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REVIEW ARTICLE

[18F]FDG brain PET and clinical symptoms in different autoantibodies of autoimmune encephalitis: a systematic review

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Abstract

Introduction Autoimmune encephalitis (AE) is caused by the antibodies that target receptors and intracellular or surface proteins. To achieve the appropriate therapeutic results, early and proper diagnosis is still the most important issue. In this review, we provide an overview of FDG-PET imaging findings in AE patients and possible relation to different subtypes and clinical features.

Methods PubMed, Web of Science, and Scopus were searched in August 2021 using a predefined search strategy.

Results After two-step reviewing, 22 studies with a total of 332 participants were entered into our qualitative synthesis. In anti-NMDAR encephalitis, decreased activity in the occipital lobe was present, in addition, to an increase in frontal, parietal, and specifically medial temporal activity. Anti-VGKC patients showed altered metabolism in cortical and subcortical regions such as striata and cerebellum. Abnormal metabolism in patients with anti-LGI1 has been reported in diverse areas of the brain including medial temporal, hippocampus, cerebellum, and basal ganglia all of which had hypermetabolism. Hypometabolism in parietal, frontal, occipital lobes, temporal, frontal, and hippocampus was observed in AE patients with anti-GAD antibodies.

Conclusion Our results indicate huge diversity in metabolic patterns among different AE subtypes and it is hard to draw a firm conclusion. Moreover, the timing of imaging, seizures, and acute treatments can alter the PET patterns strongly. Further prospective investigations with specific inclusion and exclusion criteria should be carried out to identify the metabolic defect in different AE subtypes.

Keywords Autoimmune encephalitis · FDG-PET · Anti-NMDAR encephalitis · Anti-LGI1 · Anti-VGKC

Introduction

Encephalitis is defined as inflammation of the brain and although there are many causes, the main etiologies can be categorized into two main categories: autoimmune and infectious [1]. Autoimmune encephalitis (AE) is caused by the antibodies that target receptors and intracellular or surface proteins [1]. AE commonly refers to a group of similarly related disease processes which share overlapping neuroimaging findings and clinical features but are differentiated by specific antibody subtypes that initiate the underlying immune attack on different structures of the central nervous system [2, 3].

AE associated antibodies can be subclassified into two groups: antibodies against synaptic proteins and neuronal cell-surface, like the leucine-rich, glioma-inactivated glycoprotein (LGI1), the gamma-aminobutyric acid (GABA)

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receptor, and the N-methyl-D-aspartate (NMDA) receptor and antibodies against intracellular antigens, like anti-glutamic acid decarboxylase 65 (GAD65), CV2/collapsin response mediator protein 5 (CRMP5), Ma2/Ta, and Hu/antineuronal nuclear antigen type 1 (ANNA-1) [4, 5].

Some clinical symptoms pointing to AE are sleep disturbance, psychiatric symptoms, and subacute memory loss [6]. AE is a challenging clinical diagnosis because of the similarities of the clinical, laboratory, and imaging findings with other types of central nervous system infections [7]. Neuroimaging findings play an important role in the evaluation of cases with suspected encephalitis [8]. It can confirm the diagnosis of encephalitis, indicate specific etiologies, or identify other conditions that mimic encephalitis [8]. Positron emission tomography (PET) is a noninvasive imaging technique that has a wide range of clinical and research applications in the pathophysiology of a variety of brain disorders, including brain tumors, psychiatric disorders, seizures, epilepsy, infection, and neurodegenerative disorders, as well as the study of the normal brain [9]. 18F-fluorodeoxyglucose [18F](FDG) was developed in 1976 to study the glucose metabolism of the brain [10]. Currently, FDG-PET is frequently utilized in nuclear medicine with the growing indication in neurology, cardiology, and oncology [9]. Based on the literature review, in all encephalitis cases, magnetic resonance imaging (MRI) is preferred over computed tomography (CT) because of more sensitiveness and specificity. Advanced brain imaging with SPECT or PET has shown promising results in detecting specific metabolism patterns in patients with Caspr2, LGI1, NMDAR, or other autoantibodies encephalitis [8, 11, 12].

To achieve the appropriate therapeutic results, early and proper diagnosis is still the most important issue [13]. In this review, we provide an overview of FDG-PET imaging findings in AE patients and possible relation to different types and clinical features. Furthermore, our results may help clinicians to better diagnose and also predict future clinical symptoms of subjects with AE.

Methods and materials

The present systematic review study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14].

Search strategy

The PubMed, Web of Science, and Scopus were searched in August 2021 using search strategy consisting of (autoimmune encephalitis OR Limbic encephalitis OR anti-NMDAR encephalitis OR anti-AMPAR encephalitis OR anti-GABA-AR encephalitis OR anti-GABA-BR encephalitis OR anti-LGI1 encephalitis OR anti-CASPR2 encephalitis OR anti-GAD encephalitis OR anti-GlyR encephalitis OR anti-DPPX encephalitis OR anti-mGluR encephalitis OR Hashimoto's encephalitis OR and steroid-responsive encephalopathy associated with autoimmune thyroiditis) AND (positron emission tomography OR PET scan).

Eligibility criteria

We included publications that reported PET features and clinical status of AE patients. We excluded studies with other types of encephalitis, unconfirmed cases of AE, and case report studies.

Study selection

Two reviewers (A.S and A.S) independently screened the title and abstracts according to our eligibility criteria. Next, the same reviewers retrieved and screened the full text of the remaining studies for final selection. Any disagreements were resolved by the third investigator (F.N) at the end of each step.

Data extraction

The following data were extracted from entered studies by the two reviewers (A.S and A.S): author, year of publication, region, study design, sample size, mean age, number of males, type of AE, PET imaging findings, clinical symptoms, and treatments.

Quality assessments

The quality of included studies was assessed using the Newcastle–Ottawa scale (NOS). Risk of bias of case–control studies assessed in the several domains such as selection, comparability, and exposure, while in cohort studies risk of bias in selection, comparability, and outcome which the highest possible score was 8.

Data synthesis and analysis

The data of entered studies were qualitatively compared and summarized.

Results

Study screen

Our literature search and manual addition yielded 630 papers after duplicate removal. At the first step of screening, 489 studies were excluded and the remaining papers

were further reviewed accurately and finally, 22 studies with a total of 332 participants were entered into our qualitative synthesis (Fig. 1).

