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REVIEW ARTICLE

Autoimmune epilepsy: findings on MRI and FDG-PET

JULIE GUERIN, MD, ROBERT E WATSON, MD, PhD, CARRIE M. CARR, MD, GRETA B LIEBO, MD and AMY L KOTSENAS, MD

Department of Radiology, Mayo Clinic, Rochester, MN, USA

Address correspondence to: Dr Julie Guerin
E-mail: guerin.julie@mayo.edu

ABSTRACT

Autoimmune epilepsy (AE) is becoming increasingly recognized as a potentially reversible cause of frequent or medically intractable seizures and cognitive deterioration. We describe various presentations of autoimmune encephalopathy which have specifically presented with seizure and describe reported imaging findings. This is organized as a review of the more common autoantibodies which can specifically precipitate seizure according to the intracellular or extracellular location of the targeted antigen. For each antibody, we illustrate their pathophysiology, characteristic clinical presentations with typical effective treatments and prognoses and imaging findings on MRI and PET/CT exams. Parenchymal involvement is variable with the limbic structures typically affected; however, non-limbic cortex, cerebellum, brainstem and basal ganglia can also be involved. In the acute setting, affected regions typically demonstrate T_2 hyperintensity with mild mass effect from edema and increased ^{18}F -fludeoxyglucose uptake. Chronically involved parenchyma will often undergo atrophy and demonstrate decreased metabolism; mesial temporal sclerosis is often the end result when the limbic system is involved. Without treatment, long-term effects from AE range from ongoing cognitive dysfunction and refractory seizures to death. Familiarity with AE may prompt appropriate antibody screening, particularly in cases of refractory seizure disorders. Early investigation and proper management of AE cases may help to prevent parenchymal and neurologic deterioration in these patients.

INTRODUCTION

Although autoimmune epilepsy (AE) is a relatively new concept in the radiology literature, evidence for immunological mechanisms in epilepsy has increased in the last several years.^{1–9} AE was originally described in the context of more generalized autoimmune encephalopathy, predominately as a paraneoplastic phenomenon targeting the limbic system. Certain tumors expressing neuronal proteins were found to provoke a cell-mediated neurological disorder as a byproduct of an attack on cancer cells. The classically described paraneoplastic limbic encephalitis (LE) reflects involvement of limbic structures including the anteromedial temporal lobe, hippocampus and amygdala and is clinically characterized by the subacute onset of temporal lobe seizures, anterograde memory impairment and psychiatric symptoms. Similar to other paraneoplastic syndromes, neurologic symptoms can present well before a cancer is detectable. Antibodies traditionally considered paraneoplastic include anti-Hu (ANNA-1) and anti CRMP-5 antibodies, usually found in conjunction with small cell lung carcinoma (SCLC), and anti-N-methyl-D-aspartate (NMDA) receptor antibodies which are often associated with ovarian teratoma.

Over time, the concept of AE has expanded to include seizure disorders without the complete features of limbic encephalitis and instigated by antibodies not typically associated with an underlying neoplasm.^{10–12} This non-paraneoplastic variety is now thought to be more common than the paraneoplastic type.^{13–15} It should be noted, however, that distinction between paraneoplastic and non-paraneoplastic types is not always clear. In many cases involving a traditionally paraneoplastic antibody an instigating malignancy is never found; likewise, an underlying tumor is identified in some non-paraneoplastic varieties. Due to this overlap, we will categorize antibodies according to the extracellular or intracellular location of the targeted antigen (Tables 1 and 2). The majority of epilepsy-associated antibodies target extracellular neuronal proteins including leucine-rich glioma inactivated-1 (LGI1) of the voltage-gated potassium channel complex (VGKC), the N-methyl-D-aspartate receptor (NMDAR), the gamma aminobutyric acid receptor (GABAR) and the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor as well as the intracellular protein glutamic acid decarboxylase (GAD). Targets less commonly associated with seizure include the intracellular proteins collapsin-responsive mediator protein-5 (CRMP-5) and the

Table 1. Antibodies targeting intracellular neuronal proteins in autoimmune epilepsy

Anti-GAD antibody	F > M Limbic encephalitis with temporal lobe seizures and memory loss; known association with other autoimmune disorders including Type 1 diabetes, thyroid disease and stiff person syndrome	Not typically related to underlying malignancy; however, lung, thymic and neuroendocrine tumors have been reported in cases with high titers	Focal or generalized slowing	<p>MRI: In LE: T2 hyperintensity and enlargement of one or both MTL; higher T2 FLAIR intensity in these regions compared with patients with VGKC or NMDAR antibodies</p> <p>In complex seizures: may see signal abnormality in non-limbic gray matter</p> <p>DTI: Widespread white matter abnormalities</p> <p>¹⁸F-FDG-PET: Corresponding hypermetabolism in affected regions in limited reports</p>	Often pharmacoresistant, particularly with high antibody titers; immunomodulatory treatment may be necessary long term
Anti-Hu antibody	Widespread neurological symptoms, most common being sensory neuropathy; limbic encephalitis in 11–20%	SCLC	Focal epileptiform activity	<p>MRI: T2 hyperintensity and enlargement of MTL, non-limbic cortex or brainstem with occasional enhancement</p> <p>¹⁸F-FDG-PET: Hypermetabolism of affected regions in acute setting</p>	Complete recovery is rare and prognosis is poor; antitumoral treatment is the best strategy
Anti-CRMP-5 antibody	Limbic encephalitis most common seizures presentation	SCLC, thymoma	Focal epileptiform activity	<p>MRI: T2 hyperintensity and enlargement of MTL, non-limbic cortex or brainstem with occasional enhancement</p> <p>¹⁸F-FDG-PET: Hypermetabolism of affected regions in acute setting</p>	Better prognosis if a tumor is found and treated; immunotherapy may stabilize

