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General review

MRI findings in autoimmune encephalitis

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ABSTRACT

Autoimmune encephalitis encompasses a spectrum of conditions characterized by distinct clinical features and magnetic resonance imaging (MRI) findings. Here, we review the literature on acute MRI changes in the most common autoimmune encephalitis variants. In N-methyl-D-aspartate (NMDA) receptor encephalitis, most patients have a normal MRI in the acute stage. When lesions are present in the acute stage, they are typically subtle and non-specific white matter lesions that do not correspond with the clinical syndrome. In some NMDA receptor encephalitis cases, these T2-hyperintense lesions may be indicative of an NMDA receptor encephalitis overlap syndrome with simultaneous co-existence of multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Encephalitis with leucine-rich glioma-inactivated 1 (LGI1)-, contactin-associated protein-like 2 (CASPR2)- or glutamic acid decarboxylase (GAD)- antibodies typically presents as limbic encephalitis (LE) with unilateral or bilateral T2/fluid attenuated inversion recovery (FLAIR) hyperintensities in the medial temporal lobe that can progress to hippocampal atrophy. Gamma aminobutyric acid-B (GABA-B) receptor encephalitis also often shows such medial temporal hyperintensities but may additionally involve cerebellar lesions and atrophy. Gamma aminobutyric acid-A (GABA-A) receptor encephalitis features multifocal, confluent lesions in cortical and subcortical areas, sometimes leading to generalized atrophy. MRI is unremarkable in most patients with immunoglobulin-like cell adhesion molecule 5 (IgLON5)-disease, while individual case reports identified T2/FLAIR hyperintense lesions, diffusion restriction and atrophy in the brainstem, hippocampus and cerebellum. These findings highlight the need for MRI studies in patients with suspected autoimmune encephalitis to capture disease-specific changes and to exclude alternative diagnoses. Ideally, MRI investigations should be performed using dedicated autoimmune encephalitis imaging protocols. Longitudinal MRI studies play an important role to evaluate potential relapses and to manage long-term complications. Advanced MRI techniques and current research into imaging biomarkers will help to enhance the diagnostic accuracy of MRI investigations and individual patient

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outcome prediction. This will eventually enable better treatment decisions with improved clinical outcomes.

1. Abbreviations

18F-FDG	18F-fluorodeoxyglucose -> (please also add in new line): AE = autoimmune encephalitis
CASPR2	contactin-associated protein-like 2
CNS	central nervous system
DWI	diffusion-weighted imaging
FBDS	faciobrachial dystonic seizures
GABA-A	gamma aminobutyric acid-A
GABA-B	gamma aminobutyric acid-B
GAD	glutamic acid decarboxylase
GENERATE	German Network for Research on Autoimmune Encephalitis
GFAP	glial fibrillary acidic protein astrocytopathy -> (please also add new line): IgLON5 = immunoglobulin-like cell adhesion molecule 5
LE	limbic encephalitis
LETM	longitudinally extensive transverse myelitis
LGI1	leucine-rich glioma-inactivated 1
MOGAD	myelin oligodendrocyte glycoprotein antibody-associated disease
MRI	magnetic resonance imaging
MS	multiple sclerosis
MTL	medial temporal lobe
NMDA	N-methyl-D-aspartate
NMOSD	neuromyelitis optica spectrum disorder
PET	positron emission tomography
PNH	peripheral nerve hyperexcitability

2. Introduction

Autoimmune encephalitides (AEs) are mediated by autoantibodies targeting neuronal antigens and are associated with distinct clinical syndromes [1]. Many patients develop severe neuropsychiatric symptoms including behavioral abnormalities, epileptic seizures, movement disorders and cognitive deficits, frequently leading to long-term impairment that affects daily living, social participation, and quality of life (Table 1) [2–4].

The range of acute imaging findings mirrors the wide variety of clinical presentations. While some AE types rarely cause abnormalities on routine brain MRI or only present with unspecific lesions, others are associated with rather distinct imaging patterns (Table 1). Understanding the typical brain imaging features associated with specific AE entities will support the diagnostic process and is important to rule out alternative diagnoses. In some cases, acute imaging features also hold important prognostic information regarding functional outcomes and long-term risk of cognitive deficits or structural epilepsy.

Here, we review acute MRI features of the most common types of AE, including NMDA receptor encephalitis, LGI1 encephalitis, GAD encephalitis, CASPR2 encephalitis, GABA-B and GABA-A receptor encephalitis, IgLON5 disease and GFAP encephalitis. We included English-language, peer-reviewed journal articles published between 2007–2024 reporting human patients with a diagnosis of antibody-positive autoimmune encephalitis, meeting the diagnostic criteria of Graus et al. [5].

3. MRI findings in autoimmune encephalitis

3.1. *NMDA receptor encephalitis*

3.1.1. *Clinical features*

Patients often experience a prodromal stage with nonspecific symptoms such as headaches or fever [6] that is followed by changes in behavior, which can include psychosis and affective symptoms. Many patients develop memory disorders, often alongside epileptic seizures and movement disorders such as orofacial dyskinesia, as well as autonomic instability and disorders of consciousness. The long-term outcome of the disease is characterized by persisting cognitive deficits affecting memory and executive functions [2,7] as well as increased levels of fatigue, depressive symptoms, anxiety and sleep disorders [8].