Study characteristics and a qualitative summary

Included studies were conducted in China ($n=7$), USA ($n=4$), Germany ($n=4$), South Korea ($n=2$), India ($n=1$), Spain ($n=1$), France ($n=1$), Mexico ($n=1$), and Denmark ($n=1$). Among included cases, there were anti-LGI1 ($n=144$), anti-NMDAR ($n=103$), anti-GAD ($n=22$), anti-GABA ($n=14$), anti-VKGC ($n=23$), anti-Hu ($n=9$), anti-CASPR2 ($n=4$), and anti-Ma2 ($n=2$) (Table 1). There was no study of acute disseminated encephalomyelitis (ADEM) which met our eligibility criteria. The included studies were published between 2005 and 2021.

Moreover, all included studies were identified as high quality with a mean score of 7.36 according to NOS criteria (Table 2).

PET findings in anti-LGI1 encephalitis

The four of 22 studies that examined PET imaging in anti-LGI1 encephalitis patients found hypermetabolism in the hippocampus which was along with memory deficits, pyramidal signs, mood disorders, and seizures [15–18]. Furthermore, six investigations reported hypermetabolism in basal ganglia in patients with psychiatric symptoms [15, 19], hyponatremia [15, 20], cognitive deficits [20, 21], and focal seizures [19, 22, 23]. The metabolic alteration was also observed in cortical regions such as the temporal lobe. In four studies, there was affected glucose uptake in the medial temporal lobe in AE patients with clinical symptoms including behavioral changes [24, 25], memory deficits [22], confusion [24, 25], sleep disorders [24], hyponatremia [20], psychiatric symptoms [19], and seizures [23, 26]. Also, other cortical regions such as frontal, parietal, occipital, cingulate gyrus, and paracentral lobule were described with abnormal metabolism [19–21, 23, 26]. These patients mainly displayed memory loss, cognitive impairment, seizure, and psychiatric symptoms. Moreover, two studies found hypermetabolism in the cerebellum in patients with loss of consciousness [19, 27]. Also, there were other reports of amygdala and

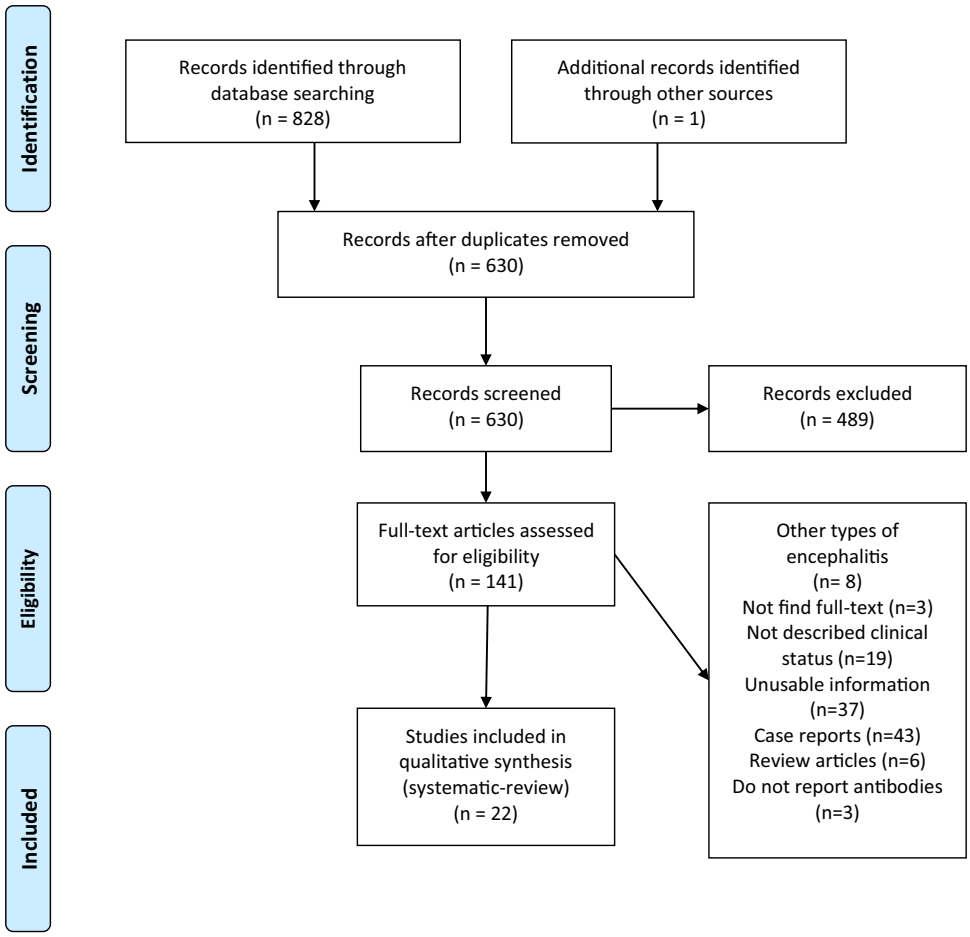

Fig. 1 PRISMA flow diagram depicting the flow of information through the different phases of a systematic review

