its distribution is wide, but

it seems to be concentrated at the juxtaparanodal region of myelinated axons.<sup>85</sup> Anti-Caspr2 antibodies are mostly found in neuromyotonia, Morvan's syndrome and limbic encephalitis. Anti-Caspr2 antibodies have been found in patients presenting psychiatric manifestations such as confusion and personality change with frontal lobe dysfunction. These psychiatric manifestations are generally associated with neurologic symptoms. FDBS, characteristic of Lgi1, is not found in patients presenting anti-Caspr2 antibodies, and confusion and cognitive impairment seem to be less frequent with anti-Caspr2 than with anti-Lgi1 antibodies.<sup>86</sup> Detection of Caspr2 antibodies in patients with neuromyotonia is often correlated with an underlying tumor (frequently a thymoma),<sup>66</sup> and patients having a tumor associated with anti-Caspr2 have a poorer prognosis. A recent work of Joubert et al<sup>59</sup> reveals that the apparent clinical diversity of anti-Caspr2 encephalitis may be linked to the site of antibody synthesis. They compared patients with anti-Caspr2 antibodies in the CSF to patients presenting neuromyotonia or Morvan's syndrome with anti-Caspr2 antibodies in the serum only. In this work, they showed that the presence of anti-Caspr2 antibodies in the CSF is associated with a much more homogeneous clinical pattern of autoimmune encephalitis, characterized by a prevalent limbic involvement and seizure occurrence.<sup>59</sup> These results emphasize the lack of functional studies focusing on antibody specificities and the importance of testing both serum and CSF samples.

### Encephalitis with anti-GAD antibodies

In more than 100 patients<sup>87-89</sup> worldwide were found antibodies directed against GAD, a rate-limiting enzyme in the synthesis of gamma-aminobutyric acid, an inhibitory transmitter.<sup>90</sup> Even if GAD is an intracellular protein, it can be exposed to antibodies during vesicular release.<sup>91</sup> High titers of GAD65 antibodies are associated with different neurological disorders, including cerebellar ataxia,<sup>92</sup> limbic encephalitis, and Stiff-person syndrome.<sup>91</sup> A few psychiatric presentations are described such as disorientation and confusion but psychiatric troubles are less frequent than for other antibodies.<sup>87</sup> Low level of GAD65 antibodies was also found to correlate with bipolar disorder presentations,<sup>93,94</sup> but the causal link was not proven since a low level of GAD antibodies was described in other neurological pathologies, such as in epilepsy,<sup>95</sup> myelopathy<sup>96</sup> and myasthenia gravis.<sup>97</sup> As a consequence, anti-GAD65 antibodies are rather considered as markers of autoimmune diseases than as pathogenic antibodies.<sup>87</sup> Explanation could be found in a disease-specific epitope hypothesis as pointed out by a study revealing distinct

epitopes between patients with Stiff-person syndrome and patients with limbic encephalitis.<sup>98</sup>

Many other antibodies directed against cell surface antigens such as GlyR, GABA<sub>A</sub>R and GABA<sub>B</sub>R, metabotropic glutamate receptor 5, dopamine receptor D2, and DPP6 exist, but isolated psychiatric phenotypes are rarely described. If psychiatric symptoms can be present, they are generally associated with important neurological deficits or alterations that lead patients rapidly to neurological investigations rather than psychiatric ones.

### How to diagnose autoimmune encephalitis in psychiatric departments?

As reported in the previous sections, limbic encephalitis patients often present initial psychiatric disorders that can lead them to psychiatric hospitalization (Table 2). Despite the fact that these diseases are rare and that studies on the frequency of anti-NMDAR antibodies failed to show particular subgroups in psychiatric illnesses such as schizophrenia, psychiatrists should pay close attention as they should statistically meet autoimmune encephalitis over the course of their career. Neurological investigations with neurological examination, lumbar puncture, and electroencephalogram (EEG) should be considered, especially when the patient has no history of psychiatric manifestations.

