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EXPERT REVIEW

FDG–PET in patients with autoimmune encephalitis: a review of findings and new perspectives

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Abstract

Purpose The present review aims to discuss the role of the brain ^{18}F-FDG–PET and ^{18}F-FDG–PET/CT (FDG–PET) in diagnosis and follow-up of the autoimmune encephalitis (AE) patients, highlighting the main findings and the new perspectives on use of these methods in the study of the disease.

Methods The literature search was performed in the following databases: PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar, according to the PRISMA statement. The main terms of search were: "autoimmune encephalitis" AND "^{18}F-FDG–PET OR ^{18}F-FDG–PET/CT", or the combination between the term "^{18}F-FDG–PET" OR "^{18}F-FDG–PET/CT" AND the antibodies receptors abbreviations (e.g., "NMDA", "VGKC", etc.). The methodological quality of the publications was assessed according to the QUADAS-2 criteria.

Results The search of the articles found 56 main articles. These articles encompassed 1,462 patients with AE positive antibodies, from which 808 had brain FDG–PET images with 714 (88.67%) showing alterations. Furthermore, some AE antibodies have specific metabolic signatures, detected in the images, which are discussed in the text. Moreover, patients at different stages of the disease may present different brain metabolic patterns. The areas of more common hypermetabolism were basal ganglia, hippocampus, amygdala, and cerebellum. The areas of more common hypometabolism were the visual cortex and a diffuse cortical metabolism.

Conclusions This extensive literature review shows the high sensitivity of FDG–PET and FDG–PET/CT in patients with AE. FDG–PET detects findings of hyper and hypometabolism which are suggestive of AE. Besides, AE caused by the different antibodies may present specific alterations which may be suggestive of each one. However, more prospective studies are necessary for these images become a standard diagnostic method of AE.

Keywords FDG–PET · FDG–PET/CT · Autoimmune encephalitis · Brain metabolism · Perspectives

Introduction

Autoimmune encephalitis (AE) is a debilitating neurological disorder characterized by inflammation of brain tissue. It is the most common cause of non-infectious acute encephalitis. This disease was described for the first time in 1888, when patients with neurological symptoms but without brain pathology were reported [1]. The post mortem investigation of patients with behavioral alterations related to acute encephalitis date from 1960s, revealing inflammation mainly in limbic region (hippocampus and amygdala), being the condition named limbic encephalitis (LE) [2], later associated with malignancy [3] and specific antibodies targeting intracellular neuronal antigens [4–8]. These onconeural autoantibodies are also associated with other paraneoplastic syndromes, characterized by relentless progression and poor treatment response, as they result from rapid and permanent neuronal loss. Over the past 20 years, novel forms of encephalitis associated with antibodies to neuronal surface or synaptic proteins have been described, generally with favorable outcome and good response to immunotherapy, even when associated with tumor, as they result from reversible neuronal dysfunction. Depending on associated antibody, AE can produce different clinical presentation and imaging findings.

The diagnosis of AE is still challenger. The clinical manifestations of AE may include behavioral, metabolic, inflammatory, infectious, due to a diversity of neurological

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damage. According to the publication of Graus et al., the background of investigation is based on guidelines already defined [9], contemplating clinical attention with laboratory tests (including blood, urine, cerebrospinal fluid—CSF), and magnetic resonance imaging (MRI) [10]. Nowadays, many types of antibodies have been associated with the disease.

Anti-NMDA receptor AE was first described in twelve women with ovarian teratomas presenting seizures, memory impairment, and behavioral alterations [11]. Antibody-mediated internalization of NMDAR affects neuronal plasticity and synaptic transmission [12]. Gamma-aminobutyric acid-A ($GABA_A$) receptor antibodies were found in the serum and CSF of patients with refractory seizures and status epilepticus associated with autoimmune comorbidities [10]. Similarly, antibodies against gamma-aminobutyric acid-B ($GABA_B$) receptor have been associated with AE patients, especially LE, with high prevalence of malignancy [13]. Antibodies against target proteins associated with voltage-gated potassium channels (VGKCs), and contactin-associated protein-like 2 (Caspr2), are associated with specific neurological manifestations: LE with faciobrachial dystonic seizures (FDS) in patients with leucine-rich glioma inactivated 1 (LGI1) antibodies [14, 15], and LE, neuromyotonia [16], and Morvan's Syndrome in patients with CASPR2 antibodies [17, 18]. Antibodies against the α-amino-3hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor are detected in patients with LE and frequently associated with tumors [19].

Dopamine-D2 receptor antibodies have been found in children with parkinsonism, chorea and psychiatric manifestations characterizing basal ganglia encephalitis [20]. The presence of Dipeptidyl-peptidase-like protein 6 (DPPX) generates similar symptoms to Dopamine-D2 receptor antibodies in adults, preceded by severe diarrhea with sudden weight loss, amnesia, dysphagia, trunk stiffness, and bladder dysfunction [21–23]. High concentration of glutamate decarboxylase (GAD) antibodies is associated with many neurological syndromes, including cerebellar ataxia (CA), LE, and stiff-person syndrome (SPS) in adult and pediatric patients [24, 25]. Recently, the SPS has also been associated with the presence of antibodies against glycine receptor (GlyR) in patients that may manifest progressive encephalomyelitis, myoclonus, and rigidity [26–29]. Although many types of AE have been described over the past years, neuronal antibody testing is not widely available, making the diagnosis of this condition frequently based on clinical aspects [10].

Positron emission tomography (PET) performed with fluorodeoxyglucose labeled with fluorine-18 (^{18}F-FDG) is an imaging technique able to identify glucose metabolic changes in several pathological conditions. When combined with computed tomography (PET/CT) or even with magnetic resonance imaging (PET/MRI), it is possible to fuse the physiological images from PET to the anatomical images from CT or MRI. FDG–PET can be applied in the diagnosis and follow-up of cardiovascular [30], infectious and inflammatory diseases, including the COVID-19 [31]. In the neurological studies, this technique has shown diagnostic and follow-up potential in the degenerative diseases [32], and epilepsy [33], being recently more explored in the AE [34]. The first case reports about the use of the PET in patients with symptoms of AE date from the 90s [35–38], and the first case series was reported in 2001, with the application of brain PET–FDG in the study of 11 patients with Rasmussen Encephalitis [39]. Given this context, this review summarizes the role of the FDG–PET and FDG–PET/CT in the diagnosis and follow-up of the patients with AE, bringing a discussion of the new perspectives for the use of these methods as a decisive tool to improve the knowledge about this disease, changing its diagnostic paradigm. Figure 1 shows examples of FDG–PET/CT images of patients with AE and the following positive antibodies: anti-NMDAR, anti-GAD and anti-LGI1.

Materials and methods

Literature search

To find the articles to compose this review, a computational organized literature search was conducted in the following databases: PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar, according to the PRISMA statement. The literature research was done using the following terms, as well as their combinations: "autoimmune encephalitis", "^{18}F-FDG–PET/CT", "^{18}F-FDG–PET", "brain inflammation". The combination between the terms "^{18}F-FDG–PET/CT" and "^{18}F-FDG–PET", and the antibodies receptors abbreviations (e.g., "NMDA", "VGKC", "Yo", and "DPPX") were also applied. The references of the articles retrieved were also checked to find another potentially relevant publications to expand the results. The search was updated until September 2021, without beginning date.

All the search and analysis of publications were performed according to the PRISMA statement [40]. The quality of the methodological approaches of the articles was assessed based on the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) [41].

