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SYSTEMATIC REVIEW

^{18}F-FDG-PET and MRI in autoimmune encephalitis: a systematic review of brain findings

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Abstract

Introduction In the diagnostic assessment of autoimmune encephalitis (AE) associated with antineural antibody (Ab) imaging with ^{18}F-fluorodeoxyglucose (FDG), positron emission tomography (PET) was initially only used to screen for occult malignancies in paraneoplastic cases. Today accumulating evidence also supports the use of PET imaging for the objective assessment of metabolic changes in the brain of patients with AE. On the other hand, magnetic resonance imaging (MRI) of the brain reveals a variable picture depending on the specific syndrome and associated antibody, and may be normal in a sizable proportion of patients.

Acquisition of evidence Among all the articles retrieved, we selected only studies and case series describing ^{18}F-PET/CT, or multimodal imaging assessments (with both PET/CT and MRI performed in the same patient) on at least five patients with AE confirmed by the presence of antineural Ab. Studies describing MRI but not PET/CT findings on at least 20 cases were also included to strengthen the morphological considerations.

Summary of evidence We summarize the findings in the literature, commenting on studies involving the use of FDG-PET/CT in patients with AE, focusing on the added value and unsolved issues of using FDG-PET as opposed to MRI, and discussing them in the context of the available diagnostic criteria for AE. We also describe neuroimaging (PET and MRI) differences between AE with Ab against surface antigens vs AE with Ab against intracellular antigens. The timing of neuroimaging after the onset of symptoms is also considered.

Conclusions From a systematic review of the literature, it seems that some specific metabolic patterns correlate with the presence of specific Ab, such as a cerebral posterior hypometabolism in anti-NMDAR encephalitis, and a mesiotemporal hypermetabolism (associated with hyperintensities and swollen structures on MRI T2) in encephalitis with LGI1 and onconeural Ab. To ascertain the prognostic value of FDG-PET and its role in driving therapy, larger (preferably longitudinal) studies are needed on age-matched, untreated patients with the same Ab status, who undergo imaging at a similar time after the onset of their symptoms. This would enable a systematic correlation between MRI and FDG-PET findings, and help to clarify a number of unsolved clinical and technical issues.

Keywords Autoimmune encephalitis · PET/CT · PET/MRI · MRI · Paraneoplastic

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Introduction

Autoimmune encephalitis (AE) is a spectrum of disorders characterized by inflammation involving brain structures, sometimes triggered by a neoplasm outside the central nervous system via immunological mechanisms. The clinical signs of AE vary. The temporal lobes are often involved, leading to epileptic seizures, memory deficits, and psychiatric symptoms. This form used to be recognized as the typical picture of limbic encephalitis [1]. More recently, other forms of AE have been described as involving extratemporal structures, and appearing with motor disorders, ataxia, dysautonomia, coma or hypoventilation, for instance [2].

At first, antibodies (Ab) targeting intracellular neuronal antigens ("onconeural Ab", e.g., Hu or Ma2-Abs) were recognized as highly specific markers in classic paraneoplastic AE. Later, Ab against neuronal membrane antigens (e.g., synaptic proteins like *N*-methyl-*D*-aspartate receptor, NMDAR) were described in AE that were frequently not paraneoplastic and that were more responsive to immunotherapy [3]. A pathogenic role has been clearly established for some of these "neuronal surface Ab" (NSAbs) [2].

Despite the growing number of Ab being identified, a careful search of Ab may still prove negative in a proportion of patients with AE: this may be because of the presence of an Ab that has yet to be characterized, or due to the limited accuracy of Ab detection techniques. Such patients are usually termed "autoantibody-negative" or "seronegative".

The diagnostic assessment of patients suspected of having AE relies on clinical and paraclinical data coming from Ab detection, cerebrospinal fluid (CSF) analysis, electroencephalography (EEG), and neuroimaging [4]. Magnetic resonance imaging (MRI) of the brain can reveal a variable picture, depending on the specific syndrome involved (e.g., limbic encephalitis) and the associated Ab, but brain MRI can be normal in a sizable proportion of patients [5]. Metabolic imaging with ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) was initially used only to screen for occult malignancies in paraneoplastic cases. Nowadays, thanks partly to its widespread availability in clinical practice, accumulating data also support the use of PET imaging in the objective evaluation of metabolic changes in the brain of patients with AE.

This review aims to summarize the available data on the structural and metabolic neuroimaging findings in patients with AE, highlighting the most often recognized patterns, their correlation with Ab, and their role in clinical practice.

Acquisition of evidence

We searched the PubMed (https://www.ncbi.nlm.nih.gov) PMC, Google Scholar, and Medline databases (as at December 2017), using the following as both text and as MeSH (Medical Subject Headings) terms: "positron emission tomography—PET", "PET/CT", "PET/MRI", "MRI", and "autoimmune encephalitis", "limbic encephalitis" and "paraneoplastic encephalitis". No language restriction was applied to the search, but only articles in the English language were reviewed. Among all the articles retrieved, we selected only studies and case series describing assessments involving functional imaging (^{18}F-PET/CT) or multimodal imaging (with both PET/CT and MRI performed in some patients) conducted on at least five patients, and with AE confirmed by the presence of antineural Ab. The articles were few enough to be discussed separately by the main Ab reported in the paper:

- Studies against surface antigens (Table 1) divided into three sections: (1) studies concerning anti-NMDAR Ab; (2) those concerning anti-VGKC complex Ab (anti-LGI1 and CASPR2 Ab); and (3) those concerning mixed/uncommon/undefined superficial Ab;
- Studies against intracellular antigens (Table 2).

Studies describing evidence acquired on MRI but not on PET/CT, with confirmed AE (positivity for antineural Ab), and at least 20 cases were also included to strengthen the morphological considerations.

Summary of evidence

We summarize the findings in the literature by selecting the studies that involved the use of FDG-PET/CT in patients with AE, and focusing on the added value of using FDG-PET vis-à-vis MRI, and any still unsolved issues relating to the former. We discuss these aspects in the context of the available diagnostic criteria for AE. We also describe the differences in the neuroimaging findings (PET and MR) between AE associated with Ab against surface antigens (Table 1), and AE associated with Ab against intracellular antigens (Table 2).

Where possible (details of this aspect were frequently imprecise and variable), the timing of the imaging studies after the onset of a patient's signs and symptoms is also considered in the discussion.