GAD, glutamic acid decarboxylase; CRMP, collapsin-responsive mediator protein; FDG, fludeoxyglucose; PET, positron emission tomography; SCLC, small cell lung carcinoma; DTI, diffusion tensor imaging; MTL, mesial temporal lobes ;

Table 2. Antibodies targeting cell surface/synaptic neuronal proteins in autoimmune epilepsy

Antibody	Clinical pearls	Tumor association	EEG pearls	Imaging pearls (active stage)	Treatment and prognosis
Anti-NMDAR antibody	F > M Multistage syndrome with a viral-like prodrome followed by psychotic symptoms, extratemporal seizures and language dysfunction with advancement to dyskinesias, autonomic dysfunction and possibly coma	Ovarian teratoma, in young adult women	Extreme delta brush	MRI: Often normal; may see transient T2 hyperintense cortical/subcortical foci in frontal, parietal or medial temporal regions, thalamus, cerebellum, brainstem and infrequently basal ganglia; may have transient enhancement of cortex, meninges or basal ganglia. DTI: Extensive white matter damage ¹⁸F-FDG-PET: Characteristic pattern of increased frontotemporal-to-occipital gradient	Large majority of patients improve with prompt immunotherapy and/or tumor removal
Anti-LGI1 antibody (VGKC complex)	M > F Limbic encephalitis with unusually high seizure burden (which can be accompanied by hyponatremia, bradycardia and piloerection), memory loss, disorientation; may have FBDS	Tumor in up to 30% of cases, typically SCLC or thymoma	Seizures of focal onset with secondary generalization; may be focal or generalized slowing	MRI: Usually positive; In LE: Enlargement and T2 hyperintensity of one or both MTL and/or non-limbic gray matter with occasional diffusion restriction and enhancement; In FBDS: Pre-contrast T1 hyperintensity in basal ganglia ¹⁸F-FDG-PET: Frequent hypermetabolism of affected regions in both LE and FBDS (MTL and basal ganglia most common), often before MRI abnormality	Good response to early immunotherapy; FBDS sensitive to early corticosteroids and plasma exchange therapy
Anti-GABAAR antibody	Limited information; rapidly progressive encephalopathy with refractory seizures or epilepsy partialis continua reported in a small case series			MRI: Multifocal cortical and subcortical areas of T2 hyperintensity in all patients of a small case series	Good response to immunotherapy in limited reports
Anti-GABABR antibody	M > F Limbic encephalitis including seizures (usually temporal lobe onset), memory loss and confusion, occasional behavioral changes and ataxia	SCLC and neuroendocrine tumors	Focal or generalized epileptic activity	MRI: Abnormal in most reported cases with T2 hyperintensity and swelling of one or both MTLs ¹⁸F-FDG-PET: (limited information) Corresponding hypermetabolism in affected MTL in three reported cases; diffuse cortical hypometabolism in three reported cases	Good response to immunotherapy and/or treatment of an underlying tumor
Anti-AMPA antibody	F > M Most commonly amnesia, confusion and psychosis; only mildly epileptogenic	SCLC and thymoma	Focal epileptic activity when present	MRI: Most commonly T2 hyperintensity and swelling of one or both MTL; signal abnormality has been reported to involve other regions ¹⁸F-FDG-PET: Corresponding hypermetabolism in affected MTL in limited reports	Good recovery with immunotherapy and/or tumor therapy

EEG, electroencephalogram; NMDAR, N-methyl-D-aspartate receptor; VGKC, voltage-gated potassium channel complex; FBDS, faciobrachial dystonic seizures; SCLC, small cell lung carcinoma; GABAAR, gamma aminobutyric acid receptor; AMPAR, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor;

Hu (ANNA-1) antigen. This paper describes various presentations of autoimmune encephalopathy, specifically focusing on the seizure manifestation as instigated by the aforementioned antibodies.

EPIDEMIOLOGICAL AND CLINICAL INVESTIGATIONS IN AE

The exact incidence and prevalence of AE is not known and depends on the involved antibody. A strong association between autoimmune disease and epilepsy, however, is well-established. The largest population study to date investigating the relationship of autoimmune disease and epilepsy found that risk of epilepsy was significantly increased among patients with autoimmune diseases. This is most pronounced in patients with systemic lupus erythematosus and antiphospholipid antibody syndrome (seven- and ninefold increased risk) followed by those with Type 1 diabetes and myasthenia gravis (fivefold increased risk). Children with autoimmune disease overall have a fivefold increased risk for epilepsy.¹⁶ Reviews of AE conclude that underlying autoimmune etiologies be investigated for epilepsy patients with resistance to antiepileptic medications, high seizure burden, multifocal seizures, inflammatory changes identified in serum, in spinal fluid or on imaging studies, a family history of autoimmunity or history of neoplasia.^{10,17} Even in the absence of an identified autoantibody, a trial of immunotherapy may be beneficial in AE.^{4,7,10,11,18,19} In a study by Toledano *et al*, 29 patients with suspected AE were given an immunotherapy trial; 62% had a substantial improvement in seizure burden and 10% became seizure free.¹¹

