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Positron Emission Tomography with ^{18}F-Fluorodeoxyglucose Imaging Patterns in Autoimmune Encephalitis

Marianne Kimura Soriano[1] · Carla Rachel Ono[1] · Artur Martins Coutinho[1,2,3]

Abstract

Purpose of Review Autoimmune encephalitis (AE) is an underrecognized and potentially curable disease, which has been the focus of intense neurologic research. In the present manuscript, we review recent updates and the current role of brain positron emission tomography imaging with ^{18}F-fluorodeoxyglucose (FDG-PET) in the detection of AE. We appraise the many metabolic imaging manifestations described in this disease, the role of PET-FDG in its diagnosis and follow-up, and the possible relationship between some patterns and specific autoantibodies. We also briefly discuss recently recognized imaging patterns and the potential impact of new technologies in recognition of such metabolic imaging appearances.

Recent Findings AE findings on FDG-PET may have various patterns, but three are dominant and can be summarized as follows: (1) hypermetabolism in cortical areas, mainly in mesial temporal regions and less frequently in basal ganglia and higher cortical regions, is a common pattern in early stages of the disease. Such pattern is highly suggestive of limbic AE, since it has not been described in many other entities, except for brain tumors and active epileptic foci. (2) Also common is a reduced metabolism in the regions described above, which could happen both in the detection of the disease or in previous hypermetabolic areas which changed their pattern during the course of illness. (3) Other areas with hypometabolism can also occur, especially the "diffuse whole-brain cortical hypometabolism" manifestation, which is unspecific and can have degenerative diseases and other conditions as differential diagnoses. Some antibodies are more related to specific metabolic imaging patterns, but others do not correlate closely with imaging appearances.

Summary We consider that FDG-PET imaging can aid in the early diagnosis of AE and may also be helpful while accessing the disease longitudinally while showing functional changes that occur after therapy. In both situations it can provide valuable information that is not provided by anatomic imaging alone.

Keywords Positron emission tomography · Fluorodeoxyglucose F18 · Autoimmune diseases of the nervous system · Autoimmune diseases · Encephalitis · Paraneoplastic

✉ Artur Martins Coutinho
artur.coutinho@hc.fm.usp.br

Marianne Kimura Soriano
mariannekimura@gmail.com

Carla Rachel Ono
crachelo@gmail.com

1 Department of Radiology, Centro de Medicina Nuclear (LIM 43), University of Sao Paulo Medical School, Travessa da Rua Ovídio Pires de Campos S/N, prédio do Centro de Medicina Nuclear, 2° andar, Cerqueira Cesar, Sao Paulo CEP: 05403-010, Brazil

2 Nuclear Medicine and PET/CT Service, Hospital Sirio Libanes, Sao Paulo, Brazil

3 MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA

Introduction

Autoimmune encephalitis (AE) or encephalopathy is a condition caused by the production of antibodies against synaptic proteins, central nervous system (CNS) membrane

antigens (cell surface antibodies), or intracellular neuronal antigens related to paraneoplastic syndromes [1, 2•]. In the last several years, AE has been progressively recognized as an underdiagnosed condition. Early diagnosis of AE is crucial as it may be a potentially reversible cause of encephalopathy and dementia [1, 3].

AE usually presents with acute symptoms such as altered sensorium, cognitive impairment, behavioral changes, or epilepsy and it typically has a fast progressive or fluctuating course. Treatment is based on immunomodulation and provides total or partial relapse of the symptoms in a considerable percentage of cases. Exceptions are AE of a paraneoplastic origin, in which additional treatment consists of the removal of the primary tumor [1, 4]. Diagnosis of AE is confirmed by immunoassays and isolation of specific antibodies in the plasma or cerebrospinal fluid (CSF) through different methods [5, 6•]. In many cases, however, the condition is detected at a late stage, which contributes to worse prognosis [7]. Additionally, in some cases with less acute presentations, autoantibodies are not always found.

Since very few cases fit in the classic "limbic encephalitis" syndrome (altered sensorium, seizures, rapid cognitive decline, altered mood and personality) and considering the spectrum of symptoms, it is often difficult to differentiate AE from other syndromes, such as *status epilepticus* of other etiologies, in which corticotherapy would be contraindicated [8, 9]. AE is also among the differential diagnoses of rapidly progressive dementia [1, 10]. In such cases, imaging methods such as magnetic resonance imaging (MRI) and positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG-PET) can be especially helpful for the diagnosis.

Most imaging physicians, however, are not aware of the potential clinical use of FDG-PET in this condition. It is of high importance for radiologists and nuclear medicine physicians to recognize the specific imaging patterns related to this condition and additional uncommon patterns, which would eventually help referring physicians in the differential diagnosis, including investigating the presence of these specific antibodies. FDG-PET may be of a particular help in the diagnosis of AE, since glucose uptake increases in active inflammation and is seen more easily in FDG-PET than in cerebral blood flow SPECT or anatomic MRI imaging [4].