3.1.2. *Acute MRI abnormalities*

Most patients (> 50%) have an unremarkable clinical routine MRI in the acute stage [9]. Consequently, a normal MRI does not contradict (but rather is in line with) a diagnosis of NMDA receptor encephalitis. In patients with an abnormal MRI, changes are usually subtle and do not correspond to clinical symptoms. They typically include non-specific T2/FLAIR hyperintense white matter lesions (Fig. 1), but also cortical grey matter changes and lesions in deep grey matter structures (e.g., basal ganglia, hippocampus), the brainstem, or the cerebellum [10]. In data of the German Network for Research on Autoimmune Encephalitis (GENERATE), white matter lesions are present in around 40% of patients, predominantly in the frontal lobe, followed by the temporal and parietal lobe (unpublished data). Importantly, the hippocampus only rarely shows T2/FLAIR hyperintense signal alterations on acute MRI, contrasting with MRI findings in limbic encephalitis (unilateral or bilateral hippocampus FLAIR hyperintensity). MRI alterations are also largely independent of clinical severity—patients often present with severe symptoms despite normal MRI scans [11–13].

3.1.3. *Contrast-enhancement*

Contrast-enhancement is observed in some cases, particularly affecting the leptomeninges [10,14–23]. Some cases show enhancement of cortical and subcortical gray matter [10,23–25].

Table 1 – Summary of clinical and imaging characteristics for antibody-mediated encephalitides.

AE type	Clinical presentation	Acute MRI findings
NMDA receptor	Nonspecific prodromal stage (headache or fever) followed by behavioral changes, psychosis, affective disorders, memory disorders, epileptic seizures, movement disorders such as orofacial dyskinesias, autonomic instability, disorders of consciousness	> 50% normal MRI In patients with imaging alterations: non-specific cortical/subcortical T2/FLAIR hyperintensities T2-hyperintensities may be indicative of overlap syndromes (with MS, NMOSD or MOGAD) Follow-up: cases with atrophy, predominantly frontotemporal and cerebellar Contrast-enhancement: – Only in a small number of patients, mainly meningeal enhancement
LGI1	Initial presentation frequently with pathognomonic faciobrachial dystonic seizures (FBDS) and focal seizures; later followed by limbic encephalitis with memory deficits, temporal lobe seizures, sleep disturbances, and hyponatremia as well as psychiatric symptoms	During FBDS stage: Normal/basal ganglia T1 and T2 hyperintensities contralateral to FBDS LE stage: majority of patients (60–70%) with T2/FLAIR hyperintense medial temporal lobe (MTL) Follow-up: MTL atrophy in almost all patients Contrast-enhancement: – Some cases with MTL contrast-enhancement
CASPR2	Limbic encephalitis, Morvan syndrome, neuromyotonia	Morvan syndrome or neuromyotonia typically with unremarkable MRI Majority of patients with limbic encephalitis show characteristic T2/FLAIR hyperintensities in MTL, amygdala, hippocampus Supratentorial white matter blurring/unspecific lesions Follow-up: normalization of signal changes in most cases, occasional hippocampal atrophy, cerebellar ataxia associated with cerebellar atrophy Contrast-enhancement: – Single case with diffuse heterogeneous enhancement basal ganglia and MTL lesions – Single case with MTL enhancement
GAD	Limbic encephalitis, stiff person syndrome, cerebellar ataxia, epilepsy	Marked T2/FLAIR hyperintense MTL affecting hippocampus and amygdala Follow-up: progression of MTL lesions to significant sclerosis or atrophy in several cases, occasional global or cerebellar atrophy Contrast-enhancement: – Some cases with faint contrast-enhancement of lesions
GABA-B receptor	Limbic encephalitis with frequent epileptic seizures, less commonly cerebellar ataxia or brainstem involvement	Majority with limbic encephalitis: T2/FLAIR hyperintense MTL In some cases: cerebellar, brainstem, basal ganglia, or frontal lobe involvement, multiple small lacunar infarctions, and white matter demyelination Single case with longitudinally extensive myelopathy in thoracic spinal cord Follow-up: remission of hyperintense lesions and swelling, occasional atrophy, particularly in temporal lobe Contrast-enhancement: – Some cases with weak temporal contrast-enhancement – One case with enhancement of adjacent meninges
GABA-A receptor	Refractory epileptic seizures and status epilepticus, cognitive deficits, disorientation, memory impairment, depression, psychosis, mutism	Common: mainly confluent lesions with T2/FLAIR hyperintense MTL, orbitofrontal cortex (OFC), parietal and occipital lobes, insula, basal ganglia, cerebellum Diffusion-weighted imaging (DWI): occasional diffusion restriction in areas with T2/FLAIR hyperintensities Follow-up: resolution of lesions in many cases, occasional generalized atrophy Contrast-enhancement: – Single case with contrast-enhancement in left parietal lobe – Single case with focal leptomeningeal enhancement

Table 1 (*Continued*)