MRI AND ¹⁸F-FDG-PET IMAGING IN AE

While imaging studies are often normal in AE, evaluation with both MRI and ¹⁸F-fludeoxyglucose (FDG) PET brain studies is warranted to confirm the diagnosis. Overall, when signal abnormalities are present on either modality, they are most commonly seen in one or both mesial temporal lobes (MTL). Most types of AE also have reported involvement of structures beyond the temporal lobe, including the basal ganglia, non-limbic cortex, cerebellum, brainstem and white matter. Positive MRI studies will reveal T₂ hyperintensity and edema within affected regions in the acute setting and atrophy of chronically involved parenchyma.^{14,19,20} Depending on the stage of encephalitis, correlative brain ¹⁸F-FDG-PET studies typically show hypermetabolism in areas of acutely reactive cortex,^{20–24} normal metabolism upon recovery^{3,22} and hypometabolism in areas of cortical atrophy such as mesial temporal sclerosis (MTS).^{3,25,26} In addition to brain findings, whole body ¹⁸F-FDG-PET may help identify an underlying tumor and detect any metastases. Findings on brain MRI do not always correlate with brain ¹⁸F-FDG-PET and vice versa; the two modalities can thus complement each other.^{3,20}

Metabolic alterations may depend on the type of antibody involved. Autoantibodies against intracellular antigens have been found to correlate closely with focal hypermetabolism,^{27,28} potentially due to increased glucose consumption from the incited T-cell mediated inflammatory response¹²; likewise, autoantibodies against extracellular/cell surface antigens are more likely to result in focal hypometabolism which may be related to receptor downregulation.²⁹

In prior reviews describing ¹⁸F-FDG-PET findings in AE (and in examples shown in this review), timing of FDG injection was not necessarily performed to coincide with seizure activity, often obtained instead to identify or exclude an underlying neoplasm. It is a noted limitation in cases of autoimmune epilepsy that if EEG monitoring is not performed at the time of FDG injection it is uncertain if ¹⁸F-FDG uptake is related to inflammation or concurrent seizure activity.

Several studies have reported a higher sensitivity of ¹⁸F-FDG-PET compared to MRI for AE, particularly early in the disease course. Brain findings on ¹⁸F-FDG-PET may precede both MRI abnormalities and patient symptoms; ¹⁸F-FDG-PET may thus serve as an early biomarker of disease and possibly offer a therapeutic window.^{3,20,23,24,27,30,31} Gradual decrease in ¹⁸F-FDG avidity has also been seen to parallel symptom improvement and normalization of CSF inflammatory markers.³

The variable array of imaging findings and symptoms in these patients requires consideration of clinical and imaging mimics such as viral encephalitis, Creutzfeldt-Jakob disease, vasculitis and psychiatric illness. Including the possibility of autoimmune causes early in the diagnostic investigation of refractory seizures may prompt initiation of immunotherapy and in many cases help to prevent parenchymal and neurologic deterioration.

ANTIBODIES TARGETING CELL SURFACE/ SYNAPTIC NEURONAL PROTEINS

Anti-NMDAR antibody related AE

The NMDA receptor is a glutamate receptor and ion channel important in synaptic plasticity and memory³² which is predominantly located in the hippocampus. NMDA receptor autoantibodies directly bind to the extracellular domain of its NR1 subunit.^{29,33,34} Typically, anti-NMDA antibodies are found in young adult females and are related to an underlying ovarian teratoma in 40–60% of cases.^{17,35,36} In cases involving children or males, the presence of an underlying teratoma or any other tumor is relatively uncommon.^{7,17,37–39}

NMDAR encephalitis has a characteristic syndrome in adults and teenagers beginning with prodromal fever, headache and malaise with progression to psychotic symptoms, hallucinations, speech difficulties and epileptic seizures. Later in the disease course, patients may develop dyskinesias, autonomic instability and impaired consciousness.^{17,36,40} Younger patients are less likely to have prodromal illness or autonomic disability; common presenting symptoms in children are behavioral and speech problems, seizures and movement disorders.^{37,39} In a case series of 100 patients with anti NMDAR antibodies (age range 5–76 years), 76 had seizures.⁴¹ Other case series or reviews report similar frequency of seizure with this syndrome.^{34,35,39} Seizures are often extratemporal and may be focal, dyscognitive or generalized.^{35,36,42} Of note, focal seizures and dyskinesias may be tightly intermingled (involving the same limb at nearly the same time) suggesting involvement of a common neural network.^{34,43} A distinct EEG pattern resembling the delta brush pattern in premature infants has been seen in adults with NMDAR encephalitis and has been coined “extreme delta

Figure 1. Anti-NMDAR AE in a 27-year-old female presenting with first time generalized, tonic-clonic seizure and aphasia. (a) Axial T_2 FLAIR MRI image obtained 2 months after presentation shows T_2 hyperintensity involving cortex and sub-cortical white matter within the left temporal lobe (arrows). (b) Axial post-gadolinium T_1 W image from the same exam demonstrates associated enhancement of the cortex, sub-cortical white matter and leptomeninges (arrows). (c) Axial FDG-PET image from 1 week later shows marked FDG avidity in the region of meningoencephalitis (arrows). (d) Axial T_2 FSE image from MRI six years later shows encephalomalacia in this region (arrows). Patient was initially treated with IV methylprednisolone and later maintenance oral steroids and anti-epileptic medication. Initial EEGs had demonstrated multiple clinical and subclinical seizures, mainly of left posterior cerebral onset. Later EEGs continued to reflect a partial seizure disorder. AE, autoimmune epilepsy; EEG, electroencephalogram; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion-recovery; FSE, fast spin echo; NMDAR, N-methyl-D-aspartate receptor; T_1 w, T_1 weighted.

brush".³⁷ With prompt immunotherapy and/or tumor removal, larger cohort studies have reported neurologic improvement in 75–81% of patients.^{17,41} In patients with undetected or recurrent tumors, relapse may occur.^{13,36,41}

