



Uncommon ^{18}F -FDG-PET/CT findings in patients affected by limbic encephalitis: hyper-hypometabolic pattern with double antibody positivity and migrating foci of hypermetabolism ☆,☆☆



Angelina Cistaro ^{a,b,c,*}, Federico Caobelli ^d, Natale Quartuccio ^e, Piercarlo Fania ^b, Marco Pagani ^{c,f}

^a Positron Emission Tomography Centre IRMET S.p.A., Euromedic Inc., Turin, Italy

^b PET Pediatric AIMN InterGroup, Turin, Italy

^c Institute of Cognitive Sciences and Technologies, National Research Council, Rome, Italy

^d Department of Nuclear Medicine, Fondazione Poliambulanza, Brescia, Italy

^e Nuclear Medicine Unit, Department of Biomedical Sciences and of Morphological and Functional Images, University of Messina, Italy

^f Department of Nuclear Medicine, Karolinska University Hospital, Solna, Stockholm, Sweden

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ABSTRACT

Autoimmune limbic encephalitis (LE) is a rare disorder; its diagnosis can be challenging. We report two uncommon cases of LE evaluated by brain 2-deoxy-2-[^{18}F]fluoro-d-glucose (^{18}F -FDG) positron emission tomography/computed tomography describing the metabolic imaging patterns, which were different from those observed in previous studies: the first one presented an unprecedented ^{18}F -FDG brain mixed pattern, involving also the mid-brain, despite negative magnetic resonance imaging exams; the second one showed migrating foci of hypermetabolism, one of which turned into hypometabolism at a later examination.

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1. Introduction

Autoimmune limbic encephalitis (LE) is a rare disorder affecting the medial temporal lobe of the brain [1]. Previous studies have identified neuronal antibodies as possibly being involved in the pathogenesis of LE, reacting either against intracellular antigens including Hu (a neuron-specific family of RNA binding proteins), crossveinless-2/collapsing response mediated protein 5 (CV2/CRMP5), paraneoplastic Ma antigen 2 (Ma2), and amphiphysin or against cell membrane antigens such as voltage-gated potassium channels, *N*-methyl-D-aspartate receptors (NMDAR), and glutamic acid decarboxylase (GAD) [2].

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* Corresponding author. Positron Emission Tomography Centre IRMET S.p.A., Euromedic Inc., Via V.O. Vigliani 89, Turin 10136, Italy. Tel.: +39 0113160158; fax: +39 0113160828.

E-mail address: a.cistaro@irmet.com (A. Cistaro).

A few studies reported 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) findings in patients with LE, typically consisting of metabolic abnormalities more prominent in the temporal lobes, often correlating with symptoms of limbic dysfunction. In particular, three different patterns have been described in literature: (a) the first one (mixed hyper-hypometabolic) is characterized by the striking disparity between temporal hypermetabolism and occipital hypometabolism [3]; (b) the second one is indistinguishable from advanced Alzheimer's disease with diffuse moderately to markedly reduced metabolism in the cortex, more prominent in the posterior temporal lobes, with sparing of the visual cortex and primary sensorimotor strips [1]; (c) the third one, very similar to the mixed hyper-hypometabolic pattern, is characterized by focal hypermetabolism in the medial temporal lobes and mainly reported in patients with paraneoplastic autoimmune encephalitis [4].

Here, we present two cases of LE with unusual brain metabolic patterns evidenced by ^{18}F -FDG PET/CT.

2. Report of the cases

2.1. Case 1: hyper-hypometabolic pattern with double antibody positivity

A 23-year-old woman was referred for the sudden onset of a psychosis-like syndrome, characterized by severe agitation, bizarre