Table 1 Studies against surface antigens: NMDAR/VGKC complex (LGI1, CASPR2)/MIXED Type

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings:	PET findings
	Studies concerning anti-NMDAR antibodies				
[6]	10 pt Late (10–15 m in anti-NMDAR and 1–12 m in anti-LGI1) Median age: anti-NMDAR: 36.5 years; anti-LGI1: 68.0 years	06/10 anti-NMDAR 04/10 anti-LGI1	05/06 anti-NMDAR pt with typical signs and symptoms including generalized seizures (treated successfully with antiepileptic drugs before PET) Pt with anti-LGI1 syndrome presented symptoms of a classic limbic encephalitis including cognitive deficits and focal seizures 02/04 pt showed faciobrachial dystonic seizures (treated successfully with methylprednisolone and antiepileptic therapy)	04/10 (40%) normal cerebral MRI (2 pt anti-NMDAR and 2 pt anti-LGI1) 04/06 NMDAR-positive pt: hippocampal T2-hyperintensities bilaterally with diffusion elevation in 01/06 patient; small single unspecific left paraventricular T2-hyperintensity without contrast enhancement or diffusion restriction in 01/06 patient; multiple very small subcortical T2-hyperintensities with T1-contrast enhancement in 01/06 patient; faint T2-hyperintensities in both cingular gyri in 01/0 patient In anti-LGI1 positive pt, multiple microangiopathic T2-hyperintensities in the subcortical white matter was shown in 01/04 pt; bitemporal T2-hyperintensities was shown in 1/4 patient	Anti-NMDAR: regionally limited hyperm. in frontotemporal areas contrasting an extensive hypome. in parietal lobes Anti-LGI1: hyperm. in cerebellar, basal ganglia, occipital and precentral areas and minor frontomesial hypome Visual and semiquantitative (statistical parametric mapping and VOI based analysis)
[7]	6 pt Acute (range 3 days–5 weeks) Median age: 10.5 years (range 3–17)	06/06 anti-NMDAR	Initial symptom was behavioural troubles in 03/06 pt, seizures in 02/06 pt and movement disorder in 01/06. During evolution, all pt presented association of seizures, movement disorders, language difficulties, and behavioural changes. Severe movement disorders (oro-facial dyskinesia) and dystonia in 03/06 pt. Other symptoms were: parkinsonism, loss of consciousness, swallowing difficulties, hemiparesis and central hypoventilation with apnea	04/06 pt (66%) normal cerebral MRI 01/06 patient had unilateral hippocampus FLAIR/T2 hypointensity 01/06 had cerebellum white-matter T2/FLAIR hypointensity without gadolinium enhancement	Alteration of cerebral metabolism were observed in 6/6 pt. Cortical extensive and symmetric relative hypome. predominant in posterior areas were observed in 06/06 pt, with: Occipital hypome. (06/06 pt); frontal hypome. (05/06 pt); temporal hypome. (04/06 pt) and parietal hypome. (03/06 pt). Coexistence of relative hypome. and hyperm. was observed in 04/06 pt, with: basal ganglia relative hyperm. (04/06 pt); Asymmetric, anterior cortical relative hyperm. (02/0 pt: one with temporal and another with frontal relative hyperm.)

Table 1 (continued)

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings:	PET findings
[8]	6 pt Acute/late: mean 10 weeks (range 10 weeks prior to 30 weeks after disease onset) Mean age: 21 years (range 19–39)	06/06 anti-NMDAR	02/06 pt had epileptic seizures prior to PET imaging (successfully treated with anticonvulsants at the time of FDG-PET). In 04/06 pt, no seizures occurred before PET imaging	04/06 pt (66%) normal cerebral MRI 01/06 patient had multiple small subcortical T2-hyperintensities without contrast enhancement 01/06 patient had three periventricular T2-hyperintense and slightly contrast enhancing lesions without corresponding FDG-PET abnormalities	01/06 pt (16.6%) normal FDG-PET 05/06 pt showed temporal glucose hyperm. 05/06 pt showed either increased frontal or decreased occipital glucose metabolism At SPM analysis, statistically significant hyperm. was confirmed in both temporomesial areas, in the right prefrontal cortex and frontobasal areas. Significant and widespread hypome. was confirmed in bioccipital areas extending to left-sided parietal areas
[9]	29 pt Acute: (3 weeks for anti-NMDAR and 8 weeks for other AE) Mean age: 26 years (range 7–57)	08/29 anti-NMDAR 21/29 other AE	na	na	Visual cortical brain regions, corresponding to the medial occipital lobes, were more hypometabolic for the pt with anti–NMDAR receptor encephalitis relative to the other pt with definite AE No other differences in brain region metabolism were noted between the 2 groups Visual and semiquantitative analysis (3D-SSP)
[10]	8 pt Acute (6/8 PET at 5–6 weeks from the onset of the disease when pt were at the peak stage of their symptoms) Age range: 12–35 years	08/08 anti-NMDAR	Various degree of severity including psychosis, intermittent involuntary movements, rigidity, tremor, unconsciousness, generalized seizures, and instability of autonomous nervous system	na	06/08 (acute) PET at 5–6 weeks from the onset demonstrated severe hypome. of the bilateral occipital lobes as well as hyperm. of the partial frontal, temporal lobe cortex, and basal ganglia 05/08 (early recovery) PET at 9–13 weeks (3 repeated) evolved to diffuse cortical hypometabolism with relative hypermetabolism in basal ganglia 04/08 (recovery) PET at > 20 weeks (4 repeated) metabolism of the brain almost returned to normal

Table 1 (continued)

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings:	PET findings
[11]	106 pt Acute (1 m from onset) Median age: 26.4 years ± 11.5 (range 9–72)	106/106 anti-NMDAR	Psychiatric symptoms (97.3%), seizures (81.3%), disorders of consciousness (65.2%), fever (63.4%), dyskinesias and movement disorders (51.8%), headache (39.3%), central hypoventilation (20.5%), dizziness (12.5%)	52/106 (49.1%) normal cerebral MRI 54/106 (50.9%) abnormal or atypical. T2/ FLAIR hyperintensity seen in 20/54 (37.0%) in the hippocampi, cerebellar, cerebral cortex and insular regions, basal ganglia, and brainstem. Progressions to hippocampal or whole-brain atrophy were found in two patients	Not performed
	Studies concerning anti-VGKC complex antibodies				
[5]	18 pt Acute or subacute (12/18p MRI and FDG-PET before immunosuppressive therapy) Mean age: 55.3 years (range 26–84)	09/18 surface Ab (7/9 VGKC+) 04/18 intraneuronal Ab 05/18 no Ab	Clinical main criteria for AE (memory deficits of subacute onset, personality changes/psychiatric symptoms of subacute onset and seizures)	06/16 (2 MRI not performed) normal (37.5%) MRI 08/16 (50%) mesiotemporal findings (FLAIR hyperintensities) 02/16 normal mesiotemporal findings but hyperintensities in the thalamus and occipital cortex on MRI	04/18 pt (22.2%) normal FDG-PET 10/18 (55.5%)PET mesiotemporal findings (hyperm.) 04/18 normal mesiotemporal findings but hypome. in the thalamus and cortical areas, sometimes accompanied by hyperm. in the striatum and cerebellum
[12]	16 pt Acute to late: (median 168 days—range 32–327 days) Mean age: 62 years (range 29–84)	16/16 anti-LGI1 (from a pool of 28 anti-VGKC)	Short-term memory loss (07/16); epileptic seizures (06/16); abnormal movements (01/16); mood disorder (01/16); dizziness (01/16)	05/16 pt (31.2%) normal MRI or unspecific white-matter lesions 11/16 (68.7%) had medial temporal T2 weighted/fluid attenuation inversion recovery (T2/FLAIR) hyperintensity, bilateral in 9 (56%) and unilateral in 02/16 cases 12 follow-up MRI 08/12 bilateral temporal lesion 01/12 unilateral temporal lesion 03/12 pt remained normal	09/16 pt underwent brain FDG-PET (visual analysis) 01/09 pt (11.1%) normal FDG-PET 07/09 pt (77.7%) showed either bilateral (45%) or unilateral (33%) hippocampal hyperm 01/09 patient had unilateral hippocampal hypome.. Among 5/16 pt with normal MRI, two underwent FDG-PET and were found to have unilateral hippocampal hyperm 03/09 pts had follow-up PET with normalization of metabolism