Inclusion criteria

The articles had to fill the following inclusion criteria: be an original article, include at least 4 patients (pediatric and/or adult) suspected or diagnosed with AE, submitted to FDG–PET or FDG–PET/CT. Therefore, reviews, case reports, commentaries, editorials, meeting procedures, letters to the editor, only abstracts, books, electronic

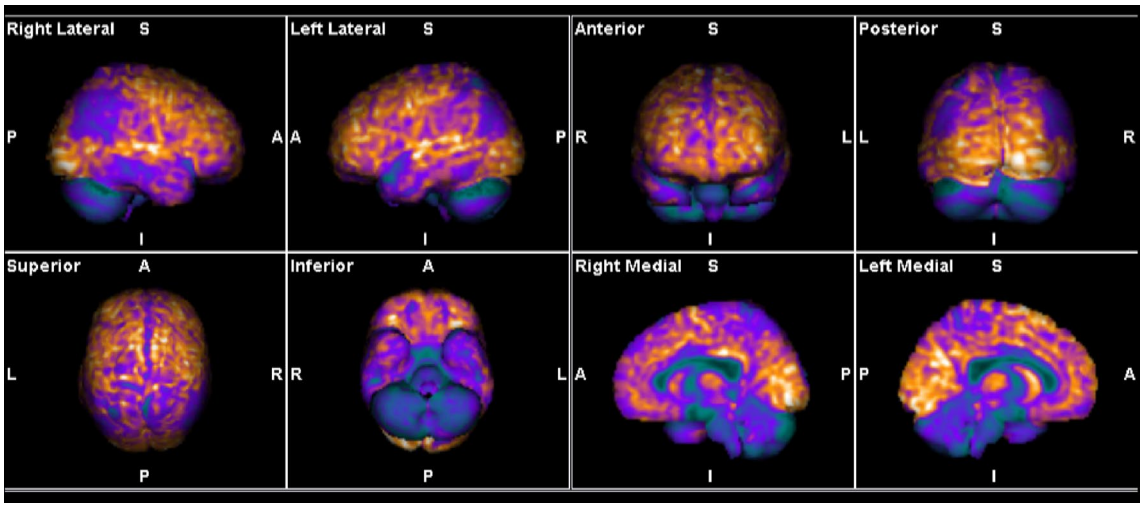

Fig. 1 Examples of ^{18}F-FDG–PET/CT images of a patient with AE and the positive NMDA antibodies. The 3D reconstructions of the ^{18}F-FDG–PET/CT show a hypometabolism in both parietal lobes and cerebellum

supplementary material, comments, preclinical studies, research reports, and other forms of scientific production were excluded.

Selection of articles

The articles which satisfied the inclusion criteria were also reviewed by our authors team, being included in this publication only after consensus. From 2,349 articles initially identified, 56 have been selected according to inclusion criteria.

Results

Literature findings and patients characterization

Figure 2 brings a diagram presenting the result of the literature search. From the literature explored, 1,462 patients

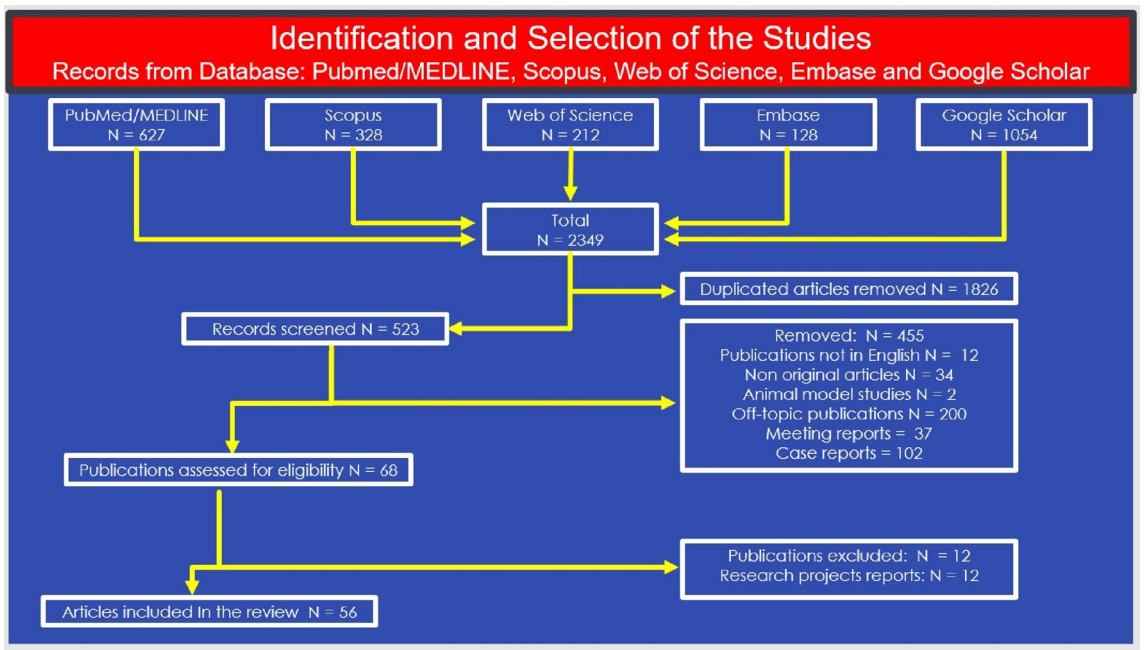

Fig. 2 PRISMA diagram outlining the identification and selection of the studies included in the review

were studied (699 male, 763 females), with age of symptoms onset 46.95 ± 17.63 years, median age 52 years. Some patients with AE presented more than one kind of antibody.

The articles encompassed 1,462 patients with AE positive antibodies, from which 808 had brain ^{18}FDG–PET (FDG–PET) images with 714 (88.67%) showing alterations. The percentage of each type of antibody is shown in Fig. 3.

The time between the PET imaging acquisition and the symptoms onset was very variable, ranging from 8 to 1,740 days (median = 87 days). Therefore, in most cases reported, FDG–PET imaging was not obtained in the acute phase of the disease.

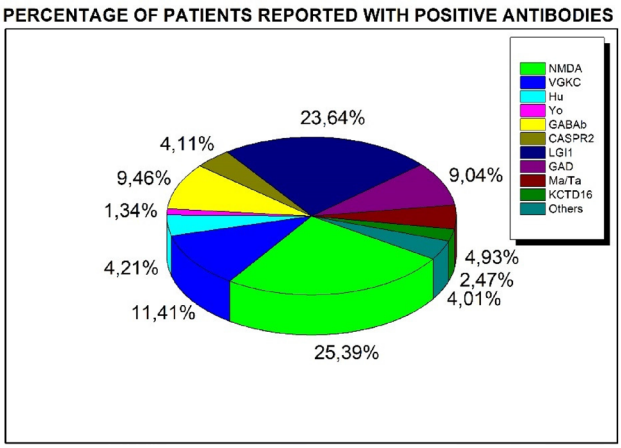

Fig. 3 Percentage of patients which present positive antibodies and brain FDG–PET alterations. In this figure, we included only patients with FDG–PET alterations and positive antibodies

General brain FDG–PET findings

Some authors analyzed the patient's data individually, whereas others worked with group statistical analysis. We compiled the results showing the brain regions with more common increased or decreased ^{18}F-FDG uptake due to AE. We analyzed the studies separating in individual or group statical analysis.

The studies analyzed patients individually or using imaging statistical tools for group evaluation. In the individual analysis, it is possible to note that basal ganglia are the brain regions more commonly affected within increased uptake of the radiotracer, followed by the hippocampus (Fig. 4A). On the other side, the visual cortex is the brain region with higher incidence of ^{18}F-FDG uptake reduction. Considering the group analysis, hypermetabolic findings were more frequently observed in cerebellum, hippocampus, basal ganglia (BG) and amygdala and hypometabolism was more frequently observed in the visual cortex, thalamus and striatum (Fig. 4B).