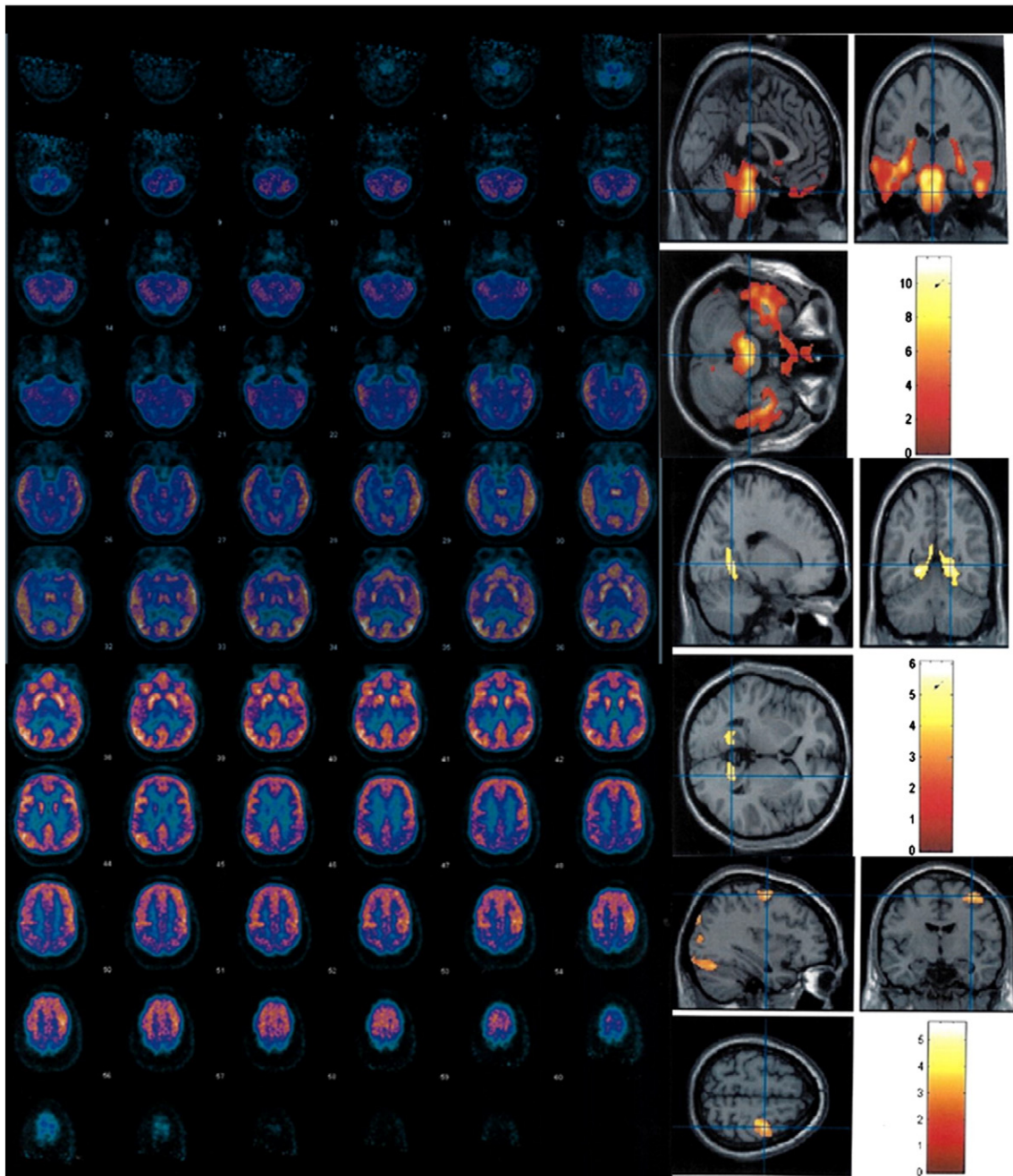


Fig. 1. ^{18}F -FDG PET/CT and SPM analysis of patient number 1 showing hypermetabolism in the lateral parietotemporal cortex bilaterally, orbitofrontal cortex (more pronounced in left hemisphere), globus pallidi, midbrain, brainstem, cerebellar tonsillae, and culmen and areas of hypometabolism in the primary visual cortex, associative visual cortex, and posterior cingulus.

behavior, euphoric status, and confused and disorganized speech. No previous major traumatic, neurological, or psychiatric disease was present in the remote clinical history. The history was negative for smoking, alcohol, and substance abuse. Only cephalgia and reduction of the sleep time were reported in the last few days.