Table 1 (continued)

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings:	PET findings
[13]	14 pt Median age: 60.5 years (range 41–78)	14/14 anti-LGI1	All pt presented with seizures (04/14 status epilepticus. Additionally, 10/14 (71.4%) experienced faciobrachial dystonic seizures while 12/14 pt (85.7%) showed cognitive dysfunction (mainly deficits in memory and abnormal behavior) and 3 pt (21.4%) exhibited autoimmune dysautonomias, such as orthostatic hypotension, constipation, and urinary incontinence	28.6% normal cerebral MRI 71.4% pt showed increased signals on MRI fluid-attenuated inversion recovery or T2 sequences: 64.3% pt had medial temporal lesions 55.6% pt exhibited bilateral lesions, while 1 patient showed multiple lesions in the bilateral basal ganglia, thalamus, white matter, and central pons	07/10 pt showed (visual analysis) hyperm. in the medial temporal areas (3 of them exhibited hyperm. bilaterally) 07/10 pt demonstrated bilateral hyperm. in the basal ganglia
[14]	8 pt Mean age: 54.1 years	06/08 anti-LGI1 02/08 CASPR2	08/08 were previously suspected of having sporadic Creutzfeldt–Jakob disease. All pt had rapidly progressive cognitive decline, focal neurological signs and suspicious myoclonus	02/08 pt (25%) normal cerebral MRI 06/08 (75%) pt limbic hyperintensity All of them showed discrepant results between MRI and PET, in which MRI showed more involved regions than PET	05/08 pt underwent FDG-PET (visual analysis) 02/05 pt (40%) normal FDG-PET 02/05 showed hyperm. (hippocampal, corpus striatum and dorsal thalamus) 01/05 showed hypome. (temporal and occipital)
[15]	7 pt Acute/subacute (8–185 days in VFKC; 19 days in NMDAR. Mean: 48.6 d) Mean age: 56.7 years (range 22–91)	06/07 anti-VGKC 01/07 anti-NMDAR	All presented with the chief complaint or altered mental status	03/07 (42%) normal cerebral MRI 04/07 pt had mesial temporal lobe hyperintensity on T2/FLAIR weighted MRI (1/7 patient with VGKC AE had T2/FLAIR weighted hyperintensity of the restiform bodies; 1/7 patient with VGKC AE had global atrophy) The patient with positive NMDAR AE had serial MRIs that were all unremarkable except development of generalized atrophy	06/07 pt underwent FDG-PET (visual analysis) 06/06 showed hyperm. of mesial temporal structures

Table 1 (continued)

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings:	PET findings
[16]	42 pt Acute and subacute Median age: 56 years (range 8–79)	42/42 anti-VGKC	42/42 seizures 16/42 cognitive decline 13/42 memory deficits	Acute phase 13/42 normal (30.9%) imaging findings 29/42 imaging (69%) abnormalities as enlargement of amygdala and hippocampus with signal hyperintensity on T2w images 02/42 nonmesial temporal findings Short-term follow-up (> 1 years) 03/42 pt with initially negative findings showed progression of disease 33/42 temporal abnormalities at follow-up. 16/33 showed mesial temporal sclerosis during follow-up period (2 to 39 months). 05/33 abnormal findings resolved on follow-up imaging with immunotherapy	Not performed
[17]	30 pt Acute subacute (median time after onset 23 m) Mean age: 65 years	27/30 anti-LGI1	Acute onset FBDS and limbic encephalitis 20% pts Pilomotor/Autonomic Seizures 97% Memory deficits Marked impaired verbal and visuo-spatial memory	07/25 normal (28.9%) imaging findings 22/27 (81%) pt unilateral or bilateral hippocampal hyperintensity 01/27 pt transient diffusion restriction of occipital cortex Follow-up routine MRI 26 pts 25/27 hippocampal atrophy (13/25 atrophy was accompanied with signal increase and loss of internal architecture aka “hippocampal sclerosis”)	Not performed
	Studies concerning mixed/uncommon/undefined superficial Ab				

Table 1 (continued)

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings:	PET findings
[18]	61 pt Acute (median of 4 weeks after symptom onset) Mean age: 54 years	32/61 pt with Ab identified 18/32 Ab against synaptic receptor, ion channel or other cell surface proteins 07/32 against intracellular Ag 04/32 against other neuronal or muscle Ag	Lethargy (47/61); memory loss (46/61); hallucinations (5/61); cerebellar signs (47/61); focal weakness (35/61); focal numbness (35/61); movement disorder (39/61); seizures (25/61); status epilepticus (10/61); cranial neuropathy (14/61); aphasia (25/61); psychiatric symptoms (22/61); focal neurologic symptoms (58/61); multiple focal neurologic findings (50/65)	Brain MRI studies for 57 pt were available, and 36/59 pt (59.6%) aspecific MRI findings 23/59 pt were consistent with the diagnosis of AE. No differences were observed across antibody status, antibody class, or AE classification	09/61 pt (14.75%) normal FDG-PET 52/61 pt abnormal FDG when compared with the healthy control database 42/61 hypome. alone 02/61 hyperm. alone 08/61 regions of abnormal hypome. and abnormal hyperm. Visual and semiquantitative analysis (3D-SSP)
[19]	23 pt Acute (1–16 weeks from onset. FDG-PET performed before therapy in 6/23 pt) Mean age: 46 years (range 7–76)	08/23 anti-VGKC 05/23 anti-NMDAR 03/23 anti-GAD 03/23 anti-Hu 02/23 anti-Ma 02/23 anti-alpha-3 acetylcholine receptor	All pt presented with either altered mentation or impaired working memory. 21/23 (87%) presented with new focal neurological deficits and 13/23 (52%) with seizures	13/23 pt (56.5%) normal cerebral MRI 10/23 pt: positive MRI showing increased T2/FLAIR signal in the medial temporal lobes	FDG-PET/CT showed lobar hypome. in 21/23 pt. Discrepancy in FDG abnormality and MRI findings was most pronounced in pt with anti-NMDAR Ab (none of these pt demonstrated abnormal MRI, while 5/5 showed abnormal FDG-PET/CT scan). Conversely, anti-VGKC + pt were more likely to have a concordant abnormal MRI and FDG Visual and semiquantitative analysis (3D-SSP)
[20]	9 pt Acute/Late (4 days to 2 m from onset) Mean age: 48.2 (range 21–80)	02/09 anti-NMDAR receptor Ab 07/09 no Ab data	05/09 pt presented with subacute cognitive decline, bizarre behavior, psychosis, and/or nonsensical speech, dysautonomia and seizures 04/09 showed subacute cognitive decline	Na (authors state only that: "In most of our patients, the MRI was unremarkable")	Two different FDG-PET (visual) patterns: (1) Hypome. in the occipital cortex and mildly reduced metabolism in the primary sensorimotor strips; Hyper. in the temporal lobes; hyperm in the orbitofrontal cortex bilaterally; borderline hyperm. in the cerebellum diffusely and borderline hypome. in the parietal cortex; (2) PET scans indistinguishable from advanced AD, eventually including occipital cortex