- Neurological examination: Particular attention should be paid on neurological symptoms that can be sometimes very discreet. They must be taken into account for the diagnosis. Memory deficits, seizures, dyskinesias and movement disorders, and headaches should be particularly questioned.<sup>99</sup>
- EEG: In a context of brain MRI and scan being normal, EEG is really useful and should be added to other investigations. Indeed EEG could present some abnormalities, even if a normal EEG does not exclude diagnosis of autoimmune encephalitis. In anti-NMDAR encephalitis, EEG is abnormal in >90% of cases, with rare but specific diffuse slow waves called extreme delta brush.<sup>17</sup> Anti-Lgi1 encephalitis patients also present ictal EEG changes underlying severe movement's abnormalities.<sup>66,100</sup> Data are lacking for other type of encephalitis. Thus, for a first psychotic or schizophrenic episode, particularly in young patients, an EEG should be systematically realized.
- Autoantibodies characterization: The diagnosis of autoimmune encephalitis is based on the detection of specific IgG autoantibodies in the patients' serum or CSF. Samples for diagnosis have to be obtained before

immunotherapy. In anti-NMDAR encephalitis, CSF samples allow a better sensitivity (100% of patients are positive in CSF, against only 85% in serum).<sup>29</sup> Detection of autoantibodies directed against neuronal cell surface antigens should be performed at least on CSF. In most cases, CSF samples will allow a better sensibility and specificity.<sup>101</sup> Detection of Caspr2, Lgi1, or GlyR antibodies in serum samples only have rarely been reported, without proof of clinical relevance.

Global evaluation of the presence of antibodies against neuronal cell surface antigens can be initially evaluated on paraformaldehyde-fixed rodent brain sections. This technique suggests a shared epitope between human beings and rodents and trained and qualified staff. To confirm the target epitope, further investigations are needed, the gold standard consisting of cell-based assay (CBA). Contrary to Western blot or enzyme-linked immunosorbent assay (ELISA) techniques, CBA allows detection of conformational epitopes. After cell transfection and treatment by autoantibodies, immunofluorescence can be detected by flow cytometry or microscopy.<sup>5,102,103</sup>

## Incidence in psychiatric diseases

The possible contribution of autoantibodies against neuronal cell surface antigens to psychiatric disease has drawn lots of interest over the past few years. Anti-NMDAR antibodies are of particular interest in these studies for many reasons. Among autoimmune encephalitis, anti-NMDAR encephalitis is the most frequent case reported so far, and patients often exhibit psychiatric manifestations. In addition, the central role of NMDAR hypofunction in psychotic symptoms' origin particularly interested psychiatrists.

Following case reports of anti-NMDAR encephalitis mimicking psychosis (such as Lebon et al<sup>28</sup>) and following the hypothesis of an autoimmune basis to some idiopathic psychoses, studies started to evaluate the incidence of anti-NMDAR encephalitis in psychosis.<sup>104</sup> The existence of anti-NMDAR antibodies in particular subgroups in psychiatric illnesses, such as schizophrenia, is still a matter of debate. Indeed, depending on patient's selection and on detection methods used, the studies found between 0% and 10% of NMDAR antibody-positive patients.<sup>25,32,104–108</sup>

In conclusion, specific immunoglobulin G anti-GluN1<sup>109</sup> is rarely found in psychiatric disease. If they have to be found, they will be mainly in schizophrenia.