We also analyzed the studies which have explored the brain lobes as a whole to verify increasing or decreasing of ^{18}F-FDG uptake. In the individual analysis, for most of patients, increased uptake was more frequently observed in the temporal lobe, while decreased ^{18}F-FDG uptake was more frequent in the occipital lobe (Fig. 5A). In the group

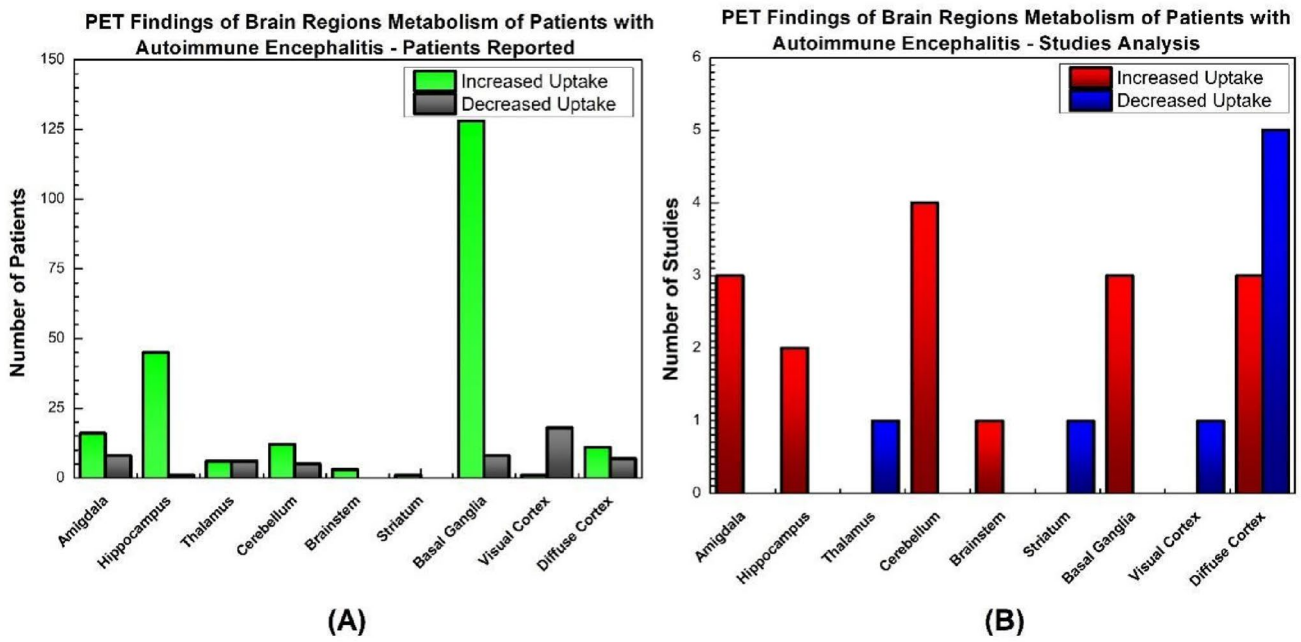

Fig. 4 Brain regions with hypermetabolism and hypometabolism on FDG–PET. Number of PET findings for brain areas of patients with AE for studies which considered individual subjects' analysis **A** and group analysis **B**

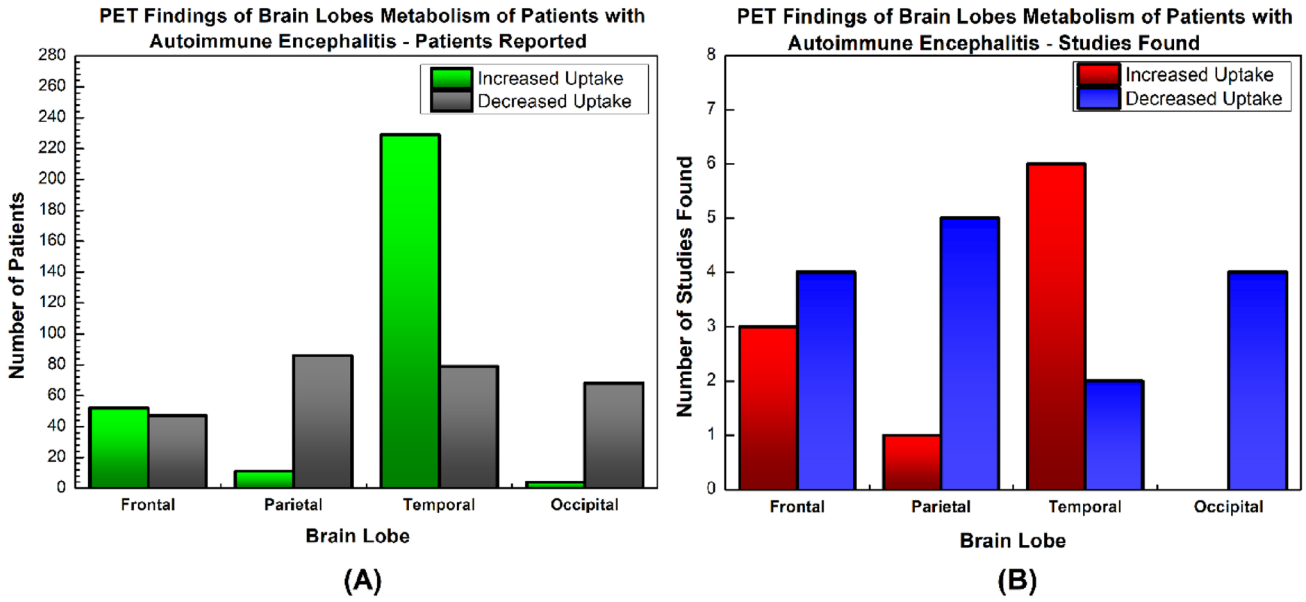

Fig. 5 Brain lobes with hypermetabolism and hypometabolism on FDG–PET. Number of PET findings for brain lobes of patients with AE for studies which considered individual subjects' analysis **A** and group analysis **B**

analysis, increased uptake was more common in the temporal lobe and decreased uptake was more common in the parietal lobe (Fig. 5B).

AE and brain FDG–PET Findings for specific antibodies

Based on subjects who presented just one type of neuronal antibody, it was possible to highlight some clinical manifestations of the specific-antibody syndrome and most common brain FDG–PET findings, which are displayed in Table 1. This table shows a correlation between antibody type, clinical manifestations of AE, and the main FDG–PET findings for patients with AE. Most studies report PET findings in patients with anti-NMDAR and anti-LGI1 encephalitis [42–45]. The following sections brings a literature overview of the clinical manifestations and the main FDG–PET findings in AE.

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is the most common type of AE [46], with higher incidence among women and frequent association with ovarian teratoma [11]. Clinically, in the early stage of the disease, the patients present fever, fatigue, and headache, followed by psychiatric alterations, such as psychosis, agitation and anxiety. Movement disorders, like choreoathetosis and orofacial dyskinesias altered consciousness, hypoventilation and dysautonomia may also occur throughout the disease course [47]. The first case series studying FDG–PET brain uptake in anti-NMDAR encephalitis, dates from 2012, when Leypoldt et al. conducted a retrospective statistical evaluation of 6 patients (mean age 21 years, 2 male), being the brain PET data extracted from the whole-body scan, acquired about 10 weeks after the symptoms started [48]. The results highlighted the increase of the ^{18}F-FDG uptake in the frontal and temporal regions in association with the occipital hypometabolism, described as a frontotemporal-to-occipital uptake gradient, in the acute phase. Some patients performed PET after the recovery phase of the disease, showing a decrease in the frontotemporal metabolism and an increase in the occipital metabolism. Probasco et al performed FDG–PET/CT in a group of 61 patients, from which 31 had antibodies detected (5 patients with anti-NMDAR) [34]. The images were acquired a median of 4 weeks after the symptom's onset, revealing an increased ^{18}F-FDG uptake in the basal ganglia, hippocampus, and in the temporal lobe as a whole, with a decreased uptake in the occipital lobe. The same antibodies were found in two patients with LE (aged 21–80 years), reported by Fisher et al. [49]. FDG–PET/CT were acquired between 4 and 60 days of disease and corroborated the previous results with increased metabolism in the temporal lobe and in the basal ganglia, and decreased metabolism in the occipital lobe.