AE type	Clinical presentation	Acute MRI findings
IgLON5	Sleep disorders, bulbar syndrome, movement disorders, neuromuscular manifestations, cognitive impairment and ocular-motor abnormalities	Unremarkable MRI in most patients Several patients with diffuse T2/FLAIR hyperintensities in temporal and frontal lobe, callosal body, hypothalamus, periventricular and juxtacortical white matter DWI: reduced diffusion in cerebellothalamic tracts in one patient, and in left tegmentum of the midbrain and occipital horn of the right lateral ventricle in a second patient Follow-up: atrophy detected in some patients, most commonly in brainstem, midbrain, cerebellum and hippocampus Contrast-enhancement: – Single case with contrast-enhancement in right temporal lobe, resolution in follow-up
GFAP	Meningoencephalitis, memory deterioration, confusion, cerebellar ataxia, autonomic dysfunction, postural tremor	T2-hyperintense lesions located in juxtacortical white matter (∼50%) and periventricular white matter (∼50%) Longitudinally extensive intramedullary spinal cord lesions (∼50%) Contrast-enhancement: – Characteristic periventricular/-vascular radial enhancement pattern (50%) – Enhancement extending to brainstem and spinal cord, also affecting leptomeninges (45%)

NMDA: N-methyl-D-aspartate; LGI1: leucine-rich glioma-inactivated 1; CASPR2: contactin-associated protein-like 2; GAD: glutamic acid decarboxylase; GABA-B: gamma aminobutyric acid-B; GABA-A: gamma aminobutyric acid-A; FBDS: faciobrachial dystonic seizures; FLAIR: fluid-attenuated inversion recovery; IgLON5: immunoglobulin-like cell adhesion molecule 5; GFAP: glial fibrillary acidic protein astrocytopathy. LE: limbic encephalitis; MS: multiple sclerosis; MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD: neuromyelitis optica spectrum disorder; MTL: medial temporal lobe

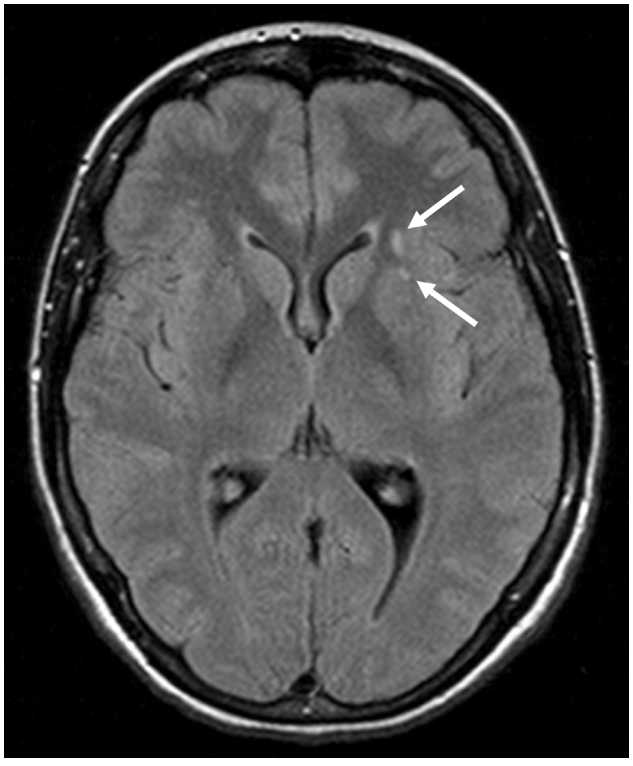

Fig. 1 – Patient with N-methyl-D-aspartate (NMDA) receptor encephalitis, with two small and non-specific T2/FLAIR hyperintense lesions in the left frontal lobe.

3.1.4. *Longitudinal studies*

Interestingly, cerebral volume loss has been described in some patients that was reversible over time and not associated with poor outcome [26,27]. In contrast, irreversible cerebellar atrophy was identified in other patients and was associated with poor clinical outcomes [26]. Similarly, another recent study found cerebellar atrophy in around 30% of patients which progressed for up to two years after disease onset, was non-reversible, and was associated with poorer clinical outcomes [28]. In the same study, cortical volume reduction was observed in 17% of patients, was not progressive over time, but was also associated with poorer outcomes. In smaller studies and case series, both diffuse cerebral and cerebellar atrophy was found in some patients. Recent analyses of a large cohort of patients from the GENERATE network similarly indicate long-term cerebral atrophy that is associated with worse clinical outcome (unpublished data).

3.1.5. *Prognostic value of MRI*

The prognostic potential of MRI lesions regarding disease outcomes was investigated in several studies, so far with inconsistent findings. In the largest study of almost 400 patients, an abnormal MRI was linked to worse functional status after one year and was included as one of five factors for the NMDA Receptor Encephalitis One-Year Functional Status (NEOS) score [29]. These findings were confirmed in another study in a Chinese patient population [30]. Furthermore, in pediatric patients, an abnormal MRI at disease onset was associated with poor outcomes [31] (further details see below).

In contrast, other studies found no correlation between conventional MRI abnormalities and long-term outcomes [32–34]. In general, it should be considered that MRI analyses in these studies were based on dichotomous normal/abnormal MRI evaluations, thus not considering the amount, size, and distribution of lesions, which might limit their predictive potential.