Table 1 (continued)

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings:	PET findings
[21]	7 pt Subacute Mean age: 47 years	06/07 surface Ab (01/06 VGKC) to the neuropil of hippocampus or cerebellum 01/07 intraneuronal Ab	04/07 showed dominant hippocampal or medial temporal lobe dysfunction characterized by severe short-term memory loss, agitation and behavioural changes 03/07 more extensive involvement of the limbic system characterized by severe confusion, inappropriate behavior and seizures limiting memory evaluation	02/07 (28.5%) T2 aspecific abnormalities in cerebral cortex and cerebellum 04/07 FLAIR MRI abnormalities restricted to one or both medial temporal lobes (1/7 with T1 contrast enhancement) 01/07 typical medial temporal lobe FLAIR and T2 abnormalities	05/06 (1 PET not executed) hyperm. in one or both temporal lobes 01/06 hyperm. in the brainstem and hypome. in the occipital lobes 02/06 hyperactivity in the cerebellum (vermis)
[22]	5 pt Acute Mean age: 63 years (range 58–71)	05/05 anti-GABA	All pt presented with behavioural disorder and mental confusion. In 03/05 pt, clinical seizures were the initial symptom	03/05 pt (60%) normal MRI 02/05 pt with T2 hyperintensities restricted to the medial temporal lobes	02/05 pt (40%) normal FDG-PET Brain FDG-PET showed medial temporal hyperm. in two pt and diffuse cortical hypome. in one patient. In two pt, mesiotemporal T2 hyperintensity in MRI and hyperm. in FDG-PET findings were correlated. The patient with hypome. in the cerebral cortex showed normal MRI
[23]	25 pt Acute/subacute Median age: 42 years (range 18–75)	12/25 pt sieropositive Anti-NMDAR (4) Anti-GAD (4) Anti TPO (4) Anti-Ma (1) 13/25 pt sieronegative	24/25 epileptic seizures Majority cognitive impairment Several psychiatric disturbances	10/25 pt (40%) normal MRI 15/25 pt MRI abnormalities related to limbic encephalitis Subacute phase 10/15 pt showed regression of MRI abnormalities	Not performed

pt patients, *Na* not available, *hyperm.* hypermetabolism, *hypome.* hypometabolism, *Ab* antibodies, *Ag* antigens, *AE* autoimmune encephalitis, *NMDAR N*-methyl-D-aspartate receptor, *VGKC* voltage gated potassium(K) channel complex, *LGI1* leucine-rich, glioma inactivated 1

Table 2 Studies against Intracellular Antigens: Anti-Hu/Ta/Ma/Gad Ab

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings	PET findings
[24]	53 pt Acute Median age of GAD: 23 years years (range 17–66).	09/53 anti-GAD 10/53 anti-VGKC 01/53 amphiphysin 33/53 negative	Temporal lobe epilepsy	Acutely (first visit) 100% amygdala–hippocampal T2/FLAIR hyperintensities, and often swelling 02/09 Gad + (but none of VGKC) had also extramediotemporal lesions (thalami, insula, parietal lobes, claustrum, brainstem)	PET performed in 04/09 GAD and 08/10 VGKC showing in 02 hyperm. (1 m and 3 m from onset) in the mediotemporal region and hypome. in the others (> 3 m)
[25]	38 pt Acute (34 pt with cancer of which 53% with testicular germ-cell tumors) Mean age: 49 (range 22–82)	38/38 anti-Ma2 (15p also additional anti- bodies)	89% presented with isolated or combined limbic, diencephalic or brainstem dysfunction 92% eye movement abnormalities in pt with brainstem dysfunction	Brain MRI (33/38 pt at symptoms onset) abnormalities in 74% of all pt and 89% of those with limbic or diencephalic dysfunction. ~ 50% of 33 pt bilateral or unilateral medial temporal lobe abnormalities (10p enhancing after mdc), while a minority had abnormalities in the amygdala, hypothalamus, thalamus, basal ganglia, midbrain, pons, anterior medulla, superior and middle cerebellar peduncles	02/38 performed PET with significant hyperm. in medial temporal lobes
[26]	10 pt Acute pt with paraneoplastic syndrome; 10/19 limbic encephalitis Timing: na Age range 26–78	02/10 anti-Hu 02/10 antineuronal cell membrane 02/10 anti-VGKC 01/10 anti-NMDAR 01/10 'atypical' ab 02/10 negative	Memory and cognitive difficulties, seizures, personality changes, motor disturbances and weakness, anxiety, insomnia	08/10 pt had temporal lobe involvement (07/10 also had bilateral temporal lobe involvement in their brain PET scans) 01/10 patient with temporal lobe abnormalities on MRI had a normal PET 01/10 patient with temporal lobe abnormalities noted on PET had only cortical and cerebellar involvement on MRI	01/10 pt (10%) without Ab had a normal PET scan 08/10 pt bilateral temporal hyperm 06/10 pt reduction in general cortical FDG uptake (including in the primary visual cortex) 01/10 patient showed severely increased ^{18}F-FDG uptake in both occipital lobes extending to the temporal lobes
[27]]	50 pt Acute to late Median age: 55 (range 11–75)	18/50 anti-HU 10/50 anti-Ta 02/50 anti-Ma 20/50 negative (4 uncharacterized)	Pt fulfilling criteria for paraneoplastic (lung 50%, testis 20%, breast 8%) limbic encephalitis (personality changes, irritability, depression, seizures, memory loss and dementia)	16/44 (06 not available MRI) pt (36.3%) normal cerebral MRI 25/44 (57%) with MR studies signal abnormalities in the limbic system (mostly T2 hyper intensities), in 05/44 enhancing after contrast administration 08/44 other abnormalities: brainstem (4), hypothalamus (4), Thalamus (1), cingulate gyrus (1)	Not performed