Exploring the correlation between the ^{18}F-FDG–PET/CT findings and AE, Baumgartner et al. evaluated a series of 18 patients (mean age 45.6 years, 8 male), 3 of them having positive NMDAR antibodies [50]. An increased uptake in the striatum and cerebellum was found, as well

Table 1 Correlation between antibodies, clinical presentation and FDG–PET findings in AE

Antibodies	Patients reported	Typical clinical manifestations	FDG–PET main findings in early stage of the disease		References
			Hypermetabolism	Hypometabolism	
NMDA	185	Children: seizures, dyskinesias; adults: behavior changes	Frontal and pre-frontal areas; basal ganglia; temporal lobe	Occipital lobe	[34, 42, 43, 46–57, 66, 71, 78, 85, 94]
VGKC	230	Memory loss, faciobrachial dystonic seizures, hyponatremia	Mesial temporal lobe (hippocampus), basal ganglia, cerebellum	Diffuse	[13, 14, 34, 45, 47, 50, 51, 55, 57, 66, 71, 84–86]
$GABA_B$	90	Seizures, confusion, behavior changes, memory loss	Medial temporal lobe (amigdala and hipoccampus) and basal ganglia	Global hypometabolism	[46, 57, 60, 63–68, 81]
GAD	88	Seizures, muscle rigidity, CA, nausea, hallucinations	Hippocampus; cerebelar hemispheres,	Brain cortex (diffusely)	[13, 34, 47, 50, 55–57, 60, 66, 71, 72, 83, 84, 86]
Ma2/Ta2	46	Altered mental status; epilepsy; memory deficit;		Temporal, frontal, occipital and parietal lobes	[34, 47, 55, 60, 69, 71, 83]
Glycine	2	Muscle spasms, stiffness, rigidity, startle, eye movement disorders; sensory stimuli		Frontal lobe and midbrain	[72]
Ach	4	Memory loss, altered mental status without seizures		Mesial temporal lobe, diffuse cortical;	[34, 55]
Tr	1	Cerebellar syndrome		Cerebellum	[70]
KCTD16	24	Seizures, cognitive deficit, hallucinations, sleep disturbances	Mesial temporal lobe		[68]
Amphiphysin	3	Stiffness, disorientation, cognitive deficit		Temporal lobe	[46, 65, 72]
LGLON5	1	Sleep disorders, gait instability, peripheral symptoms	Primary sensorimotor cortices, basal ganglia and cerebellum		[60]
Aquaporin-4	2	Optical neuromyelitis, non-multiple sclerosis related		Occipital lobe	[34, 47]
CRMP5	3	Choreiform movements, ataxia, confusion, cognitive deficit		Caudate nucleus, putamen	[34, 47]
CV2	6	Parkinsonism, autonomic dysfunction	Hippocampus, amygdala		[34, 47, 60, 83]
Striational	3	Worsening balance, confusion	Cerebellum		[34, 47]
Ganglioside	1	Altered mental status, delirium, cranial nerve involvement		Generalized cortical	[65]
Contactin-2	2	Seizures, behavioral changes	Temporal lobe		[14]
Neuropil	7	Seizures, behavioral changes, peripheral manifestations	Frontal lobe	Temporal lobe	[86]
Ri	1	Ataxia, cognitive deficit, mild hemiparesis		Mesiotemporal area (severe)	[50]
AMPA	1	Ataxic gait, psychosis, agitation		Occipital	[63]

as a decreased uptake in the associative cortex, temporal and parietal lobes. Wegner et al. compared the uptake patterns of the ^{18}F-FDG in patients with anti-NMDAR and anti-LGI1 encephalitis [43]. For the first one, there was an increased uptake in the frontotemporal areas, while for LGI1, the hypermetabolism was observed in the basal ganglia, cerebellum, occipital and precentral areas.

Seizures outcomes of patients with LE associated with NMDA antibodies have been studied by Sarkis and colleagues, with the brain FDG–PET/CT obtained for 5 antibody positive patients [51], revealing increased uptake in the temporal lobes. Lagarde et al conducted a serial study with pediatric anti-NMDAR encephalitis patients that underwent FDG–PET/CT scans 3–4 weeks after the disease onset. Eleven patients were studied (mean age 10 years, 4 male), presenting behavioral troubles, movement disorders, and seizures. The brain ^{18}F-FDG uptake pattern was similar to that seen in adults (basal ganglia hypermetabolism), with the following particular features: extensive and symmetric cortical hypometabolism in the frontal lobe, and asymmetric anterior focus of hypermetabolism [42]. Other FDG–PET/CT study of children with AE was conducted by Turpin et al. From 34 subjects evaluated, six had NMDAR antibodies, and basal ganglia hypermetabolism was visually detect in 26.5% of the cases, and quantitatively in 82.3% [52].

The brain metabolism in different stages of anti-NMDAR encephalitis was reported by Yuan et al. in 2016, which acquired FDG–PET/CT images in the subacute, acute, early recovery, recovery, and relapsing phases [53]. Considering a group of 8 patients (aged 12–35 years, 3 male), there was a hypermetabolism in the basal ganglia, temporal and frontal lobes, and a severe hypometabolism in the bilateral occipital lobes in the subacute/acute phase (5–6 weeks from the disease onset high level of antibodies). In the early recovery phase (9–13 weeks from the onset), the previous pattern is almost preserved, but there is a discrete reduction in the basal ganglia metabolism. Concurrent antibody levels were weakly positive. Finally, in the recovery phase, the brain metabolism is almost normal (no antibodies detected). Three patients presented relapsing disease, each one with positive antibodies and different symptoms: seizures, unconsciousness and abnormal behavior. Although the occipital metabolism had returned to normal, new focus of hypermetabolism were found in the temporal lobe and in the basal ganglia.

Two patients with recurrence of the disease were reported by Quian et al, that characterized the abnormalities of the brain FDG–PET in a group of 11 patients (mean age 25.9 years, 6 male) with AE, 3 of them with NMDAR antibodies [54]. The mean time between the disease onset (with two or more symptoms) and the FDG–PET acquisition was 21 days. Increased uptake was observed in the prefrontal, frontal, parietal and temporal lobes, and in the basal ganglia, with decreased metabolism seen in the occipital lobe.

In a voxel-by-voxel semiquantitative analysis, Solnes et al have found statistical differences between brain uptake in patients presenting positive NMDA or other types of antibodies, as such as those related to rubella virus, herpes simplex virus and cytomegalovirus, with characteristic occipital hypometabolism in patient positive for this antibody [55]. Even with the application of different analysis methods, recent studies have corroborated these metabolic findings on FDG–PET in anti-NMDAR AE. The increased metabolism in basal ganglia with decreased metabolism in occipital lobe is also reported in the studies of Tripathi [56], Probasco [47], Strohm [57], Turpin [52], Ge [58], Nissen [59], and Moreno-Stébanez [60].