3.1.6. *Pediatric NMDA receptor encephalitis*

More than one-third of all NMDA receptor encephalitis cases are pediatric patients [35]. In comparison to adult patients, children more often show movement disorders, cerebellar ataxia, and hemiparesis while neuropsychiatric symptoms are less common. MRI alterations are found at a similar frequency compared to adults (ca. 30–50%) [31,36,37]. An abnormal MRI was shown to be associated with worse clinical outcome in pediatric NMDA receptor encephalitis [31]. This has been further corroborated by a validation of the NEOS score that includes an abnormal MRI as one of five parameters to predict 1-year functional outcome also in a pediatric cohort [38]. In contrast, a recent study in a large cohort of 175 children could not confirm MRI abnormalities as prognostic factor after adjusting for other clinical variables from the NEOS score, including intensive care unit admission, treatment initiation and clinical improvement within 4 weeks. However, the authors found that frontal and occipital lesions were associated with poor outcomes [36]. Importantly, using volumetric analyses, we previously identified substantial global and regional brain volume loss and impairment of normal brain development in children with NMDA receptor encephalitis [31]. While the (likely) impact on the functional long-term outcome has not been studied in detail, previous studies highlighted significant cognitive impairment in children with NMDA receptor encephalitis, specifically affecting younger children [39,40].

3.1.7. *NMDA receptor encephalitis overlap syndromes*

The concurrent presentation of clinical symptoms and T2-hyperintense lesions indicative of multiple sclerosis (MS) is observed in a considerable number of NMDA receptor encephalitis patients [41,42]. These NMDARE-MS overlap patients may exhibit typical MS relapses, such as sensorimotor symptoms, gait ataxia, brainstem syndromes, and optic neuritis [43]. Of note, overlap patients display MRI lesion morphology and lesion localization characteristic of MS, fulfilling the 2017 revised McDonald criteria [44]. These include multiple T2-hyperintense lesions with periventricular, juxtacortical, infratentorial brainstem, cerebellar, and spinal cord localization indicative of dissemination in space. In addition, accumulation of new T2 lesions over time, and the simultaneous presence of gadolinium (Gd)-enhancing and non-enhancing T2 lesions in the same brain scan commonly suggest dissemination in time [45]. In a GENERATE cohort of 189 NMDA receptor encephalitis patients, we recently identified 22 (11.6%) patients with an NMDARE-MS overlap syndrome [46]. Interestingly, T2-lesion count accumulation over five years was significantly higher in NMDARE-MS (1.32 lesions p.a.) compared to NMDA receptor encephalitis patients (0.01 lesions p.a.; $P < 0.001$) and to a cohort of matched relapsing remitting MS patients (0.48 lesions p.a.; $P < 0.001$), potentially due to insufficient long-term immunotherapy in overlap syndrome patients.

Given the established evidence of NMDARE-MS overlap syndromes, we recommend a follow-up MRI at least once around 12–24 months after initial onset in all NMDA receptor encephalitis patients to detect clinically silent demyelinating lesions. In addition, MRI should be done in all patients with any new neurological symptoms. When MS-typical T2 lesions with dissemination in space and time are identified, a concurrent MS diagnosis and according MS treatment should be considered, e.g. B-cell depleting therapy which was shown to be efficacious in both NMDA receptor encephalitis [47] and MS [48].

Recent studies have also identified NMDA receptor encephalitis patients with overlapping aquaporin-4-antibody (AQP4-ab) positive neuromyelitis optica spectrum disorder (NMOSD) and myelin-oligodendrocyte-glycoprotein-antibody (MOG-ab) associated disease (MOGAD) [49–51]. Typical MRI characteristics in NMDARE-NMOSD and NMDARE-MOGAD include prechiasmal bilateral optic neuritis, spinal cord lesions often displayed as longitudinally extensive transverse myelitis (LETM), and brainstem or multifocal white matter changes. These may result in more residual clinical deficits despite intensive immunotherapy compared to classical NMDA receptor encephalitis attacks [51,52]. These overlapping syndromes should be treated early, with long-term immunosuppressive therapy following current NMOSD and MOGAD treatment recommendations.

3.1.8. *Advanced imaging*

Advanced MRI analyses identified both structural and functional MRI changes that remain undetected in clinical routine imaging, including hippocampal volume loss, impairment of white matter integrity, and disruption of functional brain networks in patients with NMDA receptor encephalitis [53–58]. Recently, we found that the T1-weighted/T2-weighted (T1/T2) ratio, a measure of white matter integrity computable from clinical MRI sequences, is significantly reduced in major white matter tracts (corticospinal tract, superior longitudinal fascicle, optic radiation and callosal body) [59]. In addition, microstructural integrity was reduced in the hippocampus, the amygdala and the thalamus in this study. Given that the analysis of the T1/T2 ratio is based on routine MRI scans, this measure holds potential to track macroscopically invisible white matter damage in clinical settings and serve as imaging outcome marker in clinical trials on NMDA receptor encephalitis. Importantly, even in patients receiving first- and second-line immunotherapy, hippocampal volume, microstructural integrity, and functional connectivity can be impaired up to ten years after the acute disease stage (unpublished data), indicating long-lasting changes in brain health despite current consensus treatment. This suggests a potential vulnerability to accelerated brain aging over time and highlights the need for more detailed and rigorous MRI studies to better understand the long-term consequences following NMDA receptor encephalitis.