Table 1 Demographic and clinical characteristics of included studies

Author	Year	Region	Study design	Sample size	Mean age	Males	AE subtype
Li et al	2021	China	Case–control	33	60.5 (median)	22	Anti-LGI1
Liu et al	2020	China	Case–control	34	61 (median)	24	Anti-LGI1
Masangkay et al	2014	USA	Case–control	10	50.9	4	Anti-Hu ($n=2$) Anti-VGKC ($n=2$) Anti-NMDAR ($n=1$)
Moreno-Ajona et al	2020	Spain	Observational	6	63.5	3	Anti-NMDAR Anti-LGI1 Anti-CASPR2
Newey et al	2016	USA	Observational case series	6	62.5	3	Anti-VGKC (6/7)
				1	22	1	Anti-NMDAR
Shin et al	2013	South Korea	Observational case series	14	58.85	8	Anti-LGI1
Solnes et al	2018	USA		5	27.6	1	Anti-NMDAR
				6	62.8	5	Anti-VGKC
				2	41.5	1	Anti-Ma2
				3	78	2	Anti-Hu
				2	64	2	Anti-LGI1
				3	67	1	Anti-GAD65
				2	27.5	2	Anti-alpha 3ACHR
Tripathi et al	2017	India	Observational case series	16	18.5	6	Anti-NMDAR
				5	59	3	Anti-LGI1
				3	53.3	1	Anti-GAD65
Wegner et al	2014	Germany	Observational case series	4	36.4 (median)	4	Anti-LGI1
				6	68 (median)	0	Anti-NMDAR
Zhu el al	2019	China	Observational case series	7	41	1	Anti-GAD65
Zhu el al	2020	China	Observational case series	14	52	9	Anti-GABA-B
Baumgartner et al	2013	Germany	Case series	18	47.5	8	Anti-VGKC Anti-NMDAR Anti-Hu Anti-GAD65
Celicanin et al	2017	Denmark	Cohort study	16	62	9	Anti-LGI1
Chen et al	2017	China	Case series	18	47	8	Anti-LGI1
Chen et al	2016	China	Case–control	8	54.1	6	Anti-LGI1 (6/8) Anti-CASPR2 (2/8)
Deusch et al	2020	Germany	Case series	20	38	5	Anti-GAD65 (8/20) Anti-LGI1 (2/20)
Fisher et al	2012	USA	Case series	9	48.22	2	Anti-NMDAR (2/9)
Ge et al	2021	China	Observational	24	29	17	Anti-NMDAR
Kerik-Rotenberg et al	2019	Mexico	Case series	33	26.7	18	Anti-NMDAR
Lagarde et al	2015	France	Case–control	6	10	2	Anti-NMDAR
Leypoldt et al	2012	Germany	Case–control	6	21	2	Anti-NMDAR
Jang et al	2018	South Korea	Observational	13	60	10	Anti-LGI1

LGI1, anti-leucine-rich glioma-inactivated 1; *GAD 65*, glutamate decarboxylase 65; *VKGC*, voltage-gated potassium channel antibody; *NR*, not reported

thalamus which were observed in patients with memory deficits and cognitive decline [21, 24] (Tables 3 and 4).

PET findings in anti-NMDAR encephalitis

All studies which described PET findings in anti-NMDAR encephalitis revealed identified metabolic alteration in the temporal lobe. Other cortical regions were also detected with abnormal glucose uptake including such as frontal lobe in subjects with psychiatric symptoms, seizures, memory deficits, and behavioral disorders [19, 20, 25–30]. In addition, parietal, occipital, cingulate gyrus is altered to be altered in anti-NMDAR encephalitis patients [19–21, 26, 27, 29, 30]. A study by Tripathi et al. reported increased metabolism

Table 2 Results of quality assessments

Author, year	Selection	Comparability	Outcome or exposure	Total score
Zhu et al., 2019	3	1	3	7
Ge et al., 2011	4	1	3	8
Deuschet al., 2020	4	1	3	8
Zhu et al., 2020	4	1	2	7
Liu et al., 1989	4	1	2	7
Baumgartner et al., 2013	4	1	3	8
Celicanin et al., 2017	4	1	3	8
Chen et al., 2016	3	1	3	7
Chen et al., 2017	4	1	3	8
Fisher et al., 2012	3	1	3	7
Kerik-Rotenberg et al., 2019	4	1	3	8
Lagarde et al., 2015	3	1	3	7
Leypoldt et al., 2012	3	1	3	7
Masangkay et al., 2014	4	1	3	8
Moreno-Ajona et al., 2020	3	1	3	7
Newey et al., 2016	3	1	3	7
Shin et al., 2013	4	1	2	7
Solnes et al., 2018	4	1	2	7
Tripathi et al., 2017	4	1	3	8
Wegner et al., 2014	4	1	3	8
Li et al., 2021	4	1	2	7
Jang et al., 2018	4	1	3	8

NOS, Newcastle–Ottawa scale

in basal ganglia, thalamus, caudate, and hippocampus, and hypometabolism in the cerebellum in patients with clinical symptoms consisting of seizures, behavioral changes, and cognitive decline [21]. On the other hand, another study found hypermetabolism in the cerebellum [19]. Baumgartner et al. reported AE patients with anti-NMDAR positive which had hypometabolism in temporal lobes, hemispheric cortex, thalamus, and crossed cerebellar diaschisis and hypermetabolism in striata which experienced brainstem syndrome and ataxia (Tables 3 and 4).

PET findings in anti-GAD encephalitis

A study that examined PET imaging as a diagnostic factor for AE found hypometabolism in parietal, frontal, and occipital lobes [26]. Another investigation found the same result in temporal, frontal, and left hippocampus in patients with epilepsy, stiff-person syndrome, cerebellar ataxia, and cognitive impairment [31]. Furthermore, increased activity in medial temporal and basal ganglia, and also decreased metabolism in the parietal lobe were reported in anti-GAD encephalitis patients suffering from behavioral disturbance, cognitive decline, and gait ataxia [21]. Another investigation reported medial temporal metabolic alterations along with nausea and hallucinations [32] (Tables 3 and 4).

PET findings in anti-VGKC encephalitis

Four studies reported PET findings in anti-VGKC encephalitis patients. Medial temporal lobe hypermetabolism and mild diffuse cortical dysfunction were observed in a study that enrolled patients with paraneoplastic anti-VGKC encephalitis who experienced a seizure, memory disturbances, and hypersomnia [33]. The anti-VGKC encephalitis patients in this study experienced memory disturbances, confusion, hyponatremia, and hypersomnia. Another study found bilateral temporal lobe hypermetabolism in these patients along with altered mental status, hyponatremia, and seizures [34]. Also, medial temporal metabolic alterations, hypometabolism in temporoparietooccipital, and hypermetabolism in striata and cerebellum were reported in anti-VGKC encephalitis patients who suffered from gait disturbance, hypomania, somnolence, hallucinations, cognitive deficits, disorientation, attention, and mania [32] (Tables 3 and 4).

Other types of AE

A study reported affected activity in temporal, frontal, occipital, and parietal lobes in patients with anti-CASPR2 encephalitis diagnosed with cognitive impairment and autonomic seizures [20]. Another PET study also described cases with hallucinations and hypometabolism in temporal and occipital cortices [17].