Tripathi et al. reported a series of 24 patients (mean age 52 years, 10 male), with 16 anti-NMDAR encephalitis patients [56]. The authors performed visual analysis and two distinct routines of semiquantitative analysis of the FDG–PET/CT brain images: GE Cortex ID and Siemens Scenium software. These computational routines were developed by the PET/CT scanners manufacturers and allow the statistical analysis of the patients' images, which are compared with an imaging database of the normal subjects to identify significant areas of hypometabolism or hypermetabolism. The visual analysis showed lower sensitivity than the semiquantitative approach. Both quantitative software led to analogous results: hypermetabolism in the basal ganglia and in the temporal lobes, with hypometabolism in the occipital region. Z-score values from both tools allowed to distinguish the FDG–PET uptake pattern of anti-NMDAR encephalitis from the AE associated with the anti-LGI1 or anti-GAD.

The GE Cortex ID software has also been used by Probasco et al. [34], which retrospectively explored a database of 61 patients (mean age 26 years), with 8 anti-NMDAR encephalitis patients. FDG–PET/CT imaging acquisitions were done about 8 weeks from symptoms start. They concluded that most of the patients have both hypo and hypermetabolic areas in the occipital and temporal lobes, respectively, from which the uptake magnitude can be evaluated statistically (e.g., Mann–Whitney *U* test with Bonferroni correction) to distinguish the brain uptake patterns in different types of AE.

Strohm et al. applied the FDG–PET to study 12 patients with new-onset status epilepticus, three of them anti-NMDAR positive. For these patients, a parietal and occipital hypometabolism that persists throughout the disease course was detected [57]. The work conducted by Ge et al. explored the acute phase of the disease in a group of 24 anti-NMDAR positive patients. The visual and the statistical analysis (comparing patients to the control group) revealed a significant occipital hypometabolism, as well as the basal ganglia and the frontal–temporal hypermetabolism [58]. In a populational study of the AE in Denmark, Nissen et al. analyzed the FDG–PET of 17 anti-NMDAR encephalitis patients, and found decreased occipital metabolism in 15 (88%) patients [59]. In the series of 43 patients reported by Moreno-Estébanez et al. (55.8% seropositive patients and 13% with NMDAR antibodies), patterns of hypermetabolism in limbic areas were identified [60].

In summary, the main alterations in the FDG–PET images are the hypermetabolism in the frontal, temporal

and striatum regions, with the occipital hypometabolism in the acute and sub-acute phases of the disease, sometimes described as a frontotemporal-to-occipital uptake gradient.

Anti-Caspr2 and anti-LGI1 encephalitis

The first reports of the AE associated initially with anti-VGKC date back to 2001, describing patients with neuromyotonia, Morvan's syndrome and LE [16, 63]. The investigation of this disease using the FDG–PET date from 2005, when Ances et al. reported 1 patient with LE and anti-VGKC antibodies with increased brain uptake in the medial temporal lobes [64]. While the clinical spectrum emerged, it became clear that the pathogenicity is associated with the antibodies against proteins complexed with the VGKC: leucine-rich-glioma-inactivaed1 (LGI1) and contactin-associated protein-like 2 (Caspr2) [65, 66]. Anti-LGI1 encephalitis is characterized by LE with faciobrachial dystonic seizures [67, 68]. Anti-Caspr2 encephalitis predominantly affects elderly men and can be associated with LE, with or without cerebellar dysfunction, Morvan syndrome and peripheral nerve hyperexcitability [66].

Irani et al. reported abnormal brain ^{18}F-FDG uptake in 8 patients (mean age 64 years) with LE and faciobrachial dystonic seizures related to VGKC antibodies, especially anti-LGI1 [12]. For most of the patients, the temporal lobe and basal ganglia hypermetabolism was found. Flanagan et al. studied 11 patients with faciobrachial dystonic seizures and LGI1 antibodies using FDG–PET, reporting basal ganglia hypermetabolism in 4 patients, basal ganglia hypometabolism in 2 patients, diffuse hypometabolism in 3, mesial temporal hypermetabolism in 3 and bifrontal hypometabolism in 2 patients [69]. LE have also been studied using FDG–PET by Baumgartner et al. [52]. From a group of the 18 patients (mean age 55.3 years, 8 male), 7 had VGKC antibodies, 2 in association with anti-CAspr2, one with anti-LGI1, and one with anti-NMDAR. A visual analysis associated with scores identified mesiotemporal hypermetabolism and hypometabolism in the association cortices in one anti-Caspr2 and anti-LGI1 patient. The patient with Caspr2 antibodies had striata hypermetabolism and the patient with anti-NMDAR had thalami hypometabolism. Similar results have been found in other study [70]. To compare the metabolic brain patterns of the anti-NMDA and anti-LGI1 AE, Wegner et al. evaluated statistically the FDG–PET/CT images of 10 patients (mean age 36.5 years, 4 males, 6 with anti-NMDAR encephalitis, and 4 with anti-LGI1 encephalitis [45]. The mean time between the symptoms onset and the imaging acquisition was 2.5 months. As a result, it was observed that the anti-LGI1 encephalitis was characterized by hypermetabolism in the basal ganglia, cerebellum, occipital and precentral areas, with hypometabolism in the frontomesial region. On the other side, images of patients with anti-NMDAR encephalitis demonstrated a regionally limited hypermetabolism in the frontotemporal areas, in addition to the occipital hypometabolism.

The outcome of the patients with anti-LGI1 AE was evaluated by Shin et al., that studied a group of 10 subjects (mean age 60.5 years, 8 male), some of them presenting faciobrachial dystonic seizures [71]. The statistical analysis of the FDG–PET/CT images acquired in the early phase of the disease and after treatment indicated a poor outcome for patients with medial temporal hypermetabolism, with greater chance of recurrence. Given the relevance of the temporal lobe metabolic alterations for the outcome of patients with anti-VGKC AE, Celicanin et al. focused on the analysis of the hippocampus using the FDG–PET/CT [47]. From a group of 9 patients (mean age 62 years), it was observed unilateral ($n = 3$) or bilateral ($n = 4$) hippocampal hypermetabolism, and unilateral hypometabolism ($n = 1$). One subject had a normal scan. Follow-up images of 3 patients were available, showing unilateral ($n = 2$) or bilateral ($n = 1$) hippocampal hypometabolism. Analogous results (bilateral hippocampal hypermetabolism) were found by Lv et al. in a study comparing the sensitivity of the visual and the semiquantitative analysis of the FDG–PET/CT applied to the 23 patients with anti-LGI1 encephalitis [72]. In the semiquantitative analysis, alterations in temporal lobe and basal ganglia were found, respectively, in 56% and 73% of the patients. These alterations were not detected in the visual analysis. It was concluded that the semiquantitative analysis of the images increases the sensitivity to identify brain metabolic alterations related to anti-LGI1 encephalitis.

A voxel-by-voxel statistical analysis of the FDG–PET/CT conducted by Dodich et al. revealed altered metabolic patterns in 2 patients with anti-LGI1: hypometabolism in the prefrontal cortex, cingulate, insula, pallidum, and in the medial temporal lobe, and hypermetabolism in the bilateral sensorimotor cortex, and in the lateral temporal lobe. They also reported an anti-Caspr2 with the FDG–PET showing hypometabolism in the bilateral orbitofrontal cortex, nucleus accumbens, cerebellum and insula, and hypermetabolism in the hippocampus and sensorimotor cortex [73].

The brain metabolic differences of the patients presenting anti-LGI1 antibodies with or without faciobrachial dystonic seizures were explore by Liu et al., for a group of 34 patients (mean age 61 years, 24 males, 50% manifesting the seizures) [74]. From the voxel-based statistical analysis of the brain FDG–PET/CT, it was verified that the basal ganglia hypermetabolism only occurs in patients with this type of seizures, reinforcing the potential of this imaging method to diagnose and to characterize the patients with AE.

Qin et al. reported 25 patients with Caspr2 antibodies and 5 patients underwent PET scan, with CNS altered metabolic findings in one patient: increased metabolism of the bilateral basal ganglia and the mesial temporal lobe [75].