3.2. *LGI1 encephalitis*

3.2.1. *Clinical features*

LGI1 encephalitis frequently manifests with a seizure-dominant syndrome including pathognomonic faciobrachial

dystonic seizures (FBDS), but most patients progressively develop limbic encephalitis associated with memory deficits, confusion, behavioral abnormalities, and temporal lobe seizures [60,61]. However, importantly, an early identification and immunotherapy of FBDS can prevent this progression to limbic encephalitis [62]. About 60% of patients develop hyponatremia [61] and, more recently, it has become evident that patients with LGI1 encephalitis commonly experience sleep disturbances [63]. The long-term outcome of the disease is characterized by prominent memory impairment, but also deficits in other cognitive domains such as attention and executive function [64–67] as well as significant fatigue and increased levels of depressive symptoms [68,69].

3.2.2. *Acute MRI findings*

During the FBDS stage, routine neuroimaging is often unremarkable [70]. However, up to one third of patients may show unilateral basal ganglia T1 and T2 signal abnormalities contralateral to the side of FBDS [71–73], with T1 hyperintensities persisting longer than the T2 hyperintensities. In a case report of a patient with typical clinical features of LGI1 encephalitis, MRI showed restricted diffusion and reduced apparent diffusion coefficient as well as T1 and T2/FLAIR hyperintensities in the basal ganglia [72]. In patients without FBDS, basal ganglia are rarely affected [73]. Detection of basal ganglia lesions in structural MRI may thus be helpful for clinical characterization and can support the diagnosis of FBDS.

During the encephalitic stage, about 70% of patients present unilateral or bilateral T2/FLAIR hyperintensities of the medial temporal lobes (MTL; Fig. 2) [61,64,73,74]. Conversely, these observations also highlight that up to one third of patients will have a normal routine MRI despite limbic encephalitis. In these patients, repeated MRI studies with high-resolution T2/FLAIR sequences may help to detect MTL alterations. Brain MRI may be less often abnormal (about 60%) during a relapse, which occurs in approximately 15% of patients [75].

Regarding relevant differential diagnoses, a recent study showed that T2/FLAIR hyperintensities less often extended beyond the temporal lobe and less frequently exhibited swelling, diffusion restriction, or contrast-enhancement [76] in patients with LGI1 or CASPR2 encephalitis compared to patients with viral encephalitis and Creutzfeldt-Jakob disease. Notably, up to 30% of patients with LGI1 encephalitis have been reported to exhibit T2/FLAIR hyperintensities of the corticospinal tract, although this finding is more commonly associated with neuromyelitis optica spectrum disorders [77].

At long-term follow-up (median 23 months after onset), almost all LGI1 encephalitis patients will develop hippocampal atrophy independent of the initial detection of acute MTL changes, with severity of atrophy correlating with the extent of memory impairment [64]. Similar rates of hippocampal atrophy were reported in other studies on the long-term outcome of the disease [78,79]. Interestingly, recent evidence suggests that temporal lobe hyperintensities in the acute phase are associated with greater functional disability at follow-up [80].

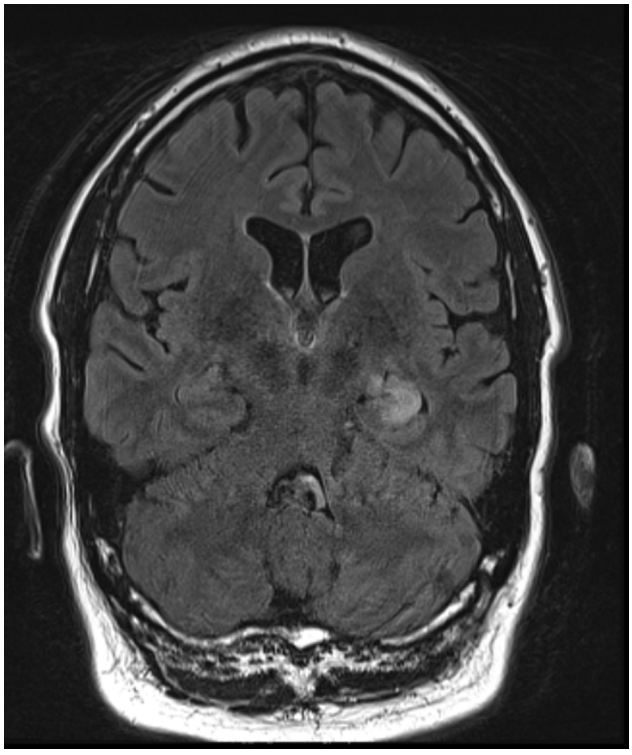

Fig. 2 – A patient with leucine-rich glioma-inactivated 1 (LGI1) encephalitis in the limbic encephalitis stage and left medial temporal hyperintensity in T2/FLAIR.