There were few cases of anti-Hu encephalitis. Based on included studies, patients with anti-Hu encephalitis had both hypo- and hypermetabolism in the medial temporal lobe and hypometabolism in cortical regions such as frontal, occipital, and parietal lobes while suffering from motor weakness, distal paresthesia, ataxia, cognitive deficits, memory deficits, altered mental status, seizure, and brainstem syndrome [26, 32, 33].

There were only two cases with anti-Ma2 encephalitis which had hypometabolism in temporal, frontal, occipital, and parietal lobes with cognitive impairment, seizure, and neurological deficits [26] (Tables 3 and 4).

Discussion

This study systematically reviewed the literature on PET studies in patients with AE. We aimed to find possible associations between clinical symptoms and metabolic patterns presented in PET imaging of patients. Our results indicate that there is huge diversity in metabolic patterns among

Table 3 Clinical characteristics and findings of included studies

Author	Year	AE subtype	PET imaging findings	Clinical symptoms	Treatments
Li et al	2021	Anti-LGI1	FIAS group displayed extensive hypermetabolism in the bilateral basal ganglia, paracentral lobule, precentral gyrus (frontal), postcentral gyrus (parietal), MTL (medial temporal lobe), cerebellum, lingual gyrus (occipital lobe), insula, right superior parietal lobule, right cuneus (occipital), and left superior frontal gyrus *low metabolism in the bilateral frontal cortex, parietal cortex, cingulate gyrus, and precuneus (parietal) FBDS-only group, limited hypermetabolism of the bilateral cerebellum and left medial globus pallidus *left middle frontal gyrus, bilateral inferior frontal gyrus, and precuneus (parietal) showed hypometabolism FBDS-plus group also presented a wide range of hypermetabolism, including the brain areas of bilateral basal ganglia, MTL, precuneus and cerebellum, left postcentral gyrus, insula and superior parietal lobule, right substantia nigra, middle occipital gyrus, and cuneus *hypometabolism regions mainly in the bilateral precuneus and right frontal cortex, small areas of the left middle frontal gyrus and posterior cingulate, right inferior parietal lobule and insula were also affected	Cognitive impairment (27/33) Focal impaired awareness seizures (FIAS) (25/33) Faciobrachial dystonic seizures (FBDS)-only (14/33) Focal aware motor seizures (FAMS) (2/33) Focal aware nonmotor seizures (FANMS) (6/33) Generalized tonic–clonic seizures (GTCS) (5/33) Behavioral or mood disorders (20/33) Sleep disorders (19/33) = increased (15/33) + decreased (3/33)	Immunotherapy (GC, IVIG, both) (33 (11, 7, 15))
Liu et al	2020	Anti-LGI1	Patients with faciobrachial dystonic seizure (FBDS) ($n = 17$), basal ganglia-only hypermetabolism (7/17) BG + medial temporal lobe (MTL) hypermetabolism (8/17) MTL-only hypermetabolism (1/17) Normal (1/17) Patients with non-FBDS ($n = 17$): BG + MTL hypermetabolism (12/17) MTL only (2/17) BG only (1/17) Normal (2/17)	FBDS 17 (50) Seizures (except FBDS) 33 (97) Memory loss 30 (88) Psychiatric symptoms 20 (59) Depression 3 (9) Hallucinations 9 (26) Disorder of behavior 8 (24) Somnipathy 17 (50) Hyponatremia, *n* (%)a 22 (65) Tumors, *n* (%) 1 (3)	All 34 patients (100%): first-line immunotherapy, including IV immunoglobulin (IVIG), IV methylprednisolone (IVMP), and oral steroids (for at least 6 months): 26 patients (76%) were administered IVIG in combination with IVMP—3 patients (9%) used isolated IVIG and 5 patients (15%) received IVMP alone Only 1 patient was administered azathioprine and mycophenolate mofetil (MMF) due to the progression of the disease

Table 3 (continued)

Author	Year	AE subtype	PET imaging findings	Clinical symptoms	Treatments
Masangkay et al	2014	Anti-Hu	Mesial (medial) temporal lobe hypermetabolism, L > R; generalized decreased cortical uptake, preservation of primary motor/sensory cortex	Memory and cognitive difficulties (confabulation, confusion, disinhibition) motor weakness, distal paresthesias, weakness, ataxia	
		Anti-NMDAR	Hyperintensity of b/l anterior temporal lobes	Decreased appetite, anxiety and insomnia (3 weeks); progressive confusion, altered cognition and inappropriate laughing and crying Baseline + 1 month (admitted to psychiatry at outside hospital): agitated, labile, anxious and depressed, illogical and disorganized thought processes. During admission, she had poor intake and rapid decline of cognitive status and became stuporous. Four days after admission, generalized tonic–clonic seizures requiring intubation	
		Anti-VGKC	b/l mesial temporal lobe hypermetabolism; mild diffuse cortical dysfunction, including visual cortex	Four-week history of difficulty writing checks, confusion, short-term memory loss, but no delirium. Temporal lobe seizures (odd smell, episodes of diaphoresis, flushing, bending knees, palinopsia). Five weeks between symptoms and diagnosis; hyperexcitability, muscle twitching (fasciculations without undulating myokymia or neuromyotonia), myoclonus, memory disturbances, hypersomnia	

Table 3 (continued)