Technical and Clinical Development

The first studies evaluating AE with both MRI and FDG-PET reported findings that restricted to mesial temporal lobes (hypometabolism and abnormal hypersignal in T2-weighted images). Recent reports now recognize this condition as having a more diverse spectrum of

manifestations, but diffuse global cortical hypometabolism has been suggested to be the most common FDG-PET finding. The second most common pattern would be focal hypometabolism or hypermetabolism in mesial temporal lobes, when limbic encephalitis and seizures are present [11], with hypermetabolism being more specific to AE [12]. Nevertheless, subsequent reports on FDG-PET abnormalities in more diverse areas shed light on the low specificity of some patterns such as "global cortical hypometabolism." Rapidly progressive causes of dementia, such as Creutzfeldt–Jakob, Lewy body disease, or even other conditions such as severe Alzheimer's disease, can have similar imaging patterns and clinical findings to AE [10, 12]. Therefore, we consider that a larger comprehension on the different FDG-PET imaging patterns of AE is still lacking. As we will describe below, a variable spectrum of findings can be seen, including impairment of deep gray matter structures.

When it comes to technical developments, the introduction to the clinical routine of different quantitative techniques such as 3D-stereotactic surface projection may have a substantial impact on the recognition of new imaging manifestations of AE in FDG-PET imaging. Such kinds of software also provide databases of subjects with "normal" brain metabolism for comparison. Focal hypermetabolism, for instance, may be hard to be correctly identified by nonexpert physicians. In some cases, global cortical hypometabolism may mimic hypermetabolism in primary sensory-motor cortices (such as paracentral gyri, visual and auditory cortices). This kind of pitfall can occur mostly due to normalization problems [13].

Another remarkable development is the clinical introduction of hybrid integrated PET/MRI machines, which offers the possibility of unifying positive attributes of both methods. Although a comprehensive investigation of AE with this modality has not been performed yet, some functional or metabolic MR sequences (i.e., spectroscopy, diffusion-weighted imaging, or perfusion) may provide additional information beyond the regular anatomic registration of both modalities separately. PET/MRI has been already used in a number of other neuropsychiatric conditions and could be useful to understand AE physiopathology better [14, 15].

Disease Detection

FDG-PET apparently increases the sensitivity of the traditional workup with MRI in the detection of AE [16], with a typical pattern of hypometabolism or hypermetabolism in mesial temporal regions, but also with extra-limbic abnormalities. Nevertheless, brain functional or structural damage in other areas (sometimes even with a reversion of

the findings) have been described [2•, 4]. These extra-limbic findings could help to identify the extent of brain damage caused by the disease and could correlate with clinical symptoms [4, 6•, 12, 17]. Some correlation between different antibodies and specific metabolic imaging patterns is seen [2•, 5]. Also, approximately 17 autoantibodies that could cause AE are known to date [3]. In the next paragraphs, we will summarize the most relevant and recent reports of the literature regarding FDG-PET imaging and AE. We tried, whenever possible, to describe the most common imaging patterns for the most common entities and their variations (Table 1).

Anti-NMDA

The most common subtype of AE is the NMDA receptor-related. NMDA receptors (N-methyl-D-aspartate, a family of L-glutamate receptors) are ionotropic neuronal gluta-matergic receptors present in higher rates in the hip-pocampi and amygdalae [18]. Young females are most commonly affected, and the condition may or may not be related to neoplastic states [19, 20]. Among them, ovarian and testicular teratomas are the most prevalent, but their relation with Hodgkin's lymphoma, small cell lung carci-noma, and neuroblastoma has already been drawn [19–22].

Prodromal signs and symptoms include low-grade fever, headaches, and fatigue, with subsequent psychiatric dis-turbs such as agitation, psychosis, central hypoventilation, hallucinations, and memory impairment [19, 20]. In later phases, movement disorders such as orofacial dyskinesia, dystonia, autonomic instability, bradykinesia, dysarthria, seizures, and decreases in awareness and arousal can occur [19, 20]. Acute symptoms are mostly related to an increase of free synaptic glutamate (an excitatory neurotransmitter), which is secondary to the occupation of receptors due to anti-NMDA binding.

Immunotherapy and tumor cytoreduction can lead to the improvement of the symptoms in up to 80 % of the cases, due to the reversion of the receptor/antibody binding [19, 20]. Correlation between antibodies levels and prog-nostic suggests its central role in the pathogenesis of this condition and the usually favorable response to immunotherapy [19]. Antibodies immunoassays in blood or CSF can be used to confirm this condition. CSF analysis may also indicate lymphocytic pleocytosis, and an eleva-tion of blood proteins and oligoclonal bands may occur [20, 23].

MRI is a part of the initial investigation and may have a typical appearance or present subtle findings, such as increased signal in the medial temporal lobe in the fluid-attenuated inversion recovery sequence (FLAIR) and T2-weighted sequences, or focal hyperintensities in the fron-tal–parietal cortex. There is, however, a clinical–radiolog-ical paradox related to MRI, where only 23–55 % of the patients present MR findings and sometimes findings are more evident in less symptomatic patients [22].