Table 2 (continued)

References	Sample (*n*) T. of imaging age	Associated Ab	Data on clinical symptoms	MRI findings	PET findings
[28]	20 pt Acute (1 days–15 years) Mean age: 44 (range 25–71)	16/20 (5 onconeural, 3 VGKC, 6 histopathologic inflammation, 5 malignant tumor) 04/20 negative	Subacute memory impairment and/or temporal lobe seizures	13/20 studied < 3 m after onset: 11 (85%) swollen temporomesial structures (after 9 months 9/10 swelling had resolved) 07/20 studied > 3 m after onset: 03 (15%) swollen temporomesial structures, 1 pt T2 hyperintensities, 3 pt atrophic temporomesial structures	Not performed

pt patients, *Na* not available, *hyperm.* hypermetabolism, *hypome.* hypometabolism, *Ab* antibodies, *Ag* antigens, *AE* autoimmune encephalitis

^{18}F-FDG-PET and MRI in AE

Diagnostic criteria for AE and PET

The criteria for diagnosing autoimmune encephalitis proposed by Zuliani et al. [3] relied mainly on Ab testing. This meant potential delays in the start of treatment, which may significantly affect a patient's final outcome [3]. For this reason, a group of experts led by Francesc Graus published a position paper in 2016 suggesting the need for a new syndrome-based diagnostic approach to AE. The aim was to provide an earlier diagnosis of "possible AE" and thus enable immunotherapy to be started without delay [4]. The criteria proposed by Graus et al. were based on:

1. the reasonable exclusion of alternative causes;
2. a subacute onset of working memory deficits, altered mental status, or psychiatric symptoms;
3. conventional neurological evaluation and standard diagnostic tests (i.e., MRI, CSF, or EEG).

Accordingly, MRI abnormalities such as T2-weighted fluid-attenuated inversion recovery in the bilateral medial temporal lobes were the imaging-based criteria used to support a hypothesis of possible AE. In this setting, FDG-PET was defined as a suitable tool for fulfilling the MRI positivity criterion in patients with limbic AE. Although FDG-PET was acknowledged as having a potentially greater sensitivity in mesiotemporal lobes (MTL) appearing normal on MRI, its inclusion in the flowchart was less clearly defined. Now, despite an increasing body of evidence to support its use [29], our systematic review of the pertinent literature confirms that available data on the use of FDG-PET in the diagnosis of AE still derive from retrospective studies or case series that:

1. involved relatively small groups of patients (ranging from 6 to 61 patients in studies concerning Ab against surface antigens, and from 10 to 53 patients in studies on paraneoplastic patients with Ab against intracellular antigens);
2. included patients found positive for Ab targeting different neuronal antigens, such as intracellular Ab (Ri, Hu, Yo, cv2/CRMP5, amphiphysin, Ma1, Ma2, SOX1, GAD), and surface Ab (VGKC complex: LGI1 and CASPR2, GABA-B, NMDAR, AMPA1, AMPA2), among others;
3. systematically used MRI and FDG-PET in all patients, in only a few cases;
4. included imaging studies performed at very different times in the course of the disease (i.e., at the baseline

and after therapy, or over a very broad time span ranging from days to years);
5. relied in the majority of cases on a simple visual inspection of the FDG-PET findings (very few studies included any semiquantification of the findings, mainly using statistical parametric mapping or three-dimensional stereotactic surface projections);
6. the possible pharmacological interactions (e.g., a number of patients underwent PET under propofol narcosis in Wegner et al. [6].) at the time of imaging were either totally disregarded, or given very little consideration.

Metabolic (PET) and morphological (MRI) patterns

We identified 24 studies matching our inclusion criteria. Studies involving homogeneous groups of patients were only available for AE associated with anti-NMDA receptor Ab (6 studies; the largest multimodal study included 10 patients, the largest MRI-only study involved 106 patients), or with anti-VGKC complex (5 studies; the largest multimodal study concerned 18 patients, and the largest MRI-only study 42 patients). Another six studies (including the largest published study on FDG-PET in patients with AE) concerned patients with mixed, uncommon or undefined superficial Ab. Five more studies with both FDG-PET and MRI findings included patients with anti-Hu/Ta/Ma/Gad Ab, but more than 5 patients ($n = 10$) underwent FDG-PET in only one of these studies [26].

Tables 1 and 2 provide details of the sample size, mean age (or age range), associated Ab, clinical symptoms, PET and MRI findings, and time of neuroimaging acquisitions after the onset of symptoms, and during the course of the disease.

In this framework, the largest study involving both FDG-PET and MRI in patients with AE was published by Probasco et al. in 2017 [18]. The authors compared the rate of abnormal metabolism identified on FDG-PET with the other paraclinical findings (EEG, MRI and CSF) in 61 patients with AE (57 of them underwent both MRI and FDG-PET; 32 were found seropositive). The FDG-PET scans obtained about 4 weeks after symptom onset were fused and projected onto predefined surfaces (three-dimensional stereotactic surface projections) after anatomical standardization. Qualitative and quantitative analyses were performed using a commercially available software and findings were compared with a database of over 250 age-stratified healthy controls. *Z* scores were calculated for standard brain regions, and only the *Z* scores with a magnitude ≥ 2.00 were interpreted as significant. FDG-PET was abnormal in 85% of patients, and proved more sensitive than EEG, MRI, or routine CSF findings. Regional ^{18}F-FDG hypometabolism was the most common finding (68.8%), while some patients revealed areas of both hyper- and hypometabolism (13.1%), and a few of them (3.3%) showed hypermetabolism alone. Compared with PET, MRI was positive in 39% of cases, while showing unspecific findings in about 61%. It is worth noting that the study was not homogeneous, however, since it included a significant number of patients with Ab against intracellular (21.8%) or undefined (12.5%) antigens.

A further study by the same group [9] included 29 patients with AE (8 with anti-NMDA receptor Ab and 21 with other types of AE), and aimed to compare the semiquantitative findings on brain FDG-PET in the acute phase of the disease in two subgroups of patients (unfortunately, no MRI findings were reported in this study). FDG-PET was abnormal in all patients with anti-NMDA receptor AE, usually showing medial occipital hypometabolism, alone or combined with hypermetabolism in other regions. This finding proved to be more typical of AE patients with anti-NMDA receptor Ab (and especially those with the most severe neurological disabilities) than of cases with other subtypes of AE.