Finally, Li et al. evaluated retrospectively the brain metabolism in the anti-LGI1 AE [76]. The authors divided the patients into four groups, according to the semiology of the disease: focal impaired awareness seizures (FIAS), faciobrachial dystonic seizures FBDS-only, faciobrachial dystonic seizures plus (FDBS-plus) and focal aware motor seizures. The number of subjects in each group was 17, 6, 8, and 2, respectively, totalizing a group of 33 patients (median age 60 years, 22 men). The average time from symptoms onset was 3.1 months. In the quantitative analysis comparing the patients to control group, it was highlighted that patients with FIAS displayed extensive hypermetabolism in the following areas: bilateral basal ganglia, cerebellum, mesial temporal lobe, insula, and precentral gyrus. In a similar way, patients with FBDS-plus also present a wide range of hypermetabolism (bilateral basal ganglia, mesial temporal lobe, precuneus, cerebellum, left postcentral gyrus, insula, and superior parietal lobule, right substantia nigra, middle occipital gyrus, and cuneus), contrasting with the findings of the patients with FBDS-only, in whom a limited hypermetabolism of cerebellum and left medial globus pallidus was found. Anti-LGI1 encephalitis may present different metabolic patterns on FDG–PET, being hypermetabolic changes more frequently observed in the medial temporal lobe, and in the basal ganglia, the latter especially in the patients with FBDS. Cerebellum hypermetabolism may also be observed. Hypometabolic changes are diverse and may be diffuse or include the basal ganglia, frontal regions, mesial temporal lobe, and thalamus.

Few data are available on anti-Caspr2 encephalitis brain metabolic patterns on FDG–PET, but the most frequent finding is the hypermetabolism in the mesial temporal lobes and basal ganglia. Areas of cortical and cerebellum hypometabolism may also be observed.

Anti-GABAB receptor encephalitis

Neurological manifestations associated with the GABA antibodies have been reported since the 1980s [61, 62]. Among these manifestations, seizures, confusion, memory loss, muscle stiffness, and sensory polyneuropathy may be highlighted. Anti-$GABA_B$ receptor AE was initially described by Lancaster et al. [13], and the first FDG–PET/CT series investigating the disease was reported by Kim et. al. in 2014, which studied a group of 5 patients with $GABA_B$ receptor antibodies (mean age 63 years, 4 male) [63]. The authors found the medial temporal lobe hypermetabolism in 2 patients, and the diffuse cortical hypometabolism in one patient. This pattern remained almost unchanged in the follow-up images of most of the patients. The time between the symptom's onset and the brain imaging acquisition was ranged from 20 days to 2 years (mean 30 days). Diffuse cortical decreased metabolism was observed in three patients.

FDG–PET/CT images was used by Zhu et al. to study a group of 14 patients with anti-$GABA_B$ receptor AE (mean age 52 years, 9 male) [64]. Increased uptake in the temporal lobe, hippocampus, and basal ganglia were observed in 6 patients. Shen et al. applied a semiquantitative analysis in a group of 15 patients with LE, 13 of them harboring $GABA_B$ receptor antibodies, and 2 patients had positive brain FDG–PET finding: the cortical hypometabolism. The authors mentioned that the cortical hypometabolism could be a characteristic of the synaptic dysfunction, while the mesial temporal hypermetabolism might be a consequence of the inflammatory process [65].

Strohm et al. verified medial temporal lobe hypermetabolism in one patient with anti-$GABA_B$ positive new-onset refractory status epilepticus [57], whereas the works of Steriade verified the mesial temporal lobe hypermetabolism in one patient with anti-$GABA_B$ receptor encephalitis [66].

The evolution of the $GABA_B$ AE, and its prognostic factors were also explored by Wen et al., which followed a group of 20 patients (mean age 59.4 years, 12 male) [67]. Three of them had an FDG–PET/CT scan, and one patient presented bilateral hippocampal hypermetabolism. Based on the follow-up of the group, it is seen that older patients had a poor outcome when compared to younger ones, which is reinforced when the hippocampal hypermetabolism remains, even after the treatment. Concluding, it was observed that in positive patients for $GABA_B$ antibodies the FDG–PET images have detected hypermetabolism mainly in the medial temporal lobe, including amygdala, hippocampus, and the basal ganglia, associated with the global cortical hypometabolism [68].

Anti-GAD encephalitis

Antibodies against the GAD, the rate limiting enzyme for the GABA synthesis, were first detected in the serum and CSF of patients with SPS, a rare CNS disease which produces rigidity, CA, and cramps commonly related to the other autoimmune conditions, usually the type I diabetes mellitus [74, 75]. These antibodies may also be associated with LE, CA, temporal lobe epilepsy and dementia [83]. Patients with LE and anti-GAD were studied with the FDG–PET/CT for the first time in 2005 [61].

In 2010, Malter et al. studied 53 LE patients (mean age 47 years), from which 10 presented anti-GAD, and brain FDG–PET/CT showing the hippocampal hypermetabolism in the earlier phase of the disease [84], which is also reported by other authors [50]. In addition to the temporal lobe hypermetabolism, some studies have described the diffuse cortical hypometabolism for this group of patients [48, 53, 58, 80, 85], as well as the brainstem and basal ganglia hypermetabolism [51]. Strohm et al. mentioned the presence of the diffuse cortical hypometabolism as a predictor of poor

outcome for patients presenting GAD antibodies alone or in combination with others [79].

Amygdala hypometabolism were related by Deuschl et al. in three patients expressing GAD antibodies, one of them with bitemporal and biparietal hypometabolism. From a sample of 20 patients (mean age 38 years, 5 male), 8 presented GAD antibodies. Combining visual and quantitative analysis, the authors also reported that patients with bitemporal and biparietal hypometabolism were the subjects with a worse outcome [86].

Wang et al. studied recently a sample of 170 subjects with SPS and CA [87]. From this sample, 50 patients (mean age 41.5 years, 16 male) had brain FDG–PET/CT images. The range time between the symptoms onset and imaging acquisition was 0–333 months, considering the follow-up exams. In a group of 30 patients with GAD65 antibodies, the visual and quantitative analysis of patients' images in the acute/subacute phase of the disease revealed different metabolic patterns depending on the clinical phenotype: SPS patients showed thalamus hypometabolism and brainstem hypermetabolism, while the brainstem, and the cerebellar hypermetabolism were observed in the patients with pure CA. Follow-up images acquired about 3 years after the symptom's onset have shown hypometabolism of the cerebellum in one patient.

From the studies reviewed, it was observed that each clinical phenotype associated with GAD antibodies presents different metabolic patterns in the FDG–PET: LE with increased or reduced uptake in the temporal lobe, including hippocampus and amygdala; SPS with thalamus hypometabolism and brainstem hypermetabolism; and CA with brainstem and cerebellar hypermetabolism. Some patients may also present diffuse cortical hypometabolism.

Other antibodies

AE associated with other antibodies may also present brain metabolic alterations showed in the FDG–PET/CT images. Ma2/Ta2, Hu and Yo are antibodies detected targeting intracellular neuronal antigens, typically associated with the paraneoplastic neurological syndromes [55]. Temporal lobe hypermetabolism has been reported in patients with anti-Ma2/Ta2 positive LE [34, 47, 69]. Patients with Hu antibodies often associated with LE, have presented hypermetabolism in the medial temporal lobes, and hypometabolism in the association cortices [34, 55]. Anti-Yo is associated with paraneoplastic cerebellar degeneration and FDG–PET studies reveal the cerebellar hypermetabolism [70, 71].

Antibodies against glycine receptors have been found in children and adult patients with SPS, or progressive encephalomyelitis, rigidity, and myoclonus [27]. There are few FDG–PET/CT images described in the literature about these patients, and they commonly presented the frontal lobe and midbrain hypometabolism [72].