Table 1 Frequent clinical and FDG-PET findings related to the most frequently isolated autoantibodies in autoimmune encephalitis

| Antibodies	Symptoms and specific clinical characteristics	FDG-PET imaging
NMDA	Viral prodromal followed by psychiatric disturbs and memory impairment	Glucose hypermetabolism of cortical areas (mostly frontotemporal): Fig. 1; associated with hypometabolism (mostly occipital)
	Clinical-radiologic paradox: only 23–55 % of the patients present positive MR findings, sometimes more evident in less symptomatic patients	Impairment of occipital lobes, basal ganglia, cingulate gyrus, cerebellum, the pons and even extensive hemispheric area in some patients
LGI1/CASPR2	Faciobrachial dystonic motor seizures, memory loss, behavioral changes, confusion, hyponatremia (LGI1)	Altered glucose metabolism in mesial temporal structures (basically the hippocampus and amygdala) and also in the basal ganglia
	Morvan syndrome (CASPR2)	
AMPA	Limbic encephalitis	Single cases presenting: (1) caudate hypometabolism associated with multiple cortical areas of hypometabolism in frontal, temporal and occipital areas, (2) bilateral hippocampal hypermetabolism, (3) no abnormalities
GABA-A/B	Limbic encephalitis, refractory seizures, episodic memory loss, and behavioral changes	Unilateral or bilateral mesial temporal lobe hypermetabolism in three cases, which could be associated with whole-brain cortical hypometabolism in two cases; isolated global hypometabolism in one case or even normal scans
GAD	Cerebellar ataxia, seizures, "stiff-person syndrome" and limbic encephalitis	Mesial temporal abnormal glucose metabolism in at least 10 cases
	Association with type 1 DM	Isolated right hippocampal hypermetabolism in one case
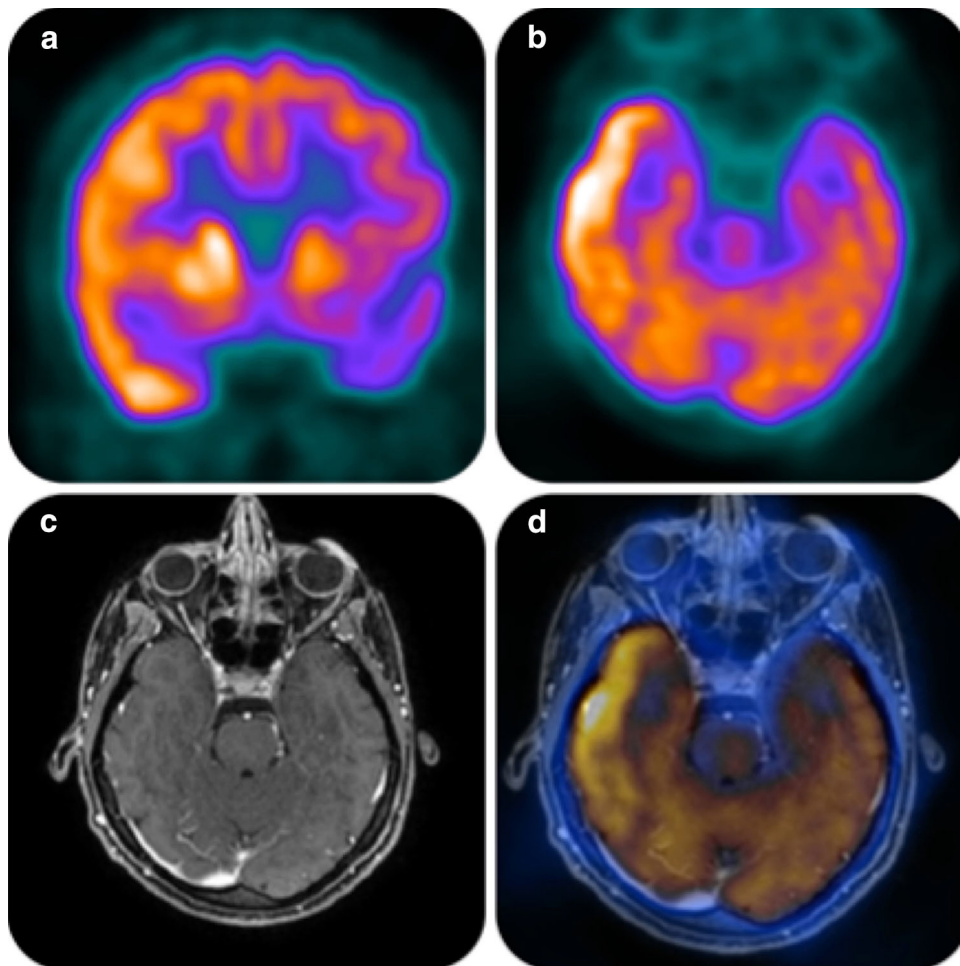
Fig. 1 Female patient, 39 years old, with AE due to NMDA antibodies presenting with right temporal lobe hypermetabolism, namely in neocortical polar and lateral areas (**a, b** coronal and axial FDG-PET images, and **d** fused FDG-PET and MRI). MRI presented with unremarkable findings (**c** post-contrast T1-weighted MRI). Initial symptoms were mental confusion, aggressiveness, and visual hallucinations for 3 months before the scan

FDG-PET imaging can show interesting findings even with normal MRI and CT scans. A classical finding is an abnormal medial temporal metabolism, in some cases associated with abnormalities in frontoparietal metabolism, varying from hypermetabolism in acute inflammation to hypometabolism in chronic cases, as shown in Fig. 1 [6•, 8, 24–28]. Occipital lobes, basal ganglia, cingulate gyrus, cerebellum, the pons, and even extensive hemispheric impairment are also reported, depending on the degree of inflammation [6•, 29–33]. Mesial temporal lobe and frontal hypermetabolism associated with reduction in occipital metabolism correspond to a big number of cases [17, 29, 31, 32].