Author	Year	AE subtype	PET imaging findings	Clinical symptoms	Treatments
Moreno-Ajona et al	2020	Anti-NMDAR	Hypermetabolism of L temporal, medial frontal, insula, PC, L&R parietal, cerebellum Hypometabolism of L&R frontal, R temporal, occipital, L&R motor cortex	Cognitive impairment Acute episodes of behavioral disorders and hallucinations (behavioral disorder) followed by status epilepticus (seizure)	Immunoglobulins 0.4 g/kg/day and methylprednisolone 1 g/day for 5 days
		Anti-LGI1	Hyper: L&R basal ganglia, cerebellar vermis, L&R MTL Hypo: L&R lateral frontal, lateral temporal, parietal, posterior cingulate	Facio-brachial seizures—cognitive impairment—hyponatremia	Immunoglobulins 0.4 g/kg/day and methylprednisolone 1 g/day for 5 days + rituximab
			Hyper: L&R MTL, cerebellar vermis, motor cortex, L&R Hypo: L&R frontal, R parietal, L&R posterior cingulate	Facio-brachial seizures—COGNITIVE impairment—hyponatremia	Immunoglobulins 0.4 g/kg/day and methylprednisolone 1 g/day for 5 days
		Anti-CASPR2	L&R medial temporal lobe R frontal	Cognitive impairment—autonomic seizures	Immunoglobulins 0.4 g/kg/day and methylprednisolone 1 g/day for 5 days + rituximab
			Hyper: L MTL, parieto-occipital Hypo: L&R fronto-temporal	Cognitive impairment—autonomic seizures	immunoglobulins 0.4 g/kg/day and methylprednisolone 1 g/day for 5 days
Newey et al	2016	Anti-VGKC (voltage-gated potassium channel antibody)	Left or right or bilateral temporal lobe hypermetabolism	Altered mental status (4/6) Hyponatremia (3/6) Autonomic seizure (1/6) Complex partial seizure (1/6) Gelastic seizure (1/6) Tonic seizure (1/6) Elevated microsomal and thyroglobulin antibodies (1/6) Flu-like symptoms (1/6)	IVMP, 1 g of intravenous methylprednisolone PLEX, plasma exchange IVIG = 0.4 g/kg/d of intravenous immunoglobulin IVIG
		Anti-NMDAR	Bilateral temporal lobe hypermetabolism	Psychosis	IVMP × 5, PLEX × 10 d, IVIG × 5, cyclophosphamide, prednisone 5 qd
Shin et al	2013	Anti-LGI1	Hypermetabolism: bilateral mT (3/14), left mT (4/14), bilateral BG (7/14) mT = medial temporal lobe; BG = basal ganglia Diffuse hypometabolism (1/14)	FBDS (faciobrachial dystonic seizure) (10/14), seizure (10/14), memory impairment (9/14), confusion (7/14), abnormal behavior (4/14), decreased mentality (2/14), insomnia (3/14), constipation (2/14), urinary incontinence (2/14)	MPd (11/14), IVIg (8/14), plasmapheresis (1/14), rituximab (3/14), tacrolimus (2/14), oral prednisolone (2/14), azathioprine (2/14), cyclophosphamide (1/14) MPd = intravenous methylprednisolone pulse therapy 500 mg or 1 g for 5 days; IVIg = intravenous immunoglobulin, 400 mg/kg for 5 days

Table 3 (continued)

Author	Year	AE subtype	PET imaging findings	Clinical symptoms	Treatments
Solnes et al	2018	Anti-NMDAR	Hypometabolism in parietal, temporal, frontal, occipital	Altered mentation or impaired working memory (23/23), focal neurologic deficits (21), seizures (13)	Steroid therapy (8 patients), intravenous immunoglobulins, and steroid therapy (2 patients); antibiotic and steroid therapy (1 patient); benzodiazepine therapy (3 patients); plasmapheresis (1 patient); plasmapheresis and steroid therapy (1 patient); or cellcept (1 patient)
		Anti-VGKC	Hypometabolism: parietal (5/6)—frontal (4/6)—temporal (3)—occipital (3) Hypermetabolism: temporal (R), frontal (R), occipital (R)		
		Anti-Ma2	Hypometabolism: parietal (2/2), temporal (2/2), frontal (R, L) (2/2), occipital (2/2)		
		Anti-Hu	Hypometabolism: parietal (1/3), frontal (R, L) (2/3), occipital (2/3) Hypermetabolic: PAR (R, L), TMP (R, L), FRT (R, L), OCC (R, L)		
		Anti-LGI1	Hypometabolism in parietal, temporal, frontal, occipital		
		Anti-GAD65	Hypometabolism in parietal, frontal, and occipital		
Tripathi et al	2017	Anti-NMDAR	Hypermetabolism: basal ganglia (6/16), superior temporal gyrus (1), thalamus (1), posterior cingulate cortex (1), caudate (1), hippocampus (1), occipital (1), Hypometabolism: parieto-occipital (5/16), cerebellum (5/16), basal ganglia (1)	Seizures (11/16), behavioral changes (4), cognitive decline (1)	
		Anti-LGI1	Hypermetabolism: basal ganglia (4), medial temporal (3), thalamus, anterior cingulate cortex Hypo: parietal (1) + frontal (1) + temporal (1) + posterior cingulate cortex (1)	Rapidly progressive dementia FBDS seizure recent onset memory loss cognitive decline	
		Anti-GAD65	Hyper: MT + BG Hypo: parietal, temporal	Acute onset behavioral disturbance, cognitive complaints + gait ataxia, symmetrical gait ataxia	

Table 3 (continued)

Author	Year	AE subtype	PET imaging findings	Clinical symptoms	Treatments
Wegner et al	2014	Anti-LGI1	Hypermetabolism: cerebellum, bilat. putamen, pallidum right, precentral, frontal mid., sup. right, putamen, pallidum left, occipital inf., mid., calcarine right, parietal supramarginal, angular, temporal sup. right, calcarine, occipital mid., sup. left, paracentral lobule, precuneus left, temporal inf. left Hypometabolism: cingulum ant. bilat., mid. frontal sup. med., med. orbital right	Psychiatric symptoms (1), cognitive deficits (6), focal seizures (4)	Methylprednisolone (4), plasmapheresis (3), immunoglobulins (2), cyclophosphamide (1)
		Anti-NMDAR	Hypermetabolism: hippocampus, parahippocampal, temporal sup., fusiform gyrus left, frontal inf., operculum, insula right, gyrus rectus, frontal supra-orbital, left, cerebellum left Hypometabolism: precuneus bilat., post. + mid. cingulum bilat., cuneus, calcarine left, parietal superior, precuneus bilat., parietal sup. bilat., precuneus bilat. parietal inf., postcentral right, pre-, postcentral, frontal mid. left, frontal mid, sup. right, occipital mid., inf. lingual, left parietal supramarginal, inf. right Parietal supramarginal, temporal sup., mid. left (77 voxels in BA 22) Postcentral left (73 voxels in BA 1, 2, 3, 4) Frontal sup. left, suppl. mot. area bilat. (60 voxels in BA 6) Temporal inf., mid. right (48 voxels in BA 20, 37)	Psychiatric symptoms (6), generalized seizures (6)	Methylprednisolone (6), plasmapheresis (4), immunoglobulins (3), azathioprine (1), cyclophosphamide (4), rituximab (3)
Zhu el al	2019	Anti-GAD65	Hypometabolism: bilateral temporal lobe (4/7) R temporal lobe (1/7) Frontal lobe (3/7) Left hippocampus (1/7) L temporal lobe (1/7)	Chronic epilepsy (5/7) Limbic encephalitis (cognitive impairment, especially impaired memory) (3/7) Stiff person syndrome (waist stiffness, difficulty walking, difficulty lifting the lower limbs, unstable walking, paroxysmal muscle spasms, and even paroxysmal falls) (3/7) Cerebellar ataxia (speech disorders, dysarthria, and walking instability) (2/7)	0.4 g/kg/day of gamma globulin for 5 days (5/7) Methylprednisolone sodium succinate (1000 mg 3 d, 500 mg 3 d, 250 mg 3 d, 120 mg 3 d), then changed to oral prednisone acetate 48 mg, 1 tablet every 2 weeks decreased in the first month, and 1 tablet every week decreased thereafter. 2 rounds (6/7) Levetiracetam: 250 mg bid. (3/7) Mycophenolate mofetil (2/7)