Despite the myriad of symptoms in NMDAR encephalitis and frequency of seizures, brain MRI tends to be normal in the majority of cases.^{17,35,36,41,44} MRI abnormalities have been reported in 23–50% of large cohort studies.⁴⁵ There may be T_2 hyperintensity and swelling involving the MTL or cortex elsewhere, including cingulate gyrus (Figure 1).^{36,40,41,45} Small

defined foci of signal abnormality may be seen within cerebral white matter, thalamus, cerebellum and/or brainstem.⁴⁵ Two reports of patients with isolated dystonia have shown selective signal abnormality involving the bilateral striatum; one of these resolved following immunotherapy⁴⁶ and the second progressed over years to striatal necrosis.⁴⁷ Transient-associated contrast enhancement can be seen within cortex, meninges or basal ganglia (Figure 2).^{36,45} On follow-up MRI imaging after recovery, there may be complete resolution of previous findings, focal cortical atrophy at the site of prior lesions or global volume loss.^{17,36,41,45} Resting state functional MRI and diffusion tensor imaging analyses have detected reduced functional connectivity of the left and right hippocampus and extensive changes of white matter integrity, respectively, in the context of an otherwise normal routine MRI exam.⁴⁸ Additionally, there have been reports of demyelinating syndromes overlapping with NMDAR encephalitis.^{34,45,49} Correlation of MR findings with seizure activity is not always straightforward though best understood in the context of recent seizure semiology and EEG findings.

Metabolic changes on ^{18}F -FDG-PET are also widely variable and have included all the cerebral lobes, including insular cortex, hippocampi, basal ganglia, cerebellum and brainstem.^{22,45,50–52} When correlative to MRI, ^{18}F -FDG-PET will typically demonstrate focal hypermetabolism in sites of acute inflammation; these findings often improve or reverse following recovery. Despite imaging variability, a distinct brain metabolic pattern has consistently been observed during acute/subacute stages of NMDAR dysfunction in which there is relative hypermetabolism in anterior brain regions (frontal or frontotemporal) and relative hypometabolism in posterior brain regions (parietal and/or occipital regions) (Figure 2).^{22,50–52} Yuan et al studied 18 serial PET scans of 8 patients with anti-NMDAR encephalitis. In the acute/subacute phase when patients were experiencing the culmination of their symptoms (including generalized seizure), a severe frontotemporal-to-occipital gradient was observed. In the early recovery phase when antibody level was declining, extensive cortical hypometabolism was seen. For patients in the recovery phase, PET images were nearly normal.⁵²

Anti-VGKCC antibody related AE

The voltage-gated potassium channel complex (VGKCC) is a transmembrane potassium channel that establishes resting membrane potential and generates neuronal action potentials. Recent studies have shown that autoantibodies previously thought to target the VGKCC itself actually target secreted cell surface proteins associated with the complex—primarily LGI1 (leucine rich glioma inactivated 1) and less frequently CASPR2 (contactin-associated protein-2).^{53,54} Although these antibodies are predominately considered non-paraneoplastic, in up to 30% of cases, an underlying tumor has been identified, most commonly SCLC or thymoma.^{14,34,53,55}

Patients with autoantibodies targeting LGI1 (often males over 50 years of age)³⁴ are most likely to exhibit symptoms of LE, including memory loss, disorientation and MTL epilepsy. These patients are known to bear an unusually high seizure burden⁵³; in studies evaluating anti-LGI1 cases specifically, 80–100% present with

Figure 2. Anti-NMDAR AE in a 21-year-old female with history of left temporal focal seizure disorder. (a) Stereotactic surface projections from a PET scan in 2007 shows characteristic pattern of increased frontotemporal-to-occipital gradient. (b) Axial post-gadolinium T_2 FLAIR images obtained in 2014 show left parietal leptomeningeal hyperintensity (arrows). During this time, EEG documented multiple seizures of left and midline central onset during which she had right arm pain, paresthesias and speech difficulty. (c,d) Axial T_2 FLAIR (c) and post-gadolinium (d) T_1 W images from 1 month later show resolution of leptomeningeal abnormality. (e) Stereotactic surface projections from a PET scan also 1 month later show persistent diminished metabolism in the parietooccipital lobes, albeit improved since 2007. EEG at this time showed a moderate degree of focal slowing over the left hemisphere without epileptiform discharges. AE, autoimmune epilepsy; EEG, electroencephalogram; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion-recovery; NMDAR, N-methyl-D-aspartate receptor; PET, positron emission tomography; T_1 W, T_1 weighted.

seizure.^{15,30,54} There is often associated hyponatremia^{15,30,53,55} and seizures may be accompanied by bradycardia and piloerection.³⁴ In a review of antibody-associated epilepsy studies, the majority of reported seizures (>70%) occurring with antibodies targeting the VGKC were of focal onset with secondary generalization.³⁴ Faciobrachial dystonic seizures (FBDS) are a presumed seizure semiology associated with anti-LGI1 antibodies in which patients experience transient episodes of unilateral facial grimacing and arm posturing; this often precedes the development of LE.^{30,56} Patients with anti-CASPR2 antibodies can also develop seizures in the context of LE (Figure 3) though this is a much less common manifestation compared to Morvan's syndrome (encephalopathy with psychiatric symptoms, dysautonomia and neuromyotonia). Anti-LGI1 limbic encephalitis tends to respond well with early immunotherapy; likewise, FBDS has been found to be very sensitive to early corticosteroids and plasma exchange therapy which can prevent later cognitive impairment.^{34,57}