Anti-VGKC Complex Antibodies (LGI1 and CASPR2)

The anti-voltage-gated potassium channel (anti-VGKC) encephalitis group comprises antibodies to proteins complexes associated with VGKC: LGI1 (leucine-rich glioma inactivated 1, commonly related to limbic encephalitis) and CASPR2 (contactin-associated protein-like 2 which causes both CNS and peripheral nervous system symptoms). Both proteins are located in pre- and postsynaptic regions of the synaptic cleft and regulate neuronal transmission [21]. Approximately 50 % of the patients presenting with anti-VGKC positivity are also positive for anti-LGI1 or CASPR2 [18]. According to recent robust data, however, anti-VGKC positivity in the absence of antibodies to LGI1/CASPR2 is probably an unspecific finding and a nonreliable marker for AE [34]. Due to this, most of the FDG-PET findings in the literature are related to anti-LGI1 and anti-CASPR2 positivity (mostly the former than the latter) in addition to anti-VGKC.

This subtype of AE usually follows a typical clinical pattern of signs and symptoms. Anti-LGI1 encephalitis frequently begins with faciobrachial dystonic motor seizures

Fig. 2 Female, 75 years old, with sudden executive dysfunction and memory impairment associated with epileptic seizures. Isolation of anti-LGI-1 in CSF confirmed an AE. Axial images show the FDG-PET images before treatment (**a1–3**) and after beginning of the treatment (**b1–3**). *Column* **a** shows a diffuse whole-brain cortical hypometabolism, associated with right caudate and right occipital focal hypometabolism (**a2**), and a focal hypermetabolic area in the posterior aspect of the right mesial temporal lobe (**a3**). After therapy with corticosteroids (*column* **b**), there is an improvement of whole-brain cortical glucose uptake, except in the right caudate and in the focal right occipital cortex (ischemic lesions confirmed in MRI images), as seen in **b2**. There is also a focal hypometabolic area in the posterior mesial right temporal lobe, where the hypermetabolic focus was seen before treatment (*lower rows* **a3** and **b3**)
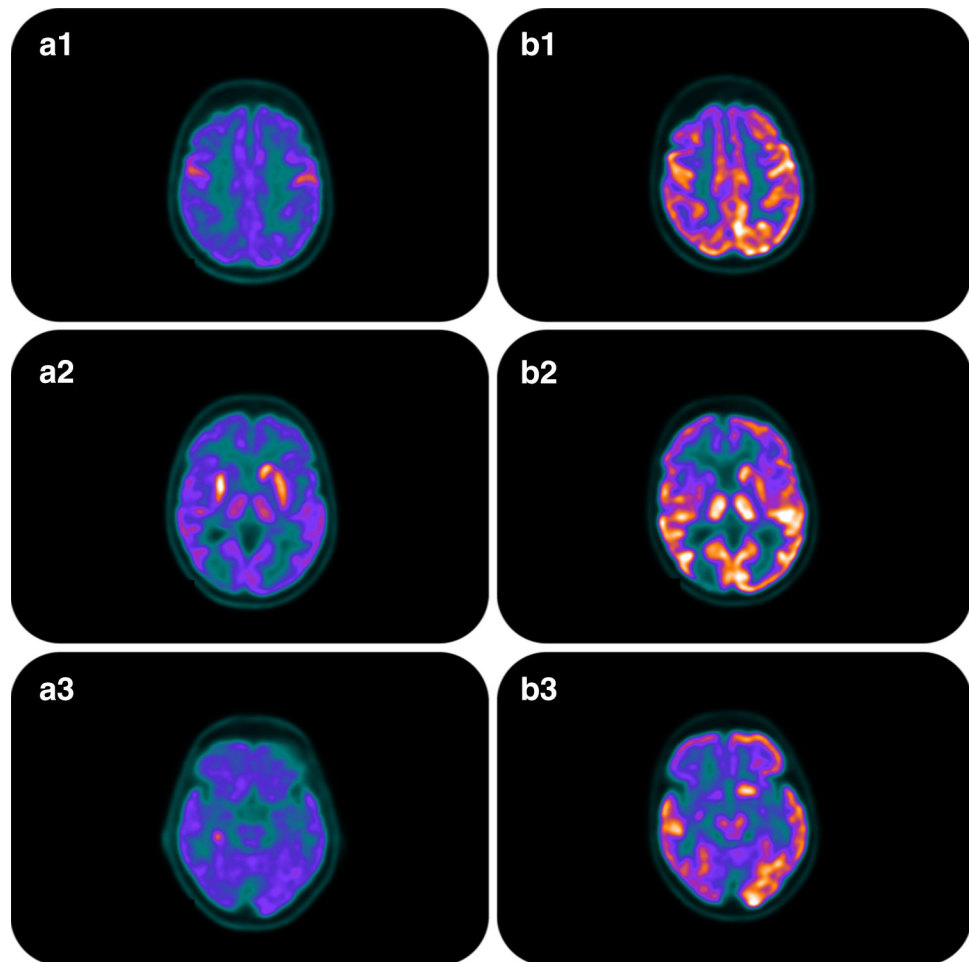
(FBDS), followed by subacute loss of memory, changes in behavior and confusion, and hyponatremia, which can eventually lead to hippocampal atrophy detected by MRI [21, 35]. Seizures normally have a poor response to antiepileptic drugs but improve after immunotherapy. In anti-CASPR2-related encephalitis, sometimes Morvan syndrome and less frequently limbic encephalitis are also seen [2•].