Table 3 (continued)

Author	Year	AE subtype	PET imaging findings	Clinical symptoms	Treatments
Zhu el al	2020	Anti-GABA-B	Metabolism of cerebral cortex (except deep occipital cortex) was decreased (1/14) The metabolism of left hippocampus, left temporal lobe, bilateral basal ganglia were increased (1/14) Bilateral lenticular nucleus and bilateral hippocampal metabolism increased (1/14) The metabolism of the left posterior central gyrus was decreased (1/14) The metabolism of the left angular gyrus, the left superior marginal gyrus and the left temporal lobe was decreased, the metabolism of the left hippocampus was increased (1/14) Metabolism of the medial and basal ganglia of both temporal lobes was increased (1/14) The metabolism of the medial temporal lobe, amygdala and hippocampus increased (1/14) The metabolic distribution of bilateral temporal lobe was slightly uneven (1/14)	Epilepsy (gtcs (12/14), cps (7/14)) (14/14) Cognitive function impairments (poor memory, especially related to decreased recent memory abilities and slow responses) (11/14) Mental behavioral abnormalities (nonsensical and forced behaviors. Four patients slept more, whereas two were restless and did not sleep at night) (9/14)	
Baumgartner et al	2013	Anti-VGKC (7/18)	Mesial temporal metabolic alterations, hypometabolism temporoparietooccipital, hypermetabolism in striata and cerebellum	Gait disturbance, hypomania, somnolence, hallucinations, cognitive deficits, disorientation, attention, mania	NR
		Anti-NMDAR (3/18)	Hypometabolism: temporal lobes Hypometabolism left hemispheric cortex and thalamus and (less pronounced) right temporal lobe; crossed cerebellar diaschisis (right); hypermetabolism in striata	Brainstem syndrome, ataxia	
		Anti-Hu (2/18)	Mesial temporal metabolic alterations Hypometabolism: association cortices	Brainstem syndrome	
		Anti-GAD65 (1/18)	Mesial temporal metabolic alterations	Nausea, hallucinations	

Table 3 (continued)

Author	Year	AE subtype	PET imaging findings	Clinical symptoms	Treatments
Celicanin et al	2017	Anti-LGI1	Hypermetabolism: bilateral hippocampal (4/9)	Memory deficits (7/16)	Corticosteroids
			Hypermetabolism: unilateral hippocampal (3/9)	Seizure (6/16)	IVIg
			Hypometabolism: focal	Hyponatremia (9/16)	Plasma exchange
			Hypometabolism: unilateral hippocampal (1/9)	FBDS (4/16)	Azathioprine
				Personality changes (4/16)	
				Mood disorder (4/16)	
				Hallucinations (4/16)	
				Autonomic dysfunction (4/16)	
Chen et al	2017	Anti-LGI1	Hypermetabolism: left amygdala	Memory deficits (18/18)	Corticosteroids
			Mesial temporal metabolic alterations	Confusion (17/18)	IVIG
				Sleep disorder (6/18)	
				Hyponatremia (8/18)	
Chen et al	2016	Anti-LGI1 (6/8)	Hypermetabolism: hippocampus	Memory deficits (4/8)	Corticosteroids
				Pyramidal signs (6/8)	Antiepileptic drugs
				Seizures (6/8)	IVIg
		Anti-CASPR2 (2/8)	Hypometabolism: left temporal and occipital cortices	Hallucination (4/8)	
Deusch et al	2020	Anti-GAD65 (8/20)	Hypometabolism: right amygdala (1/20) GAD	seizures	
		Anti-LGI1 (2/20)	Hypermetabolism: right amygdala (3/20) 2GAD + 1LGI1	Memory deficits	
			Hypermetabolism: hippocampus (2/20) 1GAD + (1) LGI1	Behavioral changes	
			Hypermetabolism: bitemporal (3/20 2GAD) + (1)LGI		
			Hypermetabolism: biparietal (3/20) 2GAD + (1)LGI1		
			Mesial temporal metabolic alterations (2/20)		
Fisher et al	2012	Anti-NMDAR (2/9)	Temporal hypermetabolism, s hypothalamic hypermetabolism, hypometabolism in occipital cortex, hypermetabolism in orbitofrontal cortex	Several days memory loss, probable seizures, progression to nearly unresponsive state; dysautonomia, acute psychosis (paranoia, delusion, hyper religiosity), agitation, then reduced responsiveness	Corticosteroids

Table 3 (continued)