Similarly, Solnes et al. [19] retrospectively compared the proportions of patients found positive for AE on MRI vs FDG-PET during the initial diagnostic work-up of 23 seropositive AE patients (again with a variety of Ab: 56.5% superficial; 34.8% intracellular; and 8.7% of uncommon antigens). They found an abnormal pattern on semiquantitative analysis of FDG-PET images in 22/23 cases. In keeping with the other two larger studies, these Authors demonstrated that hypometabolism (particularly in the parietal and occipital lobes) was the most common finding. Here again, FDG-PET proved highly sensitive, i.e., it revealed an abnormal picture more frequently than MRI (the proportion of negative or unspecific findings on MRI was 56.6%, much the same as in the larger studies), particularly in cases of AE associated with anti-NMDA receptor Ab (5 patients, all with normal MRI findings).

These recent studies on larger samples than the previously published case series confirm the potentially greater sensitivity of FDG-PET over MRI in the acute phase of AE. They also go to show that the pattern of MTL hypermetabolism seen in previous case series, and mentioned in the position paper published in 2016, might not be the most common metabolic alteration in AE [4, 5]. Hypometabolism can frequently occur too, and both hypo- and hypermetabolism may be apparent beyond the boundaries of the MTL.

The FDG-PET pattern may be affected by the different autoantibodies involved, and the consequently paraneoplastic or other nature of AE. MTL hypermetabolism was reported in a homogeneous group of patients ($n = 16$) with anti-LGI1 Ab [12], in whom both MRI (68.7%) and PET (77.7%) revealed mesiotemporal abnormalities (mainly T2/FLAIR hyperintensity or hypermetabolism, and frequently bilateral). PET showed unilateral hippocampal hypermetabolism in 2/5 cases with negative MRI findings.

MTL hypermetabolism was also demonstrated in a series of patients [5] with mixed Ab (against surface antigens in 50% of cases): 4/4 patients with Ab against intracellular antigens showed MTL hypermetabolism, while only 2/9 patients with Ab against surface antigens exhibited mesiotemporal hypermetabolism. The MRI findings were similar (though the association was less evident than on PET): patients with Ab against intracellular antigens showed mesiotemporal findings (hyperintensities) in 75% of cases, while the majority (62.4%) of patients with superficial Ab did not. Seronegative patients were randomly distributed across the two groups, probably underling unknown Ab.

As for the MRI findings, several cases (57% [27], 85% [28], 50% [25], 80% [26]) support the idea of a more likely involvement of the mesiotemporal structures (swollen structures and T2/Flair hyperintensities) in patients with paraneoplastic syndromes and Ab against intracellular antigens, rather than in non-paraneoplastic AE with Ab against anti-NMDAR (16.6% [7], 0% [8], 16.6% [6], 37% [11]).

Among the cases of AE associated with superficial Ab, those with VGKC Ab seem to show mesiotemporal structure involvement on MRI (50% [5] 68.7% [12], 64.3% [13]) more frequently than cases associated with anti-NMDAR Ab. This impression is also supported (69% [16], 81% [17]) by MRI studies on larger populations.

Using serial MRI in cases of paraneoplastic AE associated with mixed Ab (including onconeural Ab), Urbach et al. [28] showed that swollen mesiotemporal structures became apparent within 3 months after the onset of symptoms in 85% of patients, and later on in only 15%. Three months after the onset of acute AE, the mesiotemporal structures seem to show progression of atrophy (a finding confirmed by larger studies in cases associated with superficial Ab too [11, 16, 17],). The progression of atrophy of certain structures in a given AE subtype, and especially in limbic encephalitis, should be considered in longitudinal imaging assessments (using PET), and partial volume effect should be corrected in the light of MRI [30], if available, to ensure robust visual and semiquantitative evaluations.

In this context, simultaneous PET/MRI acquisitions would provide an interesting opportunity to study the morphological (T2-Flair, DWI,) and functional (^{18}F-FDG, fMRI) features of AE at the same time (Fig. 1), and to correct for partial volume effects (PVE).

Changes in metabolism on PET depending on the time elapsing between symptom onset and imaging have rarely been studied in AE. We can guess from the work done by Yuan et al. [10], however, that different patterns could be expected at different timepoints, for AE associated with anti-NMDAR Ab at least. In the *acute phase* (5–6 weeks after onset), severe hypometabolism of the bilateral occipital lobes and hypermetabolism of the frontal lobe, temporal lobe, and basal ganglia has been described, while during the *early recovery* phase (9–13 weeks) it evolves into diffuse cortical hypometabolism (Fig. 2), with a relative hypermetabolism in the basal ganglia. Then a complete *recovery phase* (> 20 weeks) has been identified with metabolism returning almost to normal.

Metabolism: pathogenic hypotheses

Different hypotheses have been advanced to explain the hypermetabolism that occurs in patients with AE. In the MTL (or even elsewhere), hypermetabolism might be due to the underlying inflammatory process [31, 18, 32], to a direct interference related to the synaptic and neuronal properties of the Ab, or (in some patients at least) to seizure activity [33, 18, 34]. In this setting, the correlation between brain hypermetabolism and inflammation is supported by rising levels of inflammatory markers in the CSF of AE patients [26]. In one [31] of the few cases with a pathological examination conducted on the region corresponding to the hypermetabolism (a patient with anti-glutamic acid decarboxylase antibody-associated AE), there was evidence of microglial proliferation and perivascular lymphohistiocytic infiltrates. On the other hand, receptors or associated proteins, such as NMDA or GABA receptors that target ion channels may interfere directly with synaptic transmission and neuronal plasticity. Using rfMRI, Heine et al. [33] demonstrated a reduced functional connectivity in patients with AE associated with anti-NMDA receptor Ab, thus suggesting further potential underlying mechanisms. In this framework, assessing metabolic connectivity by means of interregional correlation analyses on FDG-PET findings might also be suitable for addressing any abnormal patterns of connectivity, but to the best of our knowledge no such analyses are available for patients with AE.

There is little support in the literature for any relationship between seizure activity and brain hypermetabolism in patients with AE. To significantly affect brain metabolism, seizures should recur rapidly during the FDG uptake period [35]. EEG during FDG uptake is not easy to achieve in all clinical scenarios, but it would be the only way [36] to rule out multiple subclinical seizure activity as the cause of the hypermetabolism seen in AE. As far as we know, consistent data on this matter are still lacking.