There is a consistent sequence of reports of metabolism abnormalities on FDG-PET in mesial temporal structures (basically the hippocampus and amygdala) and also in the basal ganglia in this class of antibodies. In a series of cases of 10 anti-LGI1-positive patients and FDG-PET/CT images, 7 had temporal lobe hypometabolism (3 of each being bilateral), 7 presented bilateral basal ganglia hypermetabolism, and only 1 patient had no findings on FDG-PET [36]. In this group of patients, sensitivity for detection of the condition was 90 % for PET/CT, 76.9 % for electroencephalography (abnormal pattern in 10 out of 14 cases), and 71.4 % for MRI (mesial temporal T2 hypersignal being the most common pattern) [36]. Hypermetabolism in the striatum was reported in five anti-LGI1-positive patients, two of whom had restricted putaminal

hypermetabolism and three with caudate hypermetabolism. Additionally, four of the five patients with unilateral FBDS had hypermetabolism in the contralateral motor cortex, and three patients with temporal lobe epilepsy presented with mesial temporal lobe hypermetabolism [35]. Bilateral mesial temporal lobe and basal ganglia hypermetabolism were also consecutively related in case reports of patients with anti-LGI1, one of whom showed metabolism normalization after 5 months of therapy [37, 38]. An example of anti-LGI1 AE with many simultaneous imaging manifestations can be seen in Fig. 2.

Anti-AMPAr

AE related to AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (anti-AMPAr) are rare and usually have a clinical manifestation of limbic encephalitis [39, 40]. They are far more prevalent in women, and approximately two-thirds are related to tumors (mainly breast, lung, and thymus) and tend to relapse [40, 41•]. AMPAr is a subtype of glutamate receptor related to neural plasticity mechanisms, memory, and learning [9].
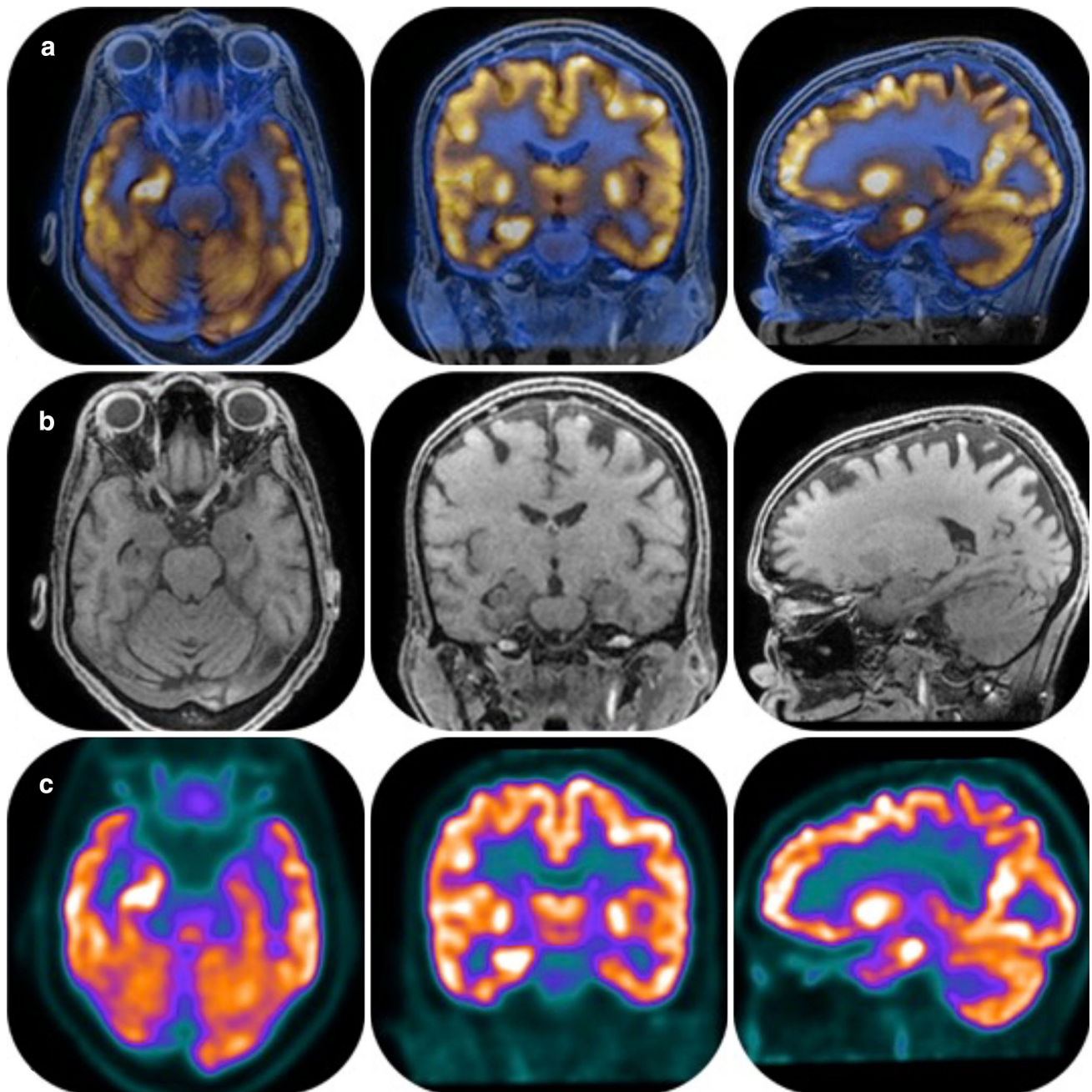
Fig. 3 Female, 56 years old, patient presenting with cerebellar ataxia and weight loss, and anti-GAD positivity confirmed an AE. Images after 3 months of the symptoms onset show hypermetabolism in the right hippocampus, parahippocampal gyrus, and amygdala (**a** fused FDG-PET and T1-weighted MRI, and **c** FDG-PET only). Anatomic T1-weighted MRI images showed no abnormalities (**b** *middle row*) in the corresponding structures