Author	Year	AE subtype	PET imaging findings	Clinical symptoms	Treatments
Ge et al	2021	Anti-NMDAR	Hypometabolism: occipital lobes (17/24)	Psychiatric symptoms	Antiepileptic drug
			Hypermetabolism: basal ganglia (16/24)	Seizures	Anti-viral drugs
			Hypermetabolism: frontal lobe (9/24)	Cognitive impairment	
			Alternation metabolism in temporal lobe (21/24)	Confusion	
Kerik-Rotenberg et al	2019	Anti-NMDAR	Hypermetabolism: frontal lobe	Seizures	Corticosteroids
			Hypermetabolism: temporal lobe	Mutism	IVIG
			Hypermetabolism: striatum	Athetosis	Rituximab
			Hypometabolism: occipital (33/33)	Unconsciousness	
			Hypometabolism: parietal lobes (29/33)	Catatonia (23/33)	
Lagarde et al	2015	Anti-NMDAR	Hypometabolism: temporal lobes (5/6)	Seizures (6/6)	Corticosteroids
			Hypometabolism: occipital lobes (6/6)	Loss of Consciousness (5/6)	IVIG
			Hypometabolism: frontal lobes (5/6)	Behavioral changes (6/6)	Intra-thecal methotrexate injections
			Hypermetabolism: basal ganglia (3/6)	Movement disorder (6/6)	Plasma exchange
			Normal metabolism in parietal lobes (5/6)	Speech disorder (6/6)	Rituximab
				Loss of consciousness	
Leypoldt et al	2012	Anti-NMDAR	Hypermetabolism: temporal lobes (6/6), (4/6) unilateral + (2/6) bilateral	Memory deficits	IVIG
			Hypermetabolism: frontal lobes (6/6), (3/6) basal + (3/6) lateral	Psychiatric symptoms	Plasma exchange
			Hypometabolism: bioccipital lobes (3/6)	Seizures	Rituximab
				Loss of consciousness	Cyclophosphamide
			Hypermetabolism: cerebellum (3/6)	Movement disorder	
Jang et al	2018	Anti-LGI1	Hypermetabolism: hippocampus (13/13), (2) bilateral + (11) unilateral	Memory deficits (13/13)	
			hypermetabolism: basal ganglia (13/13), (6) bilateral + (7) unilateral	Psychiatric symptoms (9/13)	
				Hyponatremia (5/13)	

LGI1, anti-leucine-rich glioma-inactivated 1; *GAD 65*, glutamate decarboxylase 65; *NR*, not reported

Table 4 Main FDG-PET findings in AE subtypes

AE subtype	Main PET findings	Clinical symptoms
Anti-NMDAR	Metabolic alteration (both hypo- and hypermetabolism) in the temporal lobe, frontal lobe, parietal, occipital, thalamus, and cingulate gyrus. Hypermetabolism in basal ganglia, caudate, and hippocampus, and striata hypometabolism in the cerebellum	Anxiety, insomnia, cognitive deficits, seizure, behavioral disorders, hallucinations, psychosis, neurologic deficits, brainstem syndrome, ataxia, loss of consciousness, movement disorder, speech disorders, and memory deficits
Anti-LGI1	Hypermetabolism in the hippocampus and basal ganglia. Affected glucose uptake in cortical regions such as the temporal lobe, frontal, parietal, occipital, cingulate gyrus, and paracentral lobule. Metabolic alteration (both hypo- and hypermetabolism) in amygdala and thalamus	Cognitive deficits, seizure, behavioral disorders, sleep disorders, hallucinations, depression, memory deficits, psychiatric symptoms, hyponatremia, confusion, and autonomic dysfunction
Anti-GAD	Hypometabolism in parietal, frontal, occipital lobes, temporal, frontal, and left hippocampus. Metabolic alteration (both hypo- and hypermetabolism) in medial temporal and basal ganglia	Altered mental status, seizure, neurologic deficits, memory deficits, cognitive deficits, behavioral disorders, ataxia, gait impairment, nausea, and hallucinations
Anti-VGKC	Hypermetabolism in striata and cerebellum, mild diffuse cortical dysfunction, hypometabolism in frontal, parietal, occipital, and metabolic alteration (both hypo- and hypermetabolism) in temporal	Memory deficits, confusion, seizure, hypersomnia, muscle twitching, hyponatremia, altered mental status, gait disturbance, hypomania, somnolence, hallucinations, cognitive deficits, disorientation, attention deficits, and mania
Anti-CASPR2	Metabolic alteration (both hypo- and hypermetabolism) in temporal, frontal, occipital, and parietal lobes	Cognitive deficits, seizure, and hallucination
Anti-Hu	Hypermetabolism in temporal, frontal, occipital, and parietal lobes, and metabolic alteration (both hypo- and hypermetabolism) in mesial temporal	Motor weakness, distal paresthesia, ataxia, cognitive deficits, memory deficits, altered mental status, seizure, and brainstem syndrome
Anti-Ma2	Hypermetabolism in temporal, frontal, occipital, and parietal lobes	Altered mental status and seizure
Anti-GABA	Hypermetabolism in temporal lobes	Cognitive deficits, memory deficits, altered mental status, behavioral disorders, and sleep disorders

LGI1, anti-leucine-rich glioma-inactivated 1; *GAD*, glutamate decarboxylase; *VKGC*, voltage-gated potassium channel antibody

different AE subtypes. Altered glucose uptake in cortical regions was observed in all most subtypes. However, there were some unspecific metabolic changes such as hypometabolism in the cerebellum in anti-NMDAR and metabolic alteration of the amygdala and thalamus in anti-LGI1. A reason for these findings may be the larger sample size and higher number of studies that investigated the FDG-PET in anti-NMDAR and anti-LGI1. Our findings also showed a similar metabolic pattern for anti-CASPR2, anti-Hu, anti-Ma2, and anti-alpha 3ACHR. These results should be interpreted carefully due to the small sample size and the low number of studies.

Anti-NMDAR

In almost all of the studies on anti-NMDAR encephalitis, decreased activity in the occipital lobe was present, in addition, to an increase in frontal and temporal (specifically medial temporal) activity. Some studies reported this pattern as an increased frontal to the occipital gradient in glucose metabolism [29]. Decreased occipital metabolism seems like a reliable result being reported recurrently and its correlation with patients' visual acuity has been proved [35]. Ge et al. found that this pattern could differ in patients with distant triggers; in anti-NMDAR encephalitis patients with cryptogenic etiology, an asymmetric increase in frontotemporal metabolism was found [28]. It contrasts the paraneoplastic encephalitis with symmetric increased metabolism in these regions. In patients whose viral infection triggered their encephalitis, hypermetabolism in temporal areas correlated with abnormalities in MRI while no specific MRI pattern has been found in anti-NMDAR encephalitis patients and 70% of patients come up with normal MRI results [28]. The reported correlation can be explained by inflammatory reactions and T-cell mediated necrosis in these areas following the viral infection.