While several studies tried to discuss the pathophysiological grounds for hypermetabolism in AE, hypometabolism has been less directly addressed, and it remains unclear whether this results from functional or structural changes, or a combination of the two. It is also important to remember that hypometabolic PET patterns might also be related [26] to a generalized hypoactivity caused by paraneoplastic

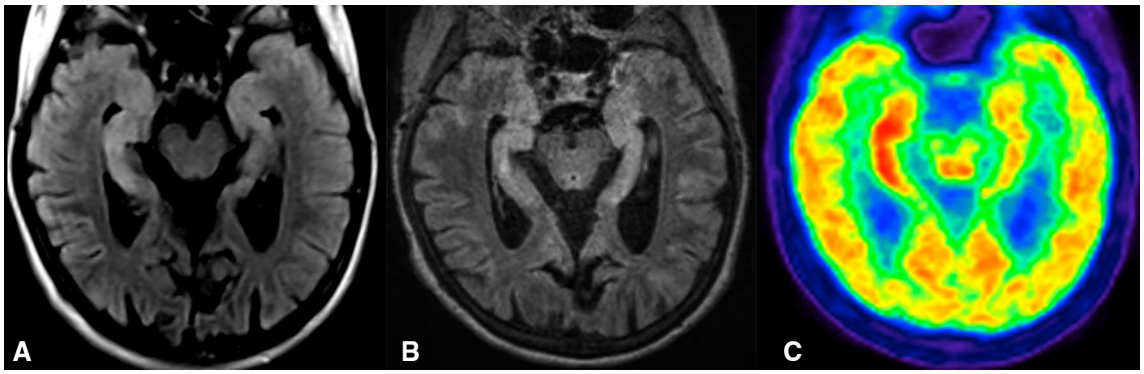

Fig. 1 MR and ^{18}F-FDG-PET/MR of a VGKC (LGI1) patient: **a** T2 weighted (Flair) MR (early after onset of symptoms) showing T2 and swollen temporomesial structures bilaterally; **b**, **c** ^{18}F-FDG-PET/RM (Biograph mMR, Siemens, Erlangen, Germany) of the same patient 3 months later showing slightly reduced bilateral T2 weighted (Flair) hyperintensities on MR (B) and clear mesiotemporal hypermetabolism on ^{18}F-FDG-PET (**c**) particularly intense on the right side

syndromes or pharmaceuticals (corticosteroids or sedatives, for instance) administered to patients.

Finally, studies [37] aiming to explain the imaging differences between cases of AE associated with Ab against intracellular vs superficial antigens have hypothesized:

- A cytotoxic T-cell effector mechanism for AE associated with intracellular Ab, which would induce inflammatory damage, and consequent tissue repair and gliosis, which in turn would lead to an increased energy turnover and FDG uptake;
- Antibody-mediated damage and a lesser T-cell involvement for AE associated with superficial Ab (a mechanism that probably also differs between different superficial Ab).

Larger studies are needed on patient groups with the same Ab status, and with a systematic correlation between

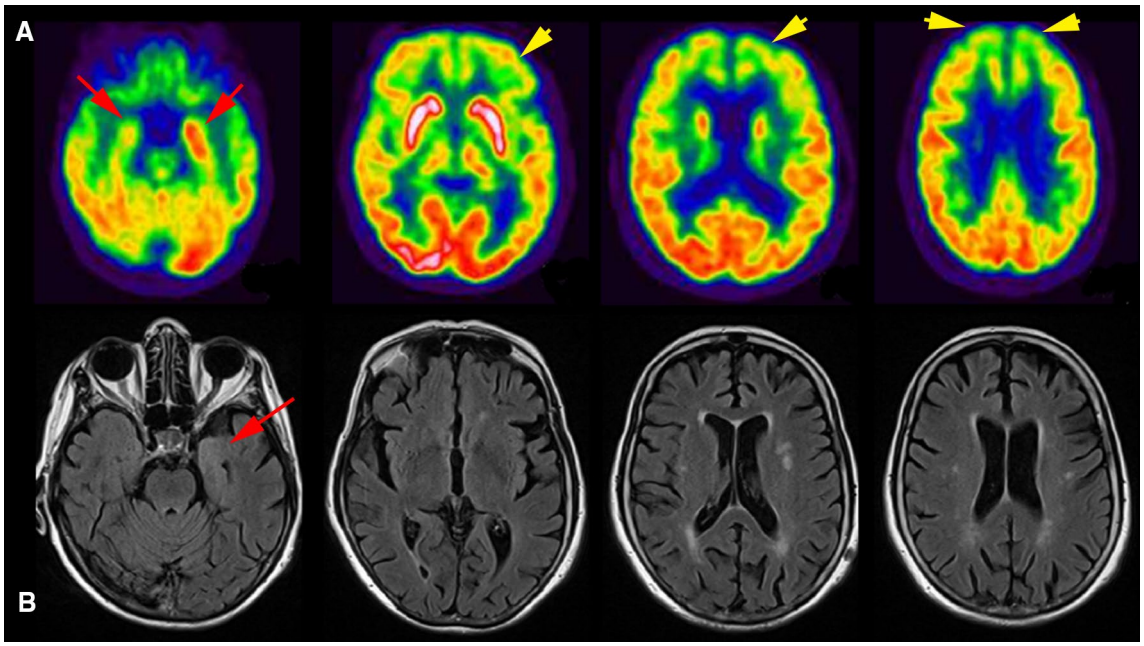

Fig. 2 Imaging results in a patient with anti-voltage-gated potassium channel (VGKC) antibody-associated limbic encephalitis. **a** ^{18}F-FDG-PET shows extensive left mesiotemporal hypermetabolism and a less severe hypermetabolism in contralateral medial temporal cortex (red arrows). Relative hypometabolism is evident in the left posterior parietal cortex and in lateral frontal cortex in both hemispheres (yellow arrows). **b** MRI (Flair) depicts only mild left mesiotemporal hyperintensity (red arrow). Described findings are in agreement with the emerging evidence that both hypo- and hypermetabolism can be observed in patients with autoimmune encephalitis also outside the boundaries of the medial temporal lobes

their MRI and FDG-PET findings, to shed light on such hypotheses.

Technical biases

From the technical standpoint, there are other relevant issues that still need to be clarified to support the inclusion of FDG-PET in the diagnostic work-up of patients with AE in clinical practice, including:

1. the need to systematically include a dedicated brain and whole-body acquisition in patients who undergo PET for paraneoplastic encephalitis;
2. the interference of ongoing treatments (corticosteroids and others);
3. the added value of normalization, semiquantification and partial volume effect correction (PVEc) vis-à-vis visual inspection of brain FDG-PET findings in patients with AE.