Autoantibodies against glutamate receptor subunits GluA1 and GluA2 can occasionally cause a sensible reduction of AMPAr levels through a cross-linking mechanism, leading to its internalization and changing its location in the synapses [9, 40].

PET imaging patterns are variable, and there are only a few reports on the literature on this issue. Caudate hypometabolism associated with multiple cortical areas of hypometabolism in frontal, temporal, and occipital areas were already described in a pregnant patient with positive anti-AMPAr after immunotherapy [42]. Bilateral hippocampal hypermetabolism was also seen in a patient with anti-AMPAr isolated in the CSF after 3 months of symptoms (seizures and memory deficit). This hypermetabolism progressively returned to normal levels after 10–25 months of treatment with immunotherapy and antiepileptic drugs [41•].
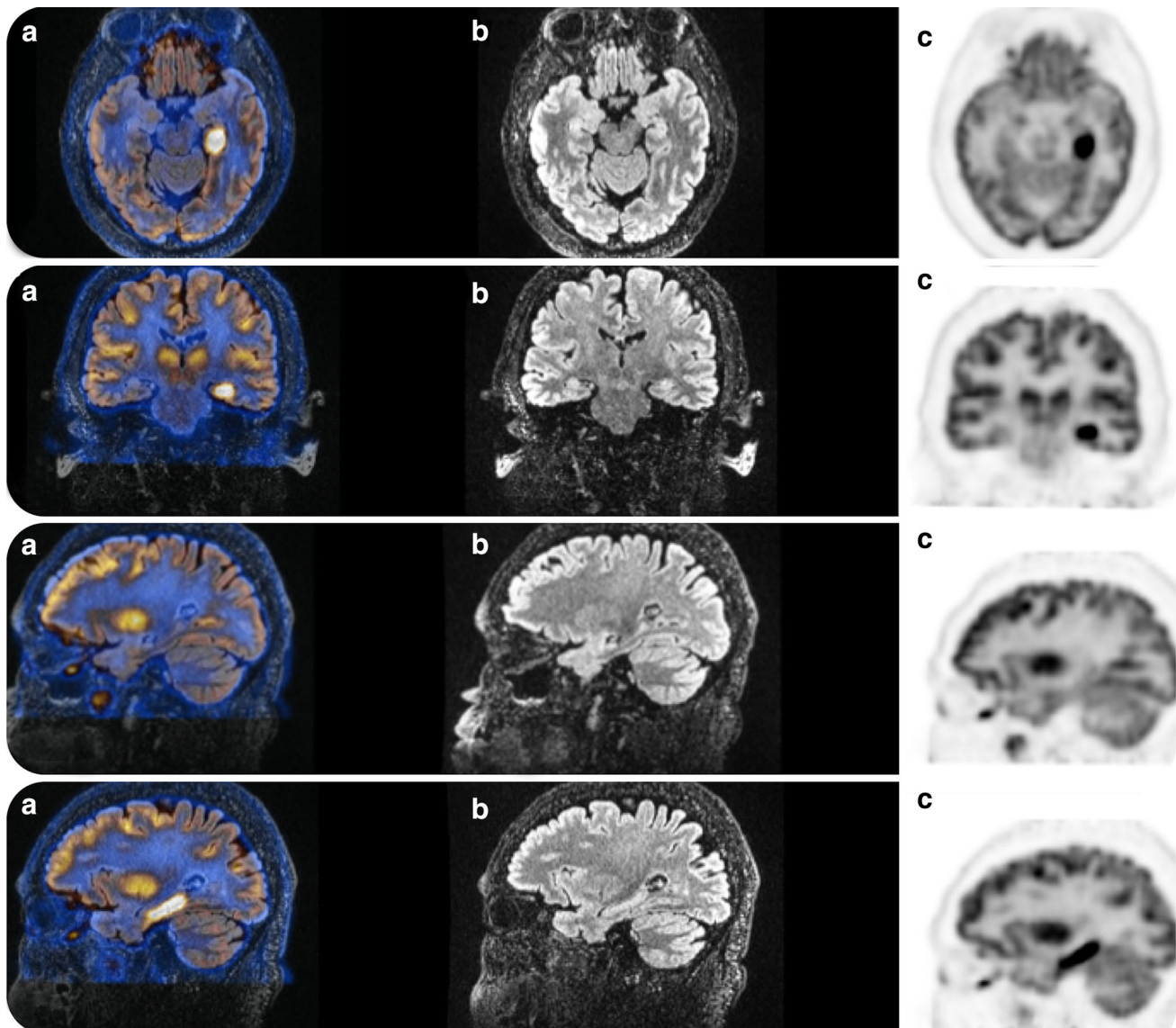
Fig. 4 Male, 49 years old, with suspicion of limbic encephalitis after two epileptic seizures. MRI shows an enlarged left hippocampus with high signal in T2-FLAIR acquisitions (*middle column* **b**) and focal hypermetabolism in the left hippocampus and parahippocampal gyrus (**a**, **c**). AE with concomitant anti-GABA-B, anti-AMPAr, and anti-GAD was confirmed. *Column* **a** fused MRI and FDG-PET images in the axial, coronal, right sagittal, and left sagittal planes. *Column* **b** FLAIR MRI images in axial, coronal, right sagittal, and left sagittal planes. *Column* **c** FDG-PET images in the axial, coronal, right sagittal, and left sagittal planes