LE associated with either LGI1 or CASPR₂ has typical imaging findings of T_2 /FLAIR hyperintensity and enlargement of one or

both MTLs on MRI in approximately 63–78% of cases (Figures 4 and 5)^{14,30,31,53,54}; the remaining cases have reportedly normal MRI. In a study of 33 VGKC antibody seropositive patients with seizures and MTL T_2 signal abnormality, 28% demonstrated hippocampal enhancement and 43% had hippocampal restricted diffusion.¹⁴ Radiologic progression was also noted with about 29% of MRI exams initially demonstrating normal or unilateral MTL findings progressing to bilateral MTL involvement. Further progression to MTS has been frequently reported. In the aforementioned study, 50% of those with MTL signal abnormality progressed to MTS and this included about two-thirds of those with enhancement and/or restricted diffusion.¹⁴ Extratemporal findings are also seen with anti-LGI1 LE, particularly involving the basal ganglia which most often demonstrates T_2 hyperintensity and diffusion restriction (Figures 4 and 5).^{14,30,53,54,56} MRI in patients with FBDS is also often normal; when abnormalities are present they are typically localized to the basal ganglia.^{57,58} In a study of 26 patients LGI1-Ab seropositivity and FBDS, 11 (42%) had T_2 and/or pre-contrast T_1 hyperintensity in the basal ganglia (Figure 5) with the T_1 hyperintensity persisting longer than the

Figure 3. Anti-VGKC (LG1 subtype) AE in a 51-year-old male who presented with two first-time seizures and abrupt onset aphasia. MRI and PET exams were obtained a week apart at the time of presentation. (a) Coronal T_2 weighted MR image shows symmetric T_2 hyperintensity in the basal ganglia (arrows) as well as additional T_2 hyperintensity in the left mesial temporal lobe (arrowhead). (b) Axial DWI image from the same exam shows corresponding diffusion restriction in the basal ganglia (arrows). (c) Concurrent PET-CT demonstrates marked FDG avidity in the bilateral basal ganglia (arrows). There was also hypermetabolism in the left MTL. (d, e) Axial T_2 FLAIR images from a follow up MRI over one year later showed resolution of signal abnormalities with bilateral caudate (arrows) and left MTL (circle) atrophy following steroid therapy. (f) Axial DWI image from the same exam shows resolution of diffusion restriction. He continues on maintenance AEDs. AE, autoimmune epilepsy; DWI, diffusion-weighted imaging; EEG, electroencephalogram; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion-recovery; MTL, mesial temporal lobes; PET, positron emission tomography; VGKC, voltage-gated potassium channel complex.

T_2 hyperintensity. The authors conclude that T_1 hyperintensity in basal ganglia is a useful biomarker for FBDS.⁵⁸ Signal abnormality has also been reported in a FBDS patient within cortex and subcortical white matter contralateral to side of dystonia.⁴⁵ Additionally, volumetric analyses of post-treatment FBDS patients has shown both hippocampal and whole brain volume loss (despite lack of MRI abnormality outside the basal ganglia) supporting FBDS as a more diffuse process.

^{18}F -FDG-PET obtained in the setting of acute disease often demonstrates hypermetabolism at sites of acutely inflamed parenchyma. In a study of 14 patients with VGKC-complex/LGI1-antibody encephalitis, 71% had signal abnormalities on MRI (64% involving the MTL and 14% involving basal ganglia). 10 of the 14 patients had a corresponding ^{18}F -FDG-PET study. Interestingly, 70% had hypermetabolism in both MTL and basal ganglia, including three patients with previous normal MRI exams.³⁰ This supports the early diagnostic value of ^{18}F -FDG-PET. Additionally, lack of MTL hypermetabolism correlated with better clinical outcome.

Anti-GABA_AR antibody related AE

The GABA_A receptor (GABA_AR) is an inhibitory transmembrane ion in the brain. Antibodies cause a selective reduction in

synaptic GABA_AR. Petit-Pedrol et al newly recognized GABA_AR as a target of autoimmunity in six patients with high concentration of GABA_AR antibodies in serum and CSF and rapidly progressive encephalopathy. All six patients developed refractory seizures or epilepsy partialis continua. An additional 12 patients with low GABA_AR titers displayed a broader array of symptoms suggestive of coexisting autoimmune disorders. The majority of patients with detected GABA_AR antibodies had a good response to immunotherapy.⁵⁹

All six patients with high titers had signal abnormalities on MRI including multifocal cortical and subcortical areas of T_2 hyperintensity.⁵⁹ There is limited information regarding ^{18}F -FDG-PET findings in anti-GABA_AR epilepsy.

Anti-GABA_BR antibody related AE

The GABA_B receptor (GABA_BR) is an inhibitory transmembrane ion most highly concentrated in the hippocampus, thalamus and cerebellum. Antibodies to GABA_BR are associated with seizures, amnesia, behavioral changes and ataxia³⁴ and are often paraneoplastic, most commonly seen with SCLC and neuroendocrine tumors. A majority of patients have T_2 /FLAIR hyperintensity in one or both MTLs on MRI.^{60–63} In an observational study of 15 patients with anti-GABA_BR antibodies, all presented with seizure which were predominately of temporal lobe onset. Seven of these patients had underlying malignancy (SCLC in five cases). MRI was normal in 4 patients and showed MTL T_2 /FLAIR hyperintensity in 10 patients.⁶³ In another observational study of 20 patients, 17 had seizures. Of these, seven had a normal MRI, nine had unilateral or bilateral MTL T_2 /FLAIR hyperintensity and one demonstrated pial enhancement. A case report of a 55-year-old male with anti-GABA_BR antibodies, SCLC and progressive seizures described marked MTL hypermetabolism on ^{18}F -FDG-PET with pronounced hypometabolism in the remaining brain in the context of a normal brain MRI.⁶⁴ A small case series of five patients reported MTL hypermetabolism on ^{18}F -FDG-PET in two patients with concomitant T_2 /FLAIR hyperintensity and widespread cortical hypometabolism in a third patient.⁶⁵ Progression to MTS has been reported with two patients having hippocampal laminar necrosis on MRI.⁶¹ Patients have good response to immunotherapy and/or treatment of an underlying tumor.³⁴