The patient underwent a brain CT without contrast, which did not show any abnormalities. Standard blood tests were normal. Due to rapid worsening of the cognitive state and onset in the following 2 days of generalized epilepsy, dyskinesia of the left side of the face, and left gaze deviation, another brain CT was performed but did not show any pathological finding. Exams for various neurotropic viruses including herpes simplex virus (HSV), hepatitis C virus, human immunodeficiency virus, and cytomegalovirus; bacteria (such as *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus*);

and toxic metabolites (mercury, manganese, lead, and aluminum) were all negative. Serial electroencephalogram (EEG) examinations did not show abnormalities.

A brain magnetic resonance imaging (MRI) with T1- and T2-weighted, fluid-attenuated inversion-recovery (FLAIR) and diffusion-weighted (DW) images revealed mild hyperintensities in the left temporomesial region, in the parahippocampal circonvolution, and in the posterior side of the uncus, consistent with LE.

Due to the severity of the clinical scenario, an empiric therapy with fentanyl, midazolam, acyclovir, ceftriaxone, and ampicillin was started. A week later, a further brain MRI showed disappearance of the previously detected imaging findings. After 2 weeks, a third brain MRI showed diffuse abnormal signals in right temporal cortex, in bilateral frontal and occipital regions, and in basal ganglia.

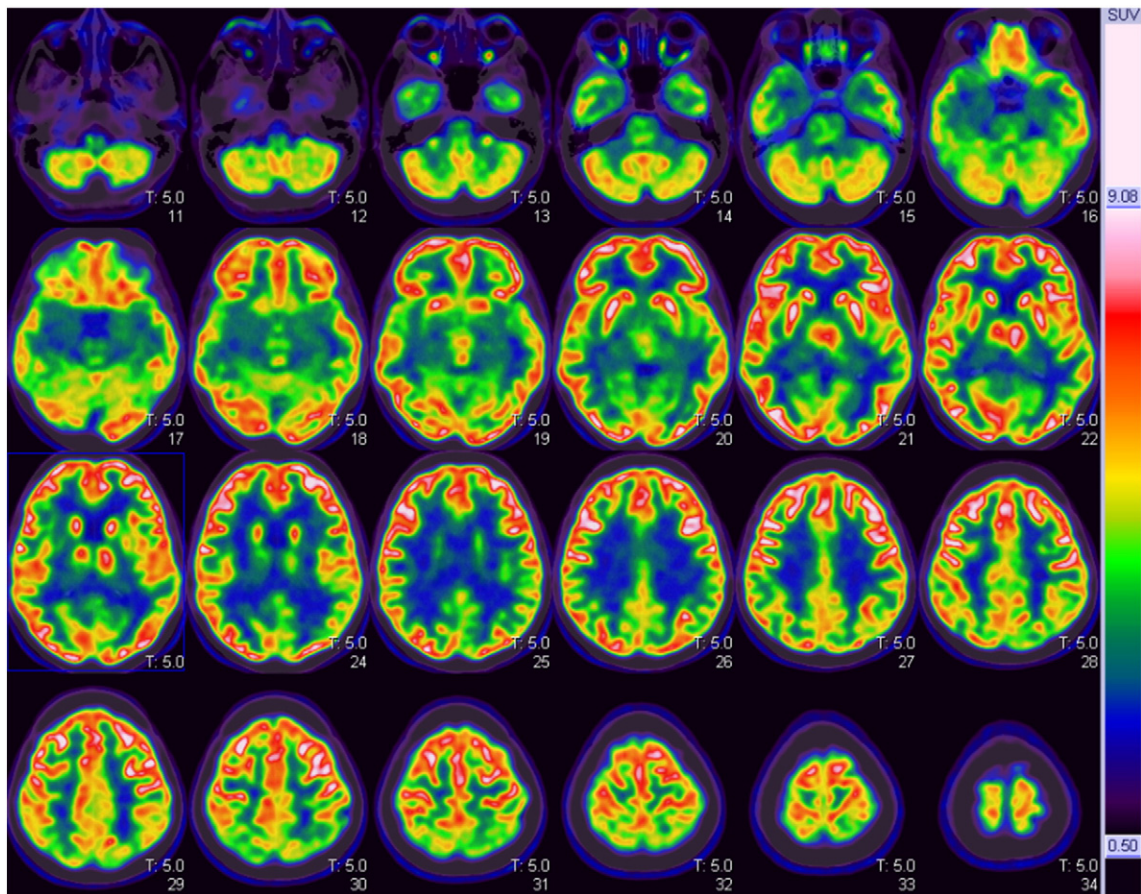


Fig. 2. A first ^{18}F -FDG brain PET/CT. Transaxial images revealed hypometabolism in temporomesial regions (more prominent on the right side), posterior cingulate, and left precuneus. Fused transaxial images.