A third report found no brain metabolism abnormalities in a patient with thymoma and *myasthenia gravis* associated with positive anti-AMPAr. In this last report, PET was important in the detection of the primary tumor [43].

Anti-GABA

Neuroreceptors such as GABA-B are linked to the inhibition of epileptogenic stimuli, while GABA-A plays a significant role in fast inhibitory synaptic transmission [44]. Antibodies against subunits of the inhibitory GABA receptors lead to its dysfunction and numeric reduction [45]. Thus, patients with anti-GABA-B AE present with limbic encephalitis symptoms and have a higher risk of associated neoplastic diseases, especially small lung cancer, and thymoma. Patients with anti-GABA-A tend to show refractory seizures, episodic memory loss, and changes in behavior [2•, 44]. On the other hand, anti-GABA-A encephalitis has no higher risk of paraneoplastic origin. Both subtypes tend to have a good response to immunotherapy as well as a better improvement when a neoplastic tissue is found in anti-GABA-B AE [45].

Only a few reports of the FDG-PET imaging pattern of anti-GABA-B AE are found. They comprise unilateral or

Fig. 5 Male, 28 years old, with febrile seizure since 13 years old. At the time of the scans, he presented with motor seizures four times a week. T2-weighted FLAIR images with high signal in left hippocampus and enlarged left amygdala (*left column*). FDG-PET images demonstrated focal hypermetabolism restricted to the posterior component of the left hippocampus and mild hypometabolism in its anterior component (*right column*). *Left column* FLAIR MRI images, and *right column* FDG-PET images, both in axial, sagittal, and coronal planes). The isolation of anti-GAD in peripheral blood confirmed the diagnosis of an AE
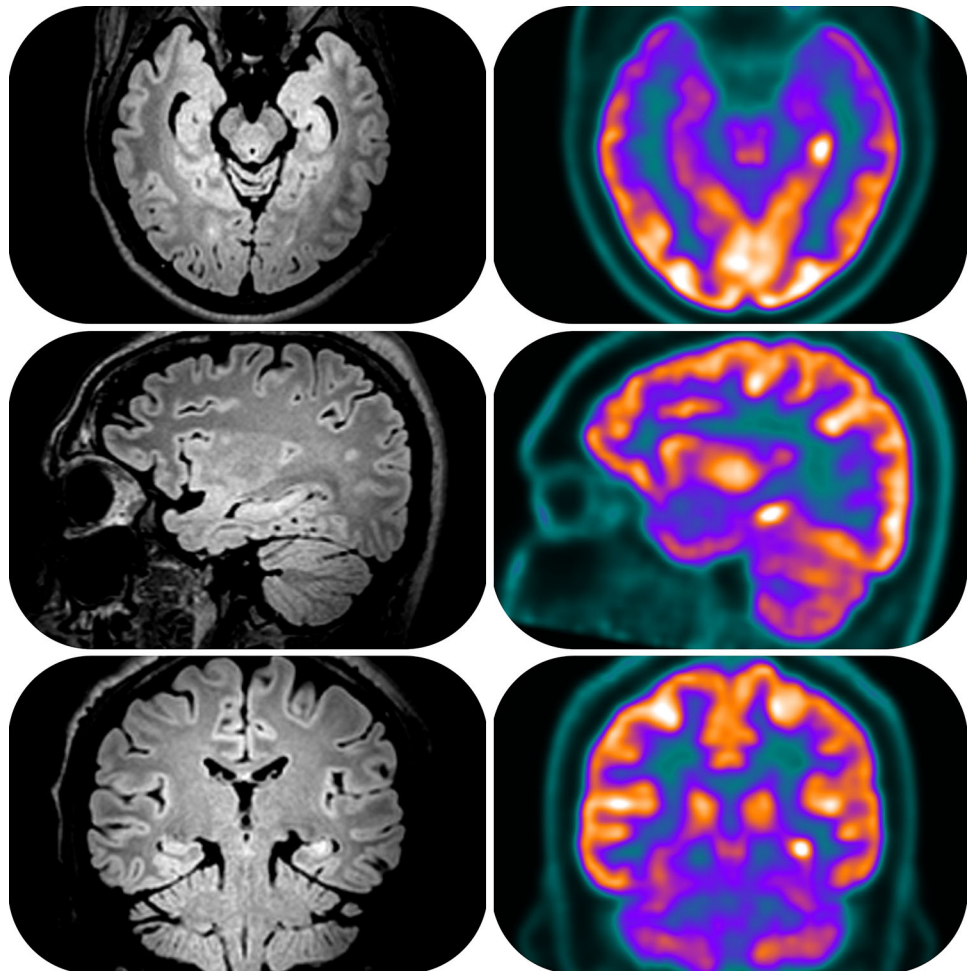
bilateral mesial temporal lobe hypermetabolism [46, 47], which could be associated with global cortical hypometabolism, the whole hippocampus and amygdaloid body [46], and isolated global hypometabolism and even normal scans [47]. In the biggest series of cases, four out of five patients presented with small cell lung cancer [47].