Anti-AMPA antibody related AE

The AMPAR is a cell membrane glutamate receptor important for plasticity and fast synaptic transmission. Anti-AMPA-antibodies have been reported in patients with LE, appear to be mildly epileptogenic and are commonly paraneoplastic. In a literature review of autoimmune epilepsy by Bakpa et al, the most common clinical presentation of patients in the anti-AMPA studies was amnesia, confusion and psychosis; only three of the five studies had patients with seizure.³⁴ The largest of these studies evaluating 22 patients with anti-AMPA encephalitis reported 6 patients (27%) with seizure and 14 patients (64%) with underlying tumor, most commonly lung cancer and thymoma.⁶⁶ Overall, patients tend to have good recovery with immunotherapy and/or tumor therapy.

Figure 4. Anti-VGKCC (LG1 subtype) AE in a 60-year-old male who presented with cognitive decline and faciobrachial dystonic seizures. (a,b) Axial T_2 FLAIR image shows T_2 hyperintensity and enlargement of the left mesial temporal lobe (a, arrow), right caudate and right lentiform nucleus (b, arrow). (c) Pre-contrast T_1 W image from the same exam shows T_1 hyperintensity in the right caudate and superior putamen (arrow). (d) Axial ADC map reveals a corresponding focus of restricted diffusion in the lentiform (arrowhead). (e, f) Axial image from a concurrent FDG-PET exam shows hypermetabolism in the left MTL (e, arrow) indicating acute inflammation and hypometabolism in the right caudate nucleus and superior putamen (f, circle), indicating changes are at least subacute. (g, h) Axial images from an FDG-PET exam 2 years later demonstrates more marked hypometabolism in the right caudate (g, arrow) and resolved hypermetabolism in the left MTL (h). (i) Axial T_2 FLAIR image from an MRI obtained 4 years later shows substantial right caudate atrophy (arrow). Multiple EEGs over the course of 6 years recorded epileptogenic abnormalities over the left frontal and temporal regions and generalized encephalopathy. (Images c and d were previously published in Flanagan EP et al. Basal ganglia T_1 hyperintensity in LG11-autoantibody faciobrachial dystonic seizures. *Neurol Neuroimmunol Neuroinflamm*. 2015;2 (6):e161 and are used with permission). ADC, apparent diffusion coefficient; AE, autoimmune epilepsy; DWI, diffusion-weighted imaging; EEG, electroencephalogram; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion-recovery; MTL, mesial temporal lobes; PET, positron emission tomography; T_1 W, T_1 weighted; VGKCC, voltage-gated potassium channel complex.

The majority of patients with anti-AMPA encephalitis (with or without seizure) have T_2 hyperintensity and swelling of one or both MTL.^{34,67,68} Extension of T_2 signal abnormality to anterior septal nuclei, extratemporal cortex and cerebellum has also been reported.⁶⁹ A case report of serial MRI and ^{18}F -FDG-PET imaging in a female with anti-AMPA LE and generalized seizures demonstrated T_2 hyperintense and hypermetabolic hippocampi which progressed to bilateral MTS and normalized metabolism after antiepileptic treatment.⁶⁷ Another case report of a female with anti-AMPA LE and status epilepticus during pregnancy described bilateral MTL, caudate and insular T_2

hyperintensity. Repeat imaging only 5 days later showed diffuse cortical atrophy; this persisted on later imaging along with concomitant hypometabolism in these areas on ^{18}F -FDG-PET.⁶⁸

ANTIBODIES TARGETING INTRACELLULAR NEURONAL PROTEINS

Anti-GAD antibody related AE

Glutamate decarboxylase (GAD) is an intracellular enzyme expressed in GABA-ergic neurons and pancreatic b-cells which transforms glutamate to GABA. Antibodies targeting GAD

Figure 5. Anti-GAD AE in a 27-year-old male who presented in 2007 with progressive cognitive decline, psychomotor slowing and asymmetrical lower extremity spasticity. He was found to have a GAD-65 level of 175 nmol l^{-1} . (a, b, c) Coronal T_2 FLAIR image from initial MRI (a) demonstrates T_2 hyperintensity in the right MTL and axial T_2 FLAIR image from the same exam (b) shows a focus of T_2 signal abnormality in the cortex of the right parietal lobe. Neither area demonstrated contrast enhancement. Axial T_2 W image of the cerebellum from the same exam (c) shows normal cerebellar parenchyma. An EEG obtained during this month demonstrated a subclinical right temporal seizure and multifocal sharp waves in the right parietal region. (d) Coronal T_2 FLAIR image from 2009 reveals mild persistent T_2 hyperintensity in the right MTL without apparent atrophy. Previous right parietal signal abnormality was resolved. Concurrent EEG recorded seven clinical and electrographic seizures arising over the right temporoparietal head region. (e) Axial T_2 W image of the cerebellum from 2012 shows interval right cerebellar volume loss. (f, g) Axial images from an FDG-PET scan from 2012 reveal hypometabolism in the right MTL and right cerebellum. (h) Axial T_2 W image of the cerebellum from 2016 shows progression in the right cerebellar atrophy, now marked. Currently, he continues on immunotherapy for intractable epilepsy and stiff person syndrome. GAD, glutamic acid decarboxylase; EEG, electroencephalogram; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion-recovery; MTL, mesial temporal lobes; PET, positron emission tomography; T_2 W, T_2 weighted.