Table 1 summarizes the main findings of the literature explored, and the number of patients reported. The table highlights the main brain areas of hypometabolism or hypermetabolism in the FDG–PET/CT studies, for the antibodies described in this session and others antibodies studied.

Paraneoplastic syndromes

The AE is a condition oftentimes expressed as a paraneoplastic syndrome. In about 60% of patients, highly specific antineuronal antibodies (e.g., Hu, Yo, Ma/Ta) can be detected. For about two-thirds of these patients, the neurological manifestation precedes the tumor diagnosis up to 4 years [70, 73].

Since the 90s, the literature has reported the findings of tumors in patients with symptoms of AE and positive antibodies, using whole-body images acquired with the PET or PET/CT techniques [37, 38]. Considering the articles revised in this work, from the 1,462 patients studied, 266 had tumors detected by ^{18}F-FDG–PET/CT, corresponding to 18,20% of the whole sample. The most commonly found tumor was the small cell lung cancer (SCLC) [8], followed by the ovarian teratoma [11, 74], and other ovarian tumors [75]. The number of the patients affected by each one of these tumors was 61, 40 and 61, respectively, corresponding to 4,17%, 2,73% and 4,17% of the whole sample.

Lymphomas and neuroendocrine tumors have also been detected in some of these patients, corresponding, respectively, to 2,32% and 0,82% of the patients reported [70]. Other less common, but also found tumors include the breast and prostate tumors, as well as seminoma, thyroid tumors, and the bronchial carcinoma [34, 50]. The graphic of Fig. 6 summarizes the distribution of the most commonly found tumors in the patients with symptoms of AE.

Meta-analysis for FDG–PET brain findings

The forest plot of Fig. 7 brings the meta-analysis results based on the odds ratio, and the random effect model [93]. From the articles explored, the detection sensitivity of the FDG–PET–CT in the AE is 87% (72 to 97%), with a heterogeneity index $I2 = 69\%$ ($p < 0.001$). The statistical analysis reveals that most articles point to the high capability of the FDG–PET–CT to diagnosis and follow-up of the patients with AE, which may include the potential to differentiate the pathology from other diseases [49, 53].

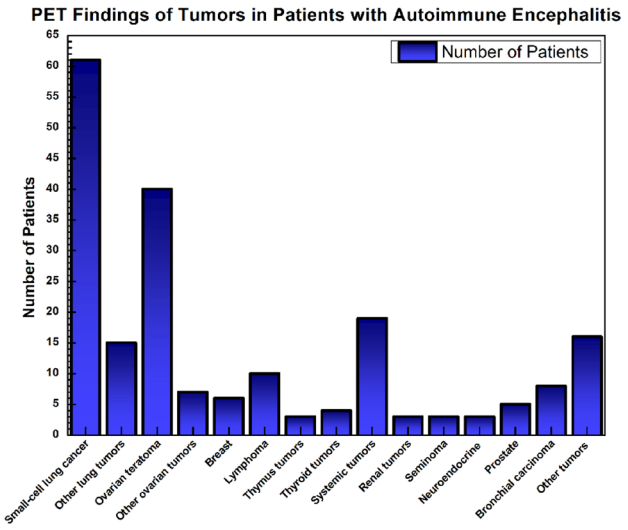

Fig. 6 Distribution of the main tumors found in the literature using PET in patients with symptoms of AE

Discussion

We presented an extensive literature review regarding the use of the FDG–PET or FDG–PET/CT in AE. One of the main findings of this review is the high sensitivity of FDG–PET (87%) to detect metabolic alterations in the large population of patients with AE ($n = 1{,}462$). FDG–PET can detect findings of hyper and hypometabolism, which may be suggestive of AE. Besides, depending on the neuronal antibody type and the clinical phenotype, different metabolic patterns are expected in the PET–FDG. These findings contribute to change the diagnostic paradigm of the AE.

This study brought a compilation of the main findings of FDG–PET for diagnosis and follow-up of patients with AE. The findings also highlight the importance of the method to discern metabolic brain patterns of AE identifying brain ^{18}F-FDG uptake suggestive of some types of antibodies, such as NMDA, $GABA_B$, GAD, and antibodies of the VGKC complex. FDG–PET can contribute to the diagnosis of the disease, especially when specific antibody tests are not available, which is the reality of many developing countries.

According to the most reported studies, patients with the anti-NMDAR encephalitis presented higher ^{18}F-FDG uptake in the temporal lobe and basal ganglia, and lower uptake in the occipital lobe [34, 47, 52, 54]. Hypermetabolism in frontal, prefrontal, and parietal areas have also been found. Some authors describe this pattern as a frontotemporal-to-occipital uptake gradient [54, 60]. Despite some differences between the common symptoms observed in children (seizures and dyskinesias), and adults (behavioral changes), the ^{18}F-FDG uptake patterns for both groups are similar [52, 76]. Few studies diverge from these findings, relating a decreased ^{18}F-FDG uptake

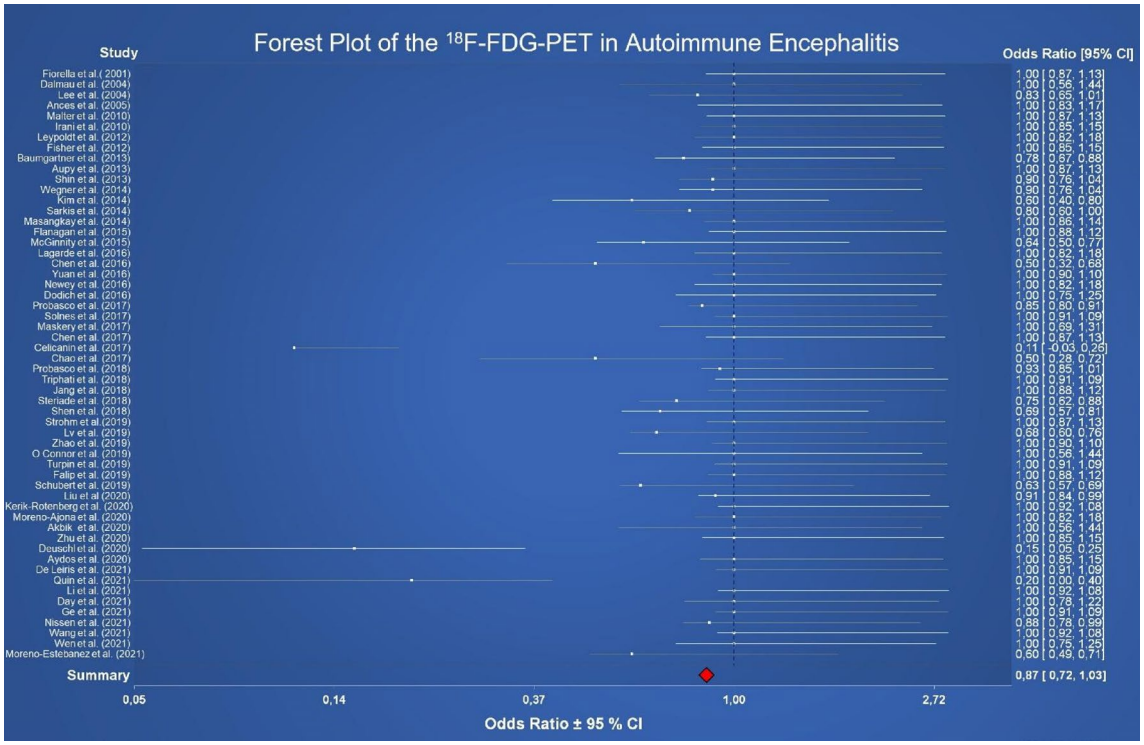

Fig. 7 Forest plot summarizing the meta-analysis of the FDG–PET for patients with AE (log scale)

in the associative cortex, temporal, and parietal lobes [49, 56, 58].