The detection of occult cancer in suspected paraneoplastic neurological syndrome (PNS) poses a diagnostic challenge. A recently-published systematic review and meta-analysis [38] aiming to assess the diagnostic performance of FDG-PET for the detection of occult malignant disease responsible for PNS showed a very good diagnostic performance of FDG-PET in detecting malignancies responsible for PNS. The accuracy of FDG-PET was also unaffected by the presence of onconeural Ab or patients' clinical characteristics. Whole-body FDG-PET is consequently often added to the paraneoplastic work-up of young and old AE patients when screening for malignancies (as PET/CT is more sensitive than CT alone). It generally adds no more than 20 min to the total time taken for the examination so a dedicated brain scan should be included in the same PET session. Brain scan could also be used to monitor response to therapy, or in the context of suspected recurrent disease [39].

Although this has not been investigated systematically, a generalized reduction in cortical metabolism was demonstrated in brain tumor patients taking corticosteroids, by comparison with other brain tumor patients or normal volunteers [40]. On the other hand, two of the studies published by the Johns Hopkins group found no such differences in brain metabolism between patients who were or were not given corticosteroids 24 h before undergoing FDG-PET [18, 9]. The theoretically more frequent occurrence of a hypometabolic pattern in patients with AE being treated with corticosteroids needs to be thoroughly explored to enable a more robust interpretation of PET findings. Fisher et al. [20] tried to address the regional effect of corticosteroid administration by comparing the effect on brain metabolism in patients with AE and in age-matched patients with oncological diseases. They found that no specific pattern of hypometabolism can be highlighted in either group. Further studies are needed to address the potential effects of corticosteroids, and possibly other pharmaceuticals too (such as sedatives), on FDG-PET patterns and sensitivity.

A systematic investigation of pharmacological interferences is closely connected to the role of semiquantitative approaches in AE patients. In the field of neurodegenerative diseases too, despite a huge amount of literature, studies have shown a very wide range of values for the sensitivity and specificity of FDG-PET. This variability has also been related to the different methods used to analyze the images (visual vs semiquantitative reading using different types of software) [41]. In patients with AE, as in other patients who undergo brain FDG-PET, a visual inspection by a trained neuroimaging physician should be the first step, taking all available morphological (MR) and functional (PET) information into account. Although the use of semiquantitative measures to obtain an objective assessment is desirable, it may sometimes prevent the recognition of the actual disease pattern (coinciding with the patient's clinical presentation). Using software for the semiquantification of FDG-PET findings in patients with AE is also complicated by the fact that some automated approaches are unsuitable for identifying areas of hypermetabolism because they were developed for the purpose of diagnosing hypometabolic patterns in Alzheimer's disease [42]. Similarly, the potential bias introduced by the reference region used for intensity normalization is a crucial issue when dealing with AE too. In the field of neurodegenerative diseases, some authors have argued over how to interpret hypermetabolic clusters highlighted by voxelwise statistical parametric analysis: do they reflect a true hypermetabolism (due to neural inflammation or microglial activation) or merely a less severe hypometabolism? This aspect, and how it relates to FDG-PET sensitivity and specificity in patients with AE, has never been systematically addressed. Despite the possible biases, it is nonetheless undeniable that—on a group basis at least—semiquantification may enable a more precise identification of concurrent hypo- and hypermetabolic patterns, and a consequently more accurate correlation with neurological and cognitive symptoms in patients with AE [43].

Conclusions and clinical considerations

Neuroimaging is a fundamental aid in the diagnosis and management of AE.

In the early diagnostic phase, when approaching clinical manifestations resembling AE, alongside laboratory and electroencephalographic data, brain MRI helps to differentiate between AE and other diagnoses with a metabolic, toxic, infectious or neoplastic etiology [4, 44].

In a variable proportion of patients, brain MRI shows specific alterations that depend on the clinical syndrome and related Ab. Limbic encephalitis with typical hyperintensity of mesiotemporal lobes (MTL) is found associated with onconeural [27, 28], LGI1 [45, 46], CASPR2 [47, 48], GABA-B R [49] and AMPAR [50] Ab. The involvement of extratemporal regions has also been reported, including: brainstem and diencephalic involvement in Ma2 Ab encephalitis [25]; and multifocal cortical–subcortical T2/fluid-attenuated inversion recovery abnormalities in GABA-A Ab encephalitis [51]. In the context of LGI1 autoimmunity, some patients with faciobrachial dystonic seizures show T1 and/or T2 hyperintensity in the basal ganglia [52].

While these specific patterns have been amply recognized, a sizable proportion of patients reveal a normal picture or nonspecific findings on brain MRI [5]. That is why FDG-PET can improve the sensitivity of neuroimaging assessments in the diagnostic work-up. The greater sensitivity of PET imaging over MRI in detecting pathological changes in AE has been widely reported [5, 6, 18, 19, 53]. As mentioned earlier, some specific metabolic patterns seem to emerge as correlating with specific Ab, such as the posterior hypometabolism in anti-NMDAR encephalitis [8, 9]. Another typical pattern is MTL hypermetabolism in limbic encephalitis associated with LGI1 Ab [12] and onconeural antibodies [5, 26, 25], a condition seen much less frequently for anti-NMDAR AE.

In our view, when dealing with AE in the clinical setting, using brain FDG-PET as a mandatory supplement to whole-body acquisition should aim to identify these specific patterns and correlate them with a patient's clinical manifestations, rather than focusing on nonspecific focal areas of hyper- or hypometabolism. Recognizing these patterns could be particularly important in seronegative cases of AE, or when Ab detection methods complying with the criteria proposed by the international panel are unavailable [4].

In the diagnostic phase, brain PET imaging can also help AE to be differentiated from diseases with other specific metabolic patterns, such as rapidly neurodegenerative or prion diseases [14].

Neuroimaging has a role in monitoring the clinical course of AE as well. Increasingly consistent data from brain MRI imaging show an atrophic evolution of the hippocampal structures in limbic encephalitis associated with LGI1 Ab [17, 54], and onconeural Ab [28]. There have been reports of reversible cerebral atrophy (and irreversible cerebellar atrophy with a poor outcome) in NMDAR encephalitis [55], confirming a more likely functional than structural neuronal damage.

Finally, some case reports [39, 56], and series [10, 21], have highlighted the role of PET imaging in correlating metabolic changes with symptom severity and response to therapy. The study by Yuan et al. [10] associated various metabolic patterns with clinical course and Ab titers in NMDAR encephalitis. While comparing the lateral and medial occipital hypometabolism in NMDAR encephalitis with other types of AE, Probasco et al. found that this pattern was more evident in patients with more severe disease.

To assess the prognostic value of FDG-PET, and its role in driving therapy, larger (preferably longitudinal) studies are needed in age-matched untreated patients with the same Ab status, who undergo imaging studies at much the same time after the onset of their symptoms. Only then, a systematic correlation between MRI and FDG-PET findings will help to clarify a number of still unsolved clinical and technical issues.

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Compliance with ethical standards

Conflict of interest DC received consultant honoraria and a liberal donation from Piramal Imaging irrelevant to the aims of the paper. The other authors have no conflicts of interest to disclose.

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