3.2.3. *Advanced MRI*

While routine clinical imaging findings cluster in the MTL, advanced neuroimaging studies have increasingly uncovered the involvement of extra-limbic brain areas in LGI1 encephalitis. Resting-state functional MRI (fMRI) analyses detected functional connectivity alterations in sensory and visual networks, even in patients without visible structural damage [81]. Furthermore, patients with hippocampal damage show disruptions in functional connectivity between the hippocampus and major resting-state networks. Alterations in the default mode network strongly correlate with memory performance, representing a potential compensatory mechanism [82].

Moreover, a recent study on long-term cognitive deficits in LGI1 encephalitis suggests that the disorder may specifically affect the brain's white matter network that connects limbic and extra-limbic brain systems. Here, patients showed a structural reorganization of white matter networks that was linked to persistent cognitive deficits in the post-acute disease stage and possibly provides an explanation for the clinical combination of classical 'limbic' encephalitis and extra-limbic symptoms [83].

3.3. *CASPR2*

CASPR2 encephalitis can present with different clinical phenotypes, including limbic encephalitis (LE), Morvan syndrome (i.e., severe peripheral nerve hyperexcitability (PNH),

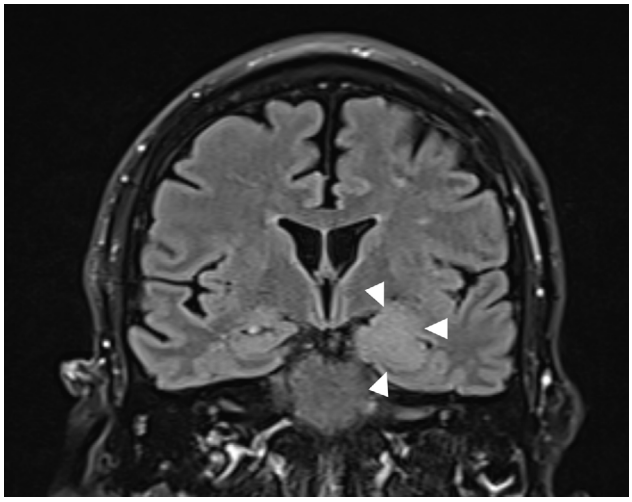

Fig. 3 – A patient with contactin-associated protein-like 2 (CASPR2) encephalitis and left T2/FLAIR medial temporal hyperintensity and swelling.

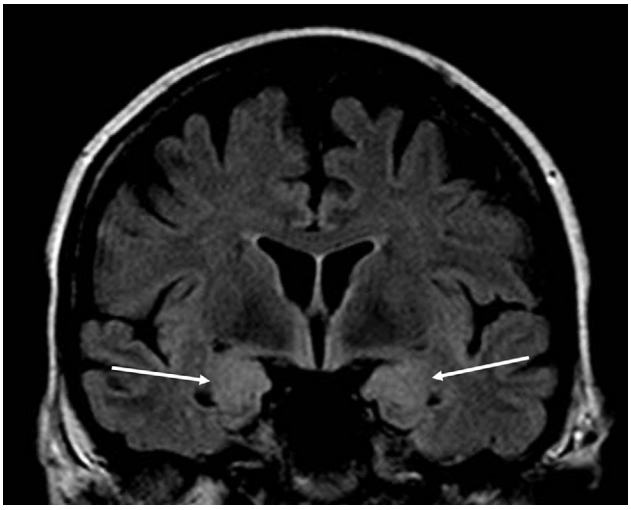

Fig. 4 – A glycoprotein antibody-associated disease (GAD) encephalitis patient with T2/FLAIR hyperintense lesions in the medial temporal lobe bilaterally (white arrows).

cognitive deficits, seizures, dysautonomia) and acquired neuromyotonia [79,84]. Most frequently, patients show symptoms of LE characterized by memory loss, confusion, behavioral changes, and temporal lobe seizures [85]. Patients with Morvan syndrome suffer from severe insomnia, hallucinations, autonomic dysfunctions such as excessive sweating and irregular heartbeat, and muscle twitching due to peripheral nerve hyperexcitability. Neuromyotonia is characterized by muscle cramps, stiffness, and delayed muscle relaxation. While these represent typical symptom clusters, patients with Morvan syndrome and neuromyotonia often also show symptoms of encephalitis including cognitive deficits.

CASPR2 encephalitis patients with only neuromyotonia or Morvan syndrome typically have no MRI abnormalities [86]. In contrast, most patients with limbic encephalitis show LE MRI abnormalities, i.e., T2/FLAIR signal increases of the MTL (Fig. 3), which can evolve into hippocampal atrophy [87–89]. Patients with cerebellar ataxia tend to develop cerebellar atrophy on follow-up imaging [88,90,91].

3.4. *GAD encephalitis*

GAD encephalitis usually presents with one of three phenotypes that can partially overlap: limbic encephalitis, stiff person syndrome, and cerebellar ataxia. As in other AE variants, limbic encephalitis manifests with memory loss, confusion, and seizures [92,93], while stiff person syndrome is characterized by severe muscle stiffness and spasms and cerebellar ataxia by uncoordinated movements and difficulties with balance.