prevent synthesis of the major inhibitory neurotransmitter. Anti-GAD is primarily considered a non-paraneoplastic antibody for its infrequent association with an underlying tumor. However, recent studies have identified patients with high titers of GAD antibodies and concomitant malignancy (typically lung, thymic or neuroendocrine).⁷⁰

Seizure is a relatively uncommon presentation in those with anti-GAD positivity, though is more likely to occur in those with high antibody titers and to present as temporal lobe epilepsy with clinical features of LE.^{71–73} Out of 61 patients with high anti-GAD antibody levels, Saiz et al reported four patients (6%) with seizures, three of whom had temporal lobe epilepsy with associated MTS.⁷² Conversely, in a sample of previous studies of patients with unexplained epilepsy, the frequency of those with high anti-GAD titers range from 3 to 5%^{73–75}; in studies

specifically evaluating those with temporal lobe epilepsy, the percentage with high anti-GAD titers is higher at 9–17%.^{71,76} Patients may also experience generalized tonic-clonic or focal seizures during the course of their disease.^{34,74} There is a strong association with other autoimmune diseases, namely Type I diabetes and thyroid disease,^{71–73} as well as comorbidity with other common manifestations of high anti-GAD positivity such as stiff person syndrome and cerebellar ataxia.^{71,72} This epilepsy is often pharmacoresistant, particularly in those with high antibody titers, and immunomodulatory treatment may be needed long term.^{34,71,74}

In those patients presenting acutely with LE, characteristic nonenhancing T_2 /FLAIR hyperintensity and enlargement of amygdala and hippocampi are often observed on MRI (Figure 6). These patients have been found to have significantly greater

Figure 6. Anti-GAD AE in a 74-year-old male with a year of fluctuating encephalopathy and refractory status-epilepticus for two weeks prior to the initial scan. (a) Axial T_2 FLAIR images during period of status-epilepticus shows cortical edema in the left occipital and parietal lobes (arrows). Corresponding EEG reports describe a focal seizure disorder arising from the left posterior, right and midline occipital regions. (b) Axial DWI image shows associated restricted diffusion (arrows). (c) Axial FDG-PET image obtained within one week demonstrates well-defined and markedly increased FDG uptake (SUV maximum 28) which followed the same geographic pattern (arrow). EEG recorded focal non-convulsive status epilepticus with seizures localized to the left posterior head region. This patient passed away 3 weeks later. DWI, diffusion-weighted imaging; EEG, electroencephalogram; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion-recovery; GAD, glutamic acid decarboxylase; MTL, mesial temporal lobes; PET, positron emission tomography; SUV, standardized uptake value; T_2W , T_2 weighted.

hippocampal FLAIR intensity values on post-processed images compared to patients with VGKC and NMDAR antibodies indicating a more severe and chronic affinity of anti-GAD antibodies for the hippocampus and possibly explaining the worse

Figure 7. Anti-Hu AE in a 38-year-old male who initially presented with seizure in 2001 and continued to have intractable complex partial seizures. He also suffered from peripheral neuropathy and short-term memory loss. An EEG in 2008 showed left hemispheric epileptiform discharges. Extensive workup for malignancy was negative. (a) Axial T_2 FSE image obtained in 2001 shows T_2 hyperintensity in the left mesial temporal lobe (arrow). There is already clear atrophy in this region. (b) Axial post-gadolinium T_1W image also from 2001 shows associated faint cortical enhancement (arrow). (c) Axial T_2 FSE image from 2005 demonstrates interval progression of atrophy, now with cystic encephalomalacia (arrow). AE, autoimmune epilepsy; EEG, electroencephalogram; FSE, fast spin echo; T_1W , T_1 weighted.

clinical outcome.⁷⁷ In those with complex partial or focal seizures outside the limbic system or generalized tonic-clonic seizures, T_2 hyperintense and sometimes diffusion restricting lesions can be seen involving cortex in other regions (Figure 7) or within the basal ganglia. These signal abnormalities may be transient or persist for years. In some cases, the involved parenchyma gradually atrophies; progression to MTS can be seen in patients with MTL involvement.^{72,76} A recent diffusion tensor imaging study showed widespread white matter changes in GAD-associated epilepsy which involved various regions of brain; this was in contrast to maintained white matter integrity in VGKC-complex-associated LE.⁷⁸

The general observation from correlative ^{18}F -FDG-PET studies in our experience is that hypermetabolism corresponds to early enlargement/edema of involved parenchyma and hypometabolism corresponds to parenchymal atrophy later in the disease course. This has been corroborated in a few case reports.^{21,79}

Anti-Hu antibody related AE

The Hu antigen is found in the nucleus and cytoplasm of all neurons of the central and peripheral nervous system.⁸⁰ Anti-Hu antibody (ANNA-1), which incites a T-cell mediated attack, was the first onconeural antibody described.⁴² In adults, 77–94% of anti-Hu antibody cases are associated with SCLC.^{80,81} In children, anti-Hu seropositivity is rare and is more likely to present with encephalitis in the absence of an underlying neoplasm^{2,82,83}; when malignancy is present it is usually neuroblastoma.