The plasma serologies of the patient were investigated, checking for antibodies directed against the anti-voltage-gated potassium channels (VOKC), alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors 1 and 2, gamma-aminobutyric-acid B (GABA-B) receptor and GAD, and NMDAR and for onconeural antibodies directed against intracellular neuronal antigens (Hu, Yo, Ri, CV2/CRMP5, amphiphysin, Ma1, Ma2/Ta antigens).

Cerebrospinal fluid (CSF) analysis showed hypercellularity with elevated IgG and mild positivity to anti-GAD and -NMDAR, without any clear triggering factor. Two further brain MRI exams were performed after 2 weeks and 1 month, respectively, and resulted negative.

Due to the suspicion of a paraneoplastic encephalitis, the patient underwent also a CT scan of the brain, chest, and abdomen with contrast medium, which did not show any abnormalities.

The patient then underwent a PET/CT study using a Discovery ST-E scanner (General Electric Medical System, Milwaukee, WI, USA) 60 min after injection of 185 MBq of ^{18}F -FDG. Semiquantitative analysis using Statistical Parametric Mapping (SPM) (SPM2, Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab 6.5 (Mathworks, Natick, MA, USA), was performed.

Visual and SPM analysis detected hypermetabolism in the lateral parietotemporal cortex bilaterally, orbitofrontal cortex (more pronounced in left hemisphere), pallidus, midbrain, brainstem, cerebellar tonsillae, and culmen. Areas of hypometabolism were evidenced in primary visual and associative visual cortex and posterior cingulus (Fig. 1).

The imaging pattern, depicting most of the hypermetabolic areas, in keeping with presence of GAD and NMDAR autoantibodies (whose triggering factor remained explained), confirmed a possible diagnosis of autoimmune encephalitis, in keeping with the immunological essay (mild positivity to anti-GAD and anti-NMDAR antibodies).

2.2. Case 2: migrating foci of hypermetabolism

A 52-year-old woman was referred to our department with suspected LE. The patient was slightly confused but otherwise asymptomatic.

Brain MRI, with FLAIR and DW sequences, showed areas of hyperintensities of a limited extent in many areas and without significant abnormality on the spectroscopy, consistent with inflammatory lesions. Antibodies directed against the VOKC, AMPA receptors 1 and 2, GABA-B receptor and GAD, and NMDAR and for onconeural antibodies directed against intracellular neuronal antigens (Hu, Yo, Ri, CV2/CRMP5, amphiphysin, Ma1, Ma2/Ta antigens) resulted negative in CSF and serum.

Also, a total body ^{18}F -FDG (140 MBq) PET/CT excluded underlying paraneoplastic syndrome. The brain scan showed hypometabolism in temporomesial region, more prominent on the right side and also involving posterior cingulate and left precuneus (Fig. 2). Therefore, the patient underwent medical therapy with corticosteroids, levetiracetam, and phenobarbital.

Six months later, the patient underwent a follow-up brain MRI, whose findings were unchanged, and an ^{18}F -FDG brain PET/CT. The areas of hypometabolism were still present, but there was evidence of a hypermetabolic focus in the left temporal lobe not present at the first examination (Fig. 3). EEG, performed at injection, was negative.

The therapy was continued and, 1 month later, the patient underwent a third MRI, still unchanged, and a third ^{18}F -FDG brain PET/CT. Again, the hypometabolic areas were still present, but there was the evidence of another hypermetabolic focus in the right temporomesial region (Fig. 4). At this time, the previously described hypermetabolic focus in the left temporal lobe showed reduced glucose metabolism.