Anti-GAD

Anti-glutamic acid decarboxylase (GAD) AE is associated with GAD enzymes, which are located in the presynaptic GABAergic terminals [48•]. Despite being an intracellular enzyme, as most of the onconeural antibodies, the neurologic symptoms mediated by anti-GAD are usually unrelated to malignant tumors, and symptoms may include cerebellar ataxia, seizures, "stiff-person syndrome," and limbic encephalitis [48•, 49]. Concomitant type 1 diabetes mellitus was also reported [48•, 50].

The etiology of the anti-GAD neurologic syndrome remains unclear. A T cell mechanism against the limbic system causing cytotoxicity and local inflammation was described as a possible origin of the tissue damage/repair and gliosis [51]. However, there is no correlation between antibodies titers and severity of the disease, there is lower inflammation than in AE related to other autoantibodies, and response to immunotherapy is usually worse than in other neurological syndromes caused by antibodies against surface antigens [51–53].

There are few FDG-PET image studies on AE due to anti-GAD published in literature, and they mostly describe limbic hypermetabolism [6•, 29, 54, 55], usually associated with T2-FLAIR hyperintensity in the medial temporal lobes on cerebral MRI studies [2•]. In a case report of a 66-year-old female, a subtle onset of seizures progressing within 1 week to aphasia, confusion, weakness, and *status epilepticus* was reported, in addition to multiple hypermetabolic lesions in bilateral frontal, right temporal lobe, and left anterior superior frontal gyrus on FDG-PET [54]. Another study described mesial temporal hypermetabolism on FDG-PET performed in a 43-year-old female with hallucinations and nausea [6•]. FDG-PET images showed hypermetabolism in the pallidus, midbrain, brainstem,

lateral parietotemporal and orbitofrontal cortex bilaterally, cerebellar tonsillae, and culmen in a 23-year-old female patient with subtle onset of psychosis-like syndrome, epilepsy, and dyskinesia, with both anti-GAD and anti-NMDA-positive serology [29]. In a group of nine anti-GAD-positive patients, one presented with right hippocampal hypermetabolism, while the eight remaining presented with mesial temporal hypometabolism [55]. Figures 3, 4, and 5 show different manifestations of anti-GAD AE. In one of those patients, anti-GAD was isolated in conjunction with anti-AMPA and anti-GABA-B.

Whole-Body FDG-PET Imaging

AE or rapidly progressive dementia may occur as an aberrant by-product of an immune response directed against nonneurologic cancers [10]. In this case, AE would be due to paraneoplastic autoantibodies, most commonly onconeural antibodies. In such situations, whole-body FDG-PET/CT imaging may be included in the workflow of cancer investigation, in addition to conventional anatomic modalities. Nevertheless, the different imaging patterns seen on the numerous types of cancers related to paraneoplastic AE is beyond the scope of this manuscript.

Future Challenges and Conclusions

Studies with larger samples and prospective cohorts still lack in the literature. Such systematic investigations would be useful to demonstrate changes in brain imaging patterns through time (before and after therapy), the clinical meaningfulness of different imaging findings during early diagnosis and also possible prognostic implications. It is still an open question whether or not treatment of patients with hypermetabolic cortical areas (which could mean acute inflammation or active epileptic foci) has a better outcome than subjects with hypometabolic lesions.

Overall, after reviewing the most relevant reports in the literature, it can be concluded that AE findings on FDG-PET may have various patterns, but three are dominant and can be summarized as follows: (1) hypermetabolism in cortical areas, mainly in mesial temporal regions and less frequently in basal ganglia and higher cortical regions, is a common pattern in early stages of the disease [4, 6•, 17]. As noted by Fisher et al. [12], this pattern is highly suggestive of limbic AE, since it has not been described in many other entities, except for brain tumors and active epileptic foci [12], (2) also common is a reduced metabolism in the regions described above, which could happen both in the detection of the disease or in previously

hypermetabolic areas which changed their pattern during the course of illness, (3) other areas with hypometabolism can also occur, especially the "diffuse whole-brain cortical hypometabolism" manifestation, which is unspecific and can have neurodegenerative diseases and other conditions as differential diagnoses. As shown above, some antibodies are more related to specific metabolic imaging patterns, but others do not correlate closely with imaging appearances.

In conclusion, we consider that FDG-PET imaging can aid in the early diagnosis of AE and may also be helpful while accessing the disease longitudinally while showing functional changes that occur after therapy. In both situations, it can provide valuable information that is not found in anatomic imaging alone.

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