Patients with anti-Hu antibodies have widespread neurological symptoms with the most common being sensory neuropathy.⁸⁰ LE is seen in 11–20% of cases.^{80,84,85} Two prior studies of anti Hu syndrome reported seizures in 21% (15/71 patients)⁸⁵ and 16% (27/173 patients),⁸⁶ respectively. Epilepsia partialis continua, repetitive focal motor seizures of the hands and face that can persist for days to years, has also been reported. Due to difficulty in controlling these immune responses and the severity of associated cancers, complete recovery of encephalitis is rare and overall prognosis is poor.⁸⁷ In paraneoplastic cases, antitumoral treatment is the best strategy.⁸⁴ Concomitant immunotherapy generally results in little improvement but can help stabilize the disease course.⁸⁸

In LE patients, initial MRI typically shows T_2 hyperintensity and enlargement of the MTL. Over time, there is regression of edema with atrophy of the affected MTL (Figure 8); this seems to occur regardless of treatment. MRI findings in cases of epilepsia partialis continua show multifocal T_2 hyperintensity and enlargement of non-limbic cortical areas,^{89–91} though focal limbic involvement has also been seen.⁹² Focal inflammation may recur and/or the disease may progress to more diffuse parenchymal involvement over the following months to years.^{90,91}

On PET-CT, acutely inflamed brain parenchyma will typically be hypermetabolic. Atrophy of involved areas typically has concomitant decreased ^{18}F -FDG uptake. With anti-Hu antibody AE, PET-CT is particularly useful for detecting underlying

Figure 8. Anti-CRMP-5 AE in a 78-year-old female with new onset seizure. (a) Axial T_2 FLAIR MRI image shows initial edema and enlargement of the left MTL (arrow). (b) Axial FDG-PET image of the chest at presentation shows a hypermetabolic lesion in the right hilum corresponding to primary small cell lung carcinoma (arrow). (c) Axial T_2 FLAIR MRI image 80 days following initiation of chemotherapy shows decreased T_2 hyperintensity and progressive atrophy (arrow). (d) Axial T_2 FLAIR MRI image 260 days later and following radiation therapy for the primary lung malignancy demonstrates atrophy and diminished signal abnormality in the left MTL (arrow). (e) Axial FDG-PET 3 years later shows focal hypometabolism in the left mesial temporal lobe (arrow); EEG during this same year showed left hemispheric slowing and left frontopolar to temporal seizures. CRMP, collapsin-responsive mediator protein; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion-recovery; MTL, mesial temporal lobes; PET, positron emission tomography.

malignancy early in the disease,²⁰ monitoring for metastases and following the evolution of malignancy after treatment.

Anti-CRMP-5 antibody related AE

CRMP-5 (collapsin-responsive mediator protein-5) refers to a group of five intracellular phosphoproteins found in central and peripheral neurons which play an important role in axon development. Antibodies targeting these proteins incite primarily a cytotoxic T-cell response.^{42,87} CRMP-5 antibody encephalitis is predominately associated with SCLC and, rarely, thymoma.^{93,94}

As opposed to more distinctive non-limbic symptoms described with anti-CRMP-5 antibodies, such as chorea, myoclonus and cerebellar ataxia, LE with seizure is relatively rare. In a study by Yu et al of 116 patients with anti-CRMP-5 encephalitis, seizure was seen in 11 (9%).⁹³ Reported cases have shown stability of encephalitis with immunotherapy with better prognosis if an associated tumor is found and treated.

MRI obtained early in the course of disease may be normal, though tends to show multifocal T_2 hyperintensity in non-limbic

cortex with little or no enhancement (Figure 9).^{95,96} Those patients presenting with hyperkinetic movements often have asymmetric T_2 hyperintensity in the caudate and putamen, usually without enhancement.^{97–99} Patients with LE can demonstrate T_2 hyperintensity and enlargement of the MTL.

On follow-up imaging, signal changes may regress over time with progression to cortical atrophy in the chronic setting. Imaging findings may wax and wane in cases where a primary tumor is never found, with signal abnormalities migrating to different areas of cerebral cortex. Associated enhancement can be seen within areas of T_2 hyperintensity later in the course of disease, potentially due to greater likelihood of blood-brain barrier breakdown from chronic inflammation.^{95,96} For those patients with a detected primary tumor, regression of brain lesions has been seen with tumor resection.

Although there is little in the literature regarding corresponding PET-CT, a few accounts show the typical relative hypermetabolism in areas of increased acute inflammation and hypometabolism in areas of atrophy.

Figure 9. Anti-VGKCC (CASPR2 subtype) AE in a 73-year-old male who presented with partial seizures and memory complaints. (a) Coronal T_2W MRI image at presentation demonstrates T_2 hyperintensity and enlargement of the left amygdala (arrow). (b, c) Ictal (b) and interictal (c) brain SPECT scintigraphy obtained over the two days preceding the MRI shows ictal hyperperfusion in the left MTL which continued to a lesser extent on the interictal scan. MTL, mesial temporal lobes; SPECT, single-photon emission computed tomography; T_2W , T_2 weighted; VGKCC, voltage-gated potassium channel complex.

CONCLUSION

Both MRI and PET can be valuable tools in identifying changes in autoimmune epilepsy and following their evolution. As ^{18}F -FDG-PET is often more sensitive for brain findings in AE, it is recommended to obtain an ^{18}F -FDG-PET study early in the diagnostic workup in the setting of clinically suspected AE, particularly with a normal or equivocal MRI. Inflammation most typically involves limbic structures but is also frequently seen in non-limbic cortex, cerebellum, brainstem and basal ganglia. Identification of focal edema/inflammation on MRI and/or metabolic change on ^{18}F -FDG-PET in the acute setting may enable prompt initiation of immunotherapy and trigger the search for underlying neoplasm. At this time it is not routine to consider autoimmune etiologies, though with growing evidence, obtaining a paraneoplastic panel and/or initiating immunotherapy in idiopathic epilepsy may improve neurologic function and prevent chronic parenchymal changes such as MTS.

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