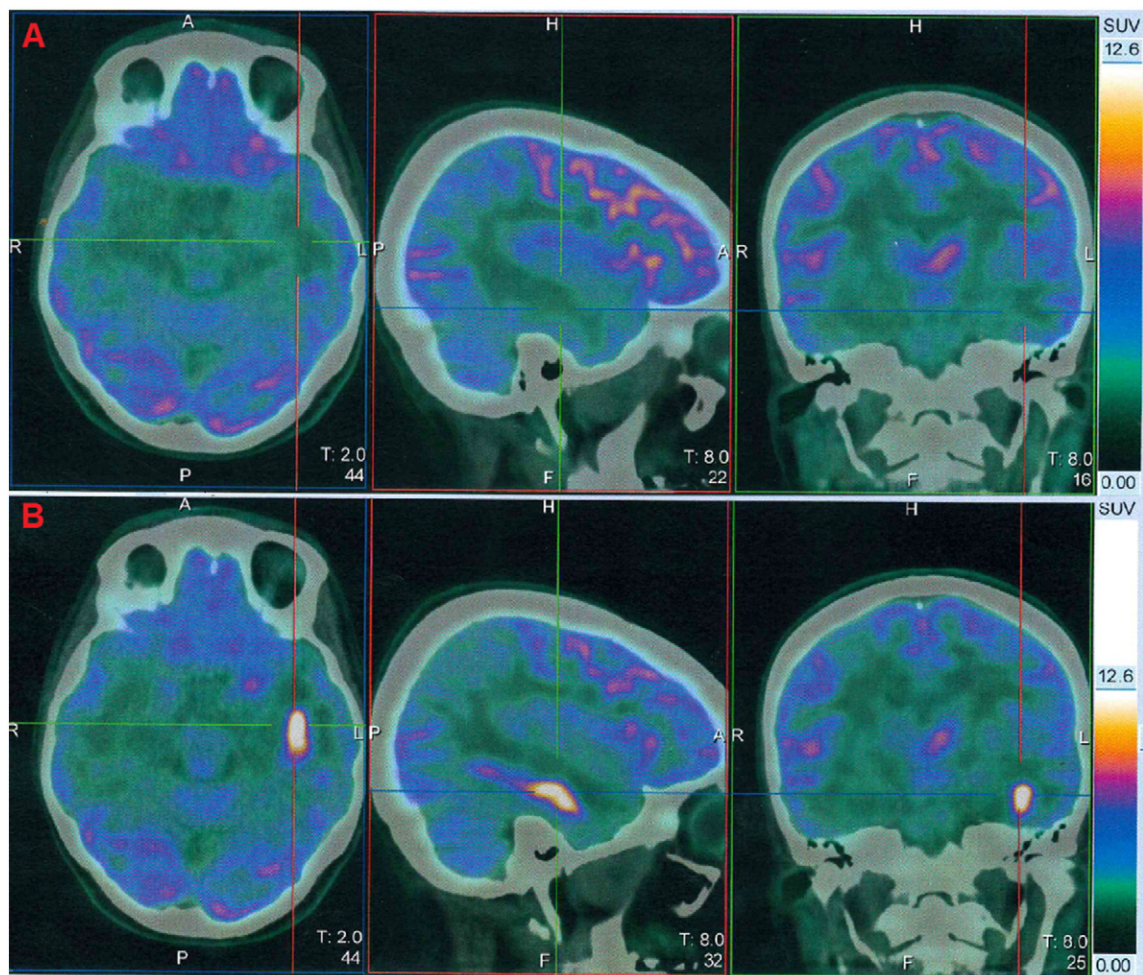


Fig. 3. Two sequential ^{18}F -FDG brain PET/CTs, transaxial view. The first examination does not show any hypermetabolic area (A), which appears on the follow-up (B) in the left temporal lobe. The color scale has been toned up in order to evidence the relative intense hypermetabolism in the affected area.

The patient is currently on follow-up, and her symptoms have been partially relieved by the ongoing therapy.

3. Discussion

The diagnosis of LE represents a clinical challenge, and previous reports show a huge variability in the neuroimaging findings [1–4].

Brain MRI usually shows, at FLAIR images or T2 sequences, hyperintense signal in the medial part of the temporal lobes, which is often asymmetric or unilateral [1]. Additionally, ^{