Only one prospective study explored the different stages of the anti-NMDAR AE using the ^{18}F-FDG–PET/CT, reporting different uptake characteristics among the disease phases: subacute and acute phase (basal ganglia, temporal and frontal lobe hypermetabolism, with severe occipital hypometabolism); early recovery phase (same pattern as the previous stages, with mild reduction in the basal ganglia metabolism); recovery phase (almost normal brain metabolism); and relapsing phase (new focus of hypermetabolism). Thereby, this study showed that the FDG–PET/CT findings depend on the disease stage [53].

During the disease, many patients have their brain metabolic alterations resolved throughout the treatment. Multiple FDG–PET acquisitions of the same patient in different phases of the AE revealed that some subjects manifested new brain alterations between different scans, and some of them have metabolic alterations which persisted throughout the disease course, pointing out a poor outcome [57, 77]. These findings reinforce the importance of the straight definition of the disease stage of each patient before the group statistical analysis.

A difference in the recovery has also been reported for the different age groups. Younger patients with anti-$GABA_BR$ have had a better outcome when compared to older ones, for whom the hippocampal hypermetabolism still remains after the treatment [67]. Even in other types of AE, younger patients' tend to have a better outcome [59].

Some uptake findings are common between different antibodies. Hypermetabolism in basal ganglia and mesial temporal lobe including the hippocampus can be observed in many cases of AE, with anti-LGI1 [44, 45, 78, 79], anti-Caspr2 [45, 80], anti-$GABA_B$ [13] and anti-Hu [70] antibodies. Another finding is the hypermetabolism in the cerebellar hemispheres which has been reported in AE related to anti-NMDAR, anti-GAD and anti-Yo antibodies. These hypermetabolic areas may be consequence of the inflammatory processes [60].

Another common finding among the patients with AE is the diffuse hypometabolism of the cerebral hemispheres, which can be observed in the anti-LGI1 [43, 81, 82] and anti-GAD AE [72, 83, 84]. Some researchers have noted that these findings of the ^{18}F-FDG uptake are hypothetically a characteristic of the synaptic dysfunction [24]. Besides, others authors consider this lower ^{18}F-FDG uptake as a predictor of poor outcome [48]. A worse outcome has also been highlighted for the patients with bitemporal and biparietal hypometabolism. Following these patients for 3 years, some authors verified that the hypermetabolic areas has become hypometabolic over time, which may also occur in other AE type [72].

It was observed a variety of different methods to analyze the brain images. Among the analysis methods applied to the PET data (visual, semi-quantitative, and quantitative), it is possible to notice that the visual analysis is complemented by semi-quantitative or quantitative analysis to evaluate the alterations due to AE. A variety of tools was applied in the imaging quantification, among which is possible to highlight the Statistical Parametric Mapping (SPM), GE CortexID®, and Siemens Scenium® as the main choices, being the SPM the most used software. Some brain metabolic changes due to the disease can be subtle, difficult to identify by visual analysis. From all articles included in this review, many of them have used quantitative analyses (43.75%), showing the importance of PET imaging quantification for an accurate evaluation of the brain metabolic changes due to AE [34, 48, 54, 55, 60, 78, 83, 85].

AE manifestations may represent paraneoplastic conditions and some authors have performed a whole-body FDG–PET for tumor screening. In the literature reviewed, from the 1,462 patients studied, 18.20% had some tumor. The most commonly found tumor was the SCLC [34, 65, 70], followed by ovarian teratoma [34, 58–60, 77], and other ovarian tumors [13, 34, 60, 70, 71, 77]. It was observed that AE has been rarely related to tumors in the pediatric population [52]. Other diseases detected were lymphomas [34, 59, 70, 71], neuroendocrine tumors [13, 65, 71], thyroid [77, 86], breast [34, 45, 50, 71] and prostate tumors [59, 87], as well as seminoma [34, 71] and bronchial carcinoma [50].

Although the studies explored in this review have brought many positive findings that corroborate for the use of FDG–PET as a tool for diagnostic, characterization, and follow-up of the patients with AE, there are some limitations to consider. First of all, there is not a standard protocol for the imaging acquisition, reconstruction, and processing of the FDG–PET data, leading to a risk of bias in the results, mainly in the quantitative analysis. In some cases, PET data were acquired and processed with different methods are compared in the same study [50, 59]. Other limitation is that most of the studies with the FDG–PET and FDG–PET/CT in AE are retrospective series [47, 50, 52, 59, 60, 67]. Unfortunately, prospective studies are still rare, despite the increase of access to PET/CT scanners [83, 88, 89]. Another important limitation is that the studies reviewed showed a large range of time between symptom's onset and PET acquisition (8–1,740 days, media*n* = 87 days). This finding reveals that each study reflects a different phase of AE. Besides, sometimes data from patients in different stages of the disease have been analyzed in the same group [34, 45, 56, 72, 85].

Some studies explored in this review also present magnetic resonance imaging (MRI) findings for patients with AE, as well as the FDG–PET/MRI data. According to the authors, FDG–PET/CT has detected brain metabolic changes even when the MRI is normal [50, 55, 83]. It is pointing out

that FDG–PET/CT can be seen as the first choice for images of AE patients, not disregarding the importance of the MRI in these cases, especially considering the great versatility of the protocols provided by this method.

The development of new radiotracers tends to improve the specificity to detect the brain physiology alterations in AE. One of these is the ^{18}F-Flortaucipir, used in studies of the Alzheimer's disease (AD) [90]. It is a compound capable of binding paired-helical filaments that comprise neurofibrillary (tau) tangles, being the first radiotracer that allows the detection of the tau pathology, a distinctive characteristic of the AD in the brain, recently identified in the recovery phase of the anti-LGI1 AE. Considering four patients in the recovery phase of this disease, normal, and AD subjects, the authors observed an increase of the standard uptake value (SUV) in the amygdala, inferior temporal lobe, lateral occipital, and entorhinal cortex for the first group. In this case more specific radiopharmaceuticals are interesting, given that in general, young patients tend to present temporal and diffuse hypermetabolism in the early phases of the disease, while older ones have PET findings of hypometabolism that may be confused with degenerative diseases [91]. Other radiotracer applied to study AE patients is the [^{18}F] GE-179, a ligand that can selectively binds to the NMDA channels. For patients with refractory epilepsy related to NMDAR antibodies, there was an increased uptake of this marker in the frontal, parietal and temporal lobes. However, antidepressant drugs can lead to bias in the results [92]. Some others radiopharmaceuticals for brain imaging, as such as ^{18}F-SMBT-1 (a reactive gliosis marker) [93], and ^{11}C-BTFP (proliferation, migration, and survival of different nerve cells) [94], should also be explored to improve the knowledge about the disease.

The work of Graus et al., reference as a diagnostic algorithm of the AE, brings the main criteria for the diagnosis of this disease. The approach includes clinical and laboratorial exams, CSF analysis and analysis of the MRI findings. FDG–PET is just mentioned as an alternative to MRI when bilateral abnormalities on T2-weighted fluid-attenuated inversion recovery are highly restricted to the medial temporal lobes [10]. Given the vast evidences collected from the articles reviewed, there is a high potential of FDG–PET to change the diagnostic paradigm of the AE.

Conclusion

This extensive literature review shows the high sensitivity of FDG–PET and FDG–PET/CT to detect brain metabolic changes in patients with AE. FDG–PET detects findings of hyper and hypometabolism which are suggestive of AE. Some metabolic patterns may suggest association with specific neuronal antibodies and clinical phenotypes, which can change the diagnostic paradigm of the disease. However, more prospective studies are necessary for these images become a standard diagnostic method of AE.

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