In children with anti-NMDAR encephalitis, the same pattern was observed besides that increased activity in basal ganglia was also reported which was correlated with movement disorders in this group [30]. On the other hand, in older patients in this AE subgroup, diffuse cortical hypometabolism was observed, a pattern that resembles what is seen in neurodegenerative diseases. These patients had cognitive problems that cannot be only due to encephalitis [21].

Patients usually suffered from cognitive disorders such as memory dysfunction, psychiatric symptoms, behavioral disorders, and seizure. Given the important role of frontal and temporal lobe networks in cognitive processes and regulation of behavior, these symptoms can be partially explained [36]. Studies have reported reduced functional connectivity between medial frontal and hippocampus and within medial temporal lobe networks. In addition, NMDAR has its highest expression in the frontal lobe and hippocampus and its specific role in learning has been fully investigated [37, 38]. Internalization of NMDAR followed by the increased amount of extra-cellular antibodies and T-cell mediated responses against intra-cellular antibodies were proposed as pathophysiologic reasons of dysfunctions in these regions [37]. Regarding epilepsy, the temporal lobe is the most common origin of epilepsy and the epileptogenic characteristics of patients can be justified by temporal lobe dysfunctions.

Anti-LGI1

LGI1 is a glycoprotein secreted from presynaptic neurons and is related to VGKCs. One in seven patients with anti-VGKC encephalitis has LGI1 antibodies [19]. Abnormal metabolism in patients with LGI1 has been reported in diverse regions of the brain including medial temporal, hippocampus, cerebellum, and basal ganglia all of which had hypermetabolism. However, hypermetabolism in the basal ganglia was the most prominent in patients with faciobrachial dystonic seizures (FBDS). As FBDS is characteristic of encephalitis with VGKC/LGI antibodies [39], movement features of FBDS may be attributed to basal ganglia dysfunction. However, this claim needs robust investigations [40]. Overall, anti-LGI1 induced metabolic changes depend on disease course, diagnosis time point, treatment regimen, and initiation time [19]. The diverse results may be due to a higher number of investigations with different methodologies and heterogenous participants which make it hard to find an association between clinical symptoms and patterns of metabolism changes. Previous studies demonstrated that anti-LGI1 patients commonly have FBDS, hyponatremia, and epileptic seizures [41, 42].

Anti-GAD

Glutamic acid decarboxylase (GAD) is an intracellular synaptic antigen that is exposed to antibodies during vesicle fusion and reuptake [43]. A high level of anti-GAD antibodies is associated with limbic encephalitis and cerebellar ataxia [44]. Based on our review, these patients generally had hypometabolism in cortical regions including parietal, frontal, occipital lobes, temporal, frontal, and hippocampus [16, 21, 32]. Also, they experienced cognitive impairment and behavioral disorders which is logical due to widespread cortical hypometabolism. Furthermore, the metabolic alteration existed in several patients at basal ganglia and cerebellum which resulted in gait impairment and ataxia [21].

Nowadays, PET scans are considered more than before due to several advantages. First, PET scan metabolic patterns are more correlated with clinical symptoms of patients rather than MRI abnormalities [45]. Second, there is an association between the place of the antigens and PET findings, intracellular antigens are more frequent in

mesiotemporal regions and show hypermetabolic patterns while surface antigens are found outside of the limbic lobe and cause diminished activity in those regions [20]. Third, although the volume of literature on the diagnostic accuracy of PET in AE is limited, PET can increase the sensitivity of MRI for the diagnosis of AE. As some subgroups such as anti-NMDAR encephalitis appear normal in MRI or do not present with exclusive findings. Fourth, the activity of NMDAR can be measured and quantified with PET studies, which may give rise to a better understanding of the pathophysiology of this disease and serve as a diagnostic marker [46].

PET is a relatively new imaging technology; therefore, it is not promptly available in clinical practice for all patients. Along with multiple advantages, we have to consider the cost-effectiveness of PET scans which are expensive [47]. Arterial spin labeling (ASL) MR perfusion recently attracted attention as a non-invasive technique that does not require intravenous contrasts. ASL-MRI given results consistent with FDG-PET and it is easily available in clinical practice to early detection of AE [3].

However, there are some challenges in using PET scan in AE. PET results do not have good specificity and altered metabolism can be related to any other condition [46]. More expertise and quantitative measures need to be considered in the analysis of PET results. Using automatic approaches for analysis may be biased based on the normalization site of the brain. In addition, all the results of PET studies should be used with caution, as most of the patients with AE were under treatment and some of these medications such as those used to induce narcosis before PET can decrease the brain metabolism. This effect is based on how long before PET scan the medications have been administered and their pharmacokinetics in the body [19]. Some of the studies had a retrospective design and the delay between symptoms onset and PET scan results differed between patients. A consensus was not reached on the diagnosis of all patients [45]. Small sample size was a drawback of all the studies and given diversity in encephalitis subgroups, conducting larger studies is advisable to substantiate present findings. Moreover, measuring the association of PET findings and clinical symptoms and also the type of AE was not the aim of the included studies.

The use of a wide range of imaging protocols with different resolutions may be one of the reasons for the diverse results of MRI and PET imaging of AE patients [12]. Also, the use of advanced imaging methods is currently limited only to common subtypes of AE which makes it difficult to reach an exact conclusion. Future extension of the imaging methods to all AE variants will pave the way for finding discriminative patterns of different AE subtypes.

Conclusion

In general, as clinical diagnosis of patients with AE may be challenging in some cases, rapid diagnosis and treatment initiation can significantly improve patients' prognoses. Our results indicate huge diversity in metabolic patterns among different AE subtypes and it is hard to draw a firm conclusion. However, the limited use of such imaging techniques in all AE variants and different settings makes it difficult to find discriminative patterns. Moreover, the timing of imaging, epileptic seizures, and acute treatments can alter the PET patterns strongly which were not addressed in our study due to the lack of sufficient demographical information of included studies. Also, neuroimaging features of each AE subtype can lead to more pathophysiological understanding. Further prospective investigations with specific inclusion and exclusion criteria should be carried out to identify the metabolic defect in different AE subtypes.

Declarations

Ethical approval This systematic review has been done in accordance with the rules of the ethical committee of Tehran University of medical sciences.

Conflict of interest The authors declare no competing interests.

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