The most common MRI findings in acute GAD encephalitis are T2/FLAIR hyperintensities and swelling of the MTL, especially in patients with LE (Fig. 4) [67,94,95]. Automated volumetry analyses showed significantly larger hippocampus and amygdala volumes in acute stage patients compared to healthy controls [96,97]. Swelling typically resolves in later stages and while many patients show resolution of imaging changes, significant sclerosis and volume loss often remain, especially in the MTL [98–102]. Patients with cerebellar ataxia often show cerebellar atrophy without brainstem involvement [103], while no specific patterns have been reported in association with stiff person syndrome.

3.5. *GABA-B receptor encephalitis*

GABA-B receptor encephalitis is primarily characterized by LE, which presents with frequent epileptic seizures, memory loss, and behavioral changes [104]. Less commonly, patients may experience cerebellar ataxia or brainstem involvement, which can cause autonomic and cranial nerve dysfunctions.

MRI findings in GABA-B receptor encephalitis are usually consistent with typical manifestations of LE. Most patients show T2/FLAIR hyperintensities in the MTL (Fig. 5) [104–106]. Individual cases exhibit laminar necrosis-like patterns in the outer hippocampal areas CA 1 and CA 2, correlating histologically to 'pan-necrosis' involving neuronal and glial cells as well as blood vessels. This pattern – also described in metabolic and hypoxic brain damage – is not specific to GABA-B receptor encephalitis and has also been observed described in other types of LE, such as AMPA receptor encephalitis [107].

Other MRI features include leukoaraiosis and diffuse ischemic lesions in the cerebral white matter [105,108–110]. Patients with cerebellar involvement can present with nystagmus, vertigo, dysarthria, cerebellar ataxia, or opsoclonus-myoclonus syndrome [111–113]. These patients show cerebellar T2/FLAIR-hyperintense lesions, sometimes extending to the brain stem and basal ganglia.

Imaging changes tend to resolve with clinical improvement [113–115]. In some cases, however, cortical atrophy remains [108,110,116,117].

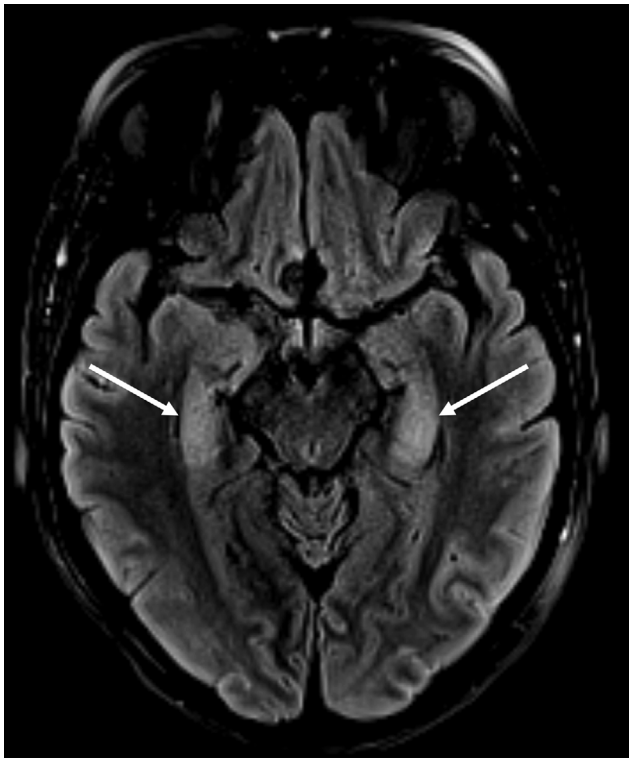

Fig. 5 – A patient with gamma aminobutyric acid-B (GABA-B) receptor encephalitis and bilateral medial temporal hyperintense T2/FLAIR lesions (white arrows).

3.6. *GABA-A receptor encephalitis*

GABA-A receptor encephalitis is associated with cognitive deficits, disorientation, and memory impairment [118], and patients often suffer from refractory epileptic seizures and status epilepticus. Additionally, they may develop depression, psychosis, and mutism.

MRI is frequently abnormal in patients with GABA-A receptor encephalitis. The most typical imaging findings are multifocal, confluent lesions with increased T2/FLAIR signal in cortical and/or subcortical areas [118]. These present as diffuse, hyperintense lesions reaching across cortical gray matter and subcortical white matter (cortico-subcortical lesions) [119,120]. Generalized atrophy in affected areas may develop after the acute disease stage.

3.7. *IgLON5 disease*

Anti-IgLON5 disease presents with a diverse clinical phenotype, most frequently including sleep disorders, bulbar syndrome, movement disorders, neuromuscular manifestations, cognitive impairment and ocular-motor abnormalities [63,121–125]. Next to autoantibodies [126], the autoimmune etiology of the disease is further supported by a strong (~85%) association with HLA-DQ, specifically HLA-DQB1*05:~ containing haplotypes [127,128].