Even if a minority of psychiatric patients presents NMDAR antibodies, psychiatrists have to be aware of this pathology because of the importance of a rapid diagnosis and because

they are very often in the first-line place in the treatment process of these patients. In a fairly recent study, authors are now recommending the screening of NMDAR antibodies in all patients with first episode of schizophrenia.<sup>110</sup>

Studies including other neuronal autoantibodies detection are sparse. A Turkish study, which screened anti-NMDAR, anti-Caspr2, anti-Lgi1, and anti-GAD presence in primary dementia patients, chronic psychiatric patients and healthy controls, found only one patient with anti-NMDAR antibodies and one with anti-GAD antibodies.<sup>93</sup> In the only study,<sup>32</sup> to our knowledge, that tested the presence of AMPAR antibodies in psychiatric presentations (schizophrenia, borderline personality disorder, major depression and healthy controls), they did not find AMPAR antibodies in healthy controls or in patients (n=230 in each group). To date, there is no study in isolated psychosis testing anti-GlyR, GABA<sub>B</sub>, DPPX, and dopamine 2 receptors' antibodies positivity.

## Management of psychiatric manifestations

There are no published clinical trials on the best therapy for patients with autoimmune encephalitis. For all antibodies, patients received corticoid, plasmapheresis, and immunotherapy, based on anti-NMDAR encephalitis knowledge and some data of case reports. Management of psychiatric manifestations is clinically important and can impact the patient's capacity to receive immunotherapy<sup>111</sup> but lack practical feedback. Mainly, information comes from NMDAR encephalitis patients' experiences. In 2014, Kuppusswamy et al<sup>112</sup> reviewed management of psychotic symptoms, mood symptoms, and catatonic symptoms in NMDAR encephalitis. Treatments should not hide disease evolution neither worsen symptoms.<sup>22</sup> They advised to choose atypical and more sedative antipsychotics rather than typical antipsychotics as dopamine antagonists that aggravate agitation, in order to treat psychotic symptoms. To treat mood symptoms, valproic acid was advised for sedation, sleep, and seizure benefits and thanks to the availability of an intravenous form. Uses of lithium and benzodiazepines are also reported in the literature but do not cause significant changes.<sup>112,113</sup> Catatonic symptoms have to be treated in first line by benzodiazepines, and use of electroconvulsivotherapy is controversial. Neuroleptics can exacerbate neuropsychiatric symptoms and abnormal movements.<sup>14,22,113</sup>

Relapse possibilities combined with long-term persistence of behavioral and cognitive deficits highlight the importance of a medical follow-up, including psychiatric monitoring.

## Conclusion

Autoimmune encephalitis is a rare and heterogeneous disease. Various psychiatric presentation can occur, associated or not with neurological symptoms. Most of the time, psychiatric symptoms appear subacutely, in patients without any psychosis history. The frequency and severity of these psychiatric features depend on antibodies. Even if case reports highlighted psychiatric features, in studies conducted in psychiatric patients, the level of autoimmune encephalitis was low, with variable results according to the studies. This apparent discrepancy is multifactorial and likely due to assays being used in the different studies, younger psychosis patients than autoimmune encephalitis patients and nonstandardized clinical definitions of psychosis and schizophrenia. Anyway, autoimmune encephalitis diagnosis is difficult and incidence in psychiatric disease is probably low. However, autoimmune encephalitis has to be in the differential diagnosis process of psychiatrists because they often have primary psychiatric presentations and a rapid treatment is essential.

For all patients, particular attention has to be paid on neurological signs, such as autonomic disability, disorientation, movement disorders, seizures, or hyponatremia. Neurological examination and early biological testing should be realized:

- for patients presenting neurological symptoms, even soft one;
- for young women with first psychiatric manifestations; and
- for all patients with atypical psychiatric presentation, evolution or treatment response.

In these specific cases, EEG and MRI can be performed but are generally non-indicative of the disease because they are not always abnormal and very rarely pathognomonic. The biological sample, CSF preferentially otherwise sera, should be sent to reference center and tested according to the gold standard guidelines. If patients tested are positive for autoimmune encephalitis antibodies, they should be referred to neurological centers. In any case, such biological samples associated with psychiatric history of the patients are interesting elements helping for prospective studies.

## Disclosure

The authors report no conflicts of interest in this work.

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