Cohort studies show that MRI is frequently unremarkable in IgLON5 disease [122,129], but an increasing array of case reports suggests the presence of diverse abnormalities in individual patients. Leptomeningeal inflammation was identified in two case reports [130,131], while others identified atypical inflammatory lesions together with brainstem and hippocampal atrophy [132]. Further reports include T2/FLAIR hyperintensities in the hypothalamus [133]; swelling and T2/FLAIR hyperintense signal in the hippocampus [134]; symmetric T2/FLAIR hyperintensities in the cerebellum, the cerebellar peduncles, and brainstem that improved following treatment [135]. Interestingly, two recent cases were reported with anti-IgLON5 autoantibodies and a clinical presentation with bulbar-onset motor neuron disease-like phenotype. In both patients, a cerebral MRI revealed bilateral T2/FLAIR hyperintensities and enlargement of trigeminal nerves without gadolinium enhancement, suggesting that the presence of symmetric trigeminal nerve T2/FLAIR hyperintensities should prompt anti-IgLON5 antibody testing in patients exhibiting evocative symptoms [136]. Further reports on anti-IgLON5 disease included the occurrence of reduced diffusion in the dorsal midbrain, cerebellum, cerebellar peduncles, and ventrolateral thalamus [137].

In addition to MRI reports, positron emission tomography (PET) studies utilizing tau tracers identified tau deposition in the brainstem [138] and cerebellum [131], concurrent with the localization of tau pathology that was described in pathological studies [125,139,140]. Lastly, while individual reports previously highlighted atrophy of the midbrain [141], brainstem [122,132], hippocampus [122,132] and cerebellum [129], we recently identified substructure-specific atrophy with preferential involvement of the brainstem, the nucleus accumbens, and the basal ganglia in a large cohort study investigating spatial atrophy patterns in anti-IgLON5 disease (unpublished data).

3.8. *Glial fibrillary acidic protein astrocytopathy (GFAP)*

Glial fibrillary acidic protein (GFAP) astrocytopathy can present with a variety of neurological symptoms, including encephalopathy, myelitis, optic neuritis, ataxia, and psychiatric disturbances, while common manifestations also include fever, headache, and visual disturbances [142]. Neuroimaging often reveals predominantly periventricular, extensive, confluent, and hazy T2-hyperintensities but the brainstem, diencephalon, cerebellum, corpus callosum, and optic nerves may also be involved [143]. Characteristic MRI morphology with linear perivascular radial enhancement is one of the hallmarks of the disease, which is reported in 45% of patients. In addition, leptomeningeal enhancement is commonly detected. These patterns of enhancement should prompt the consideration of a GFAP astrocytopathy and antibody testing, and can help in distinguishing the disease from other inflammatory and demyelinating neuroimmunological conditions [143]. Spinal cord abnormalities most commonly manifesting as longitudinally extensive transverse myelitis (LETM) involving the thoracic spine and the total length of the spinal cord are detected in about 50% of patients [144].

Of note, severe hippocampal atrophy together with global and subcortical regional brain atrophy and longitudinally extensive spinal cord lesions in the absence of cerebral T2-hyperintense lesions has been recently reported in a GFAP astrocytopathy patient with persistent cognitive impairment, indicating heterogeneous MRI patterns to occur in the disease [145].

4. Conclusions

This review of the most common autoimmune encephalitis variants and associated MRI patterns highlights the complexity and heterogeneity of these conditions, but also indicates shared patterns such as in limbic encephalitis. The presented findings demonstrate the clinical relevance of brain imaging as a diagnostic and prognostic tool for AE.

While some AE variants are associated with relatively unspecific lesions, other imaging patterns are highly characteristic. Observing such patterns can enhance clinical confidence in establishing the correct diagnosis and is important to rule out alternative diagnoses. Furthermore, first studies have now started to explore the potential of MRI measures as predictor for clinical outcome. Further refinement of imaging markers (e.g., lesion location, size, and number) that go beyond a dichotomy between normal and abnormal MRI will likely increase their predictive value. Longitudinal imaging studies are needed to better understand the progression from acute to chronic disease phase MRI findings and to study potential compensatory and maladaptive processes. Moreover, regular follow-up imaging and clinical assessments can help to detect early signs of relapses and long-term complications. Finally, some studies have started to identify structural and functional imaging patterns that correspond to acute and long-term clinical symptoms, thereby advancing the pathophysiological understanding of these diseases.

Given the variability in MRI findings, it is important to develop improved imaging markers that can also capture subtle changes associated with each type of encephalitis. Advanced imaging techniques are currently adapted for clinical routine to improve detection of micro- and mesoscopic tissue alterations. Such techniques may include diffusion tensor imaging, the T1/T2 ratio or quantitative multi-parameter mapping [54,59,146,147], which can potentially help to predict disease severity and long-term outcomes. Furthermore, advanced imaging techniques can complement immunological studies by non-invasively providing information on physical tissue properties [54,59,147].

Finally, while this review provides a general overview of imaging changes in some of the most relevant AE types, systematic reviews and meta-analyses across all AE entities will be pivotal to estimate the prevalence of imaging alterations in these diseases and synthesize knowledge regarding specific imaging patterns.

Disclosure of interest

The authors declare that they have no competing interest.

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Data availability

No primary data have been reported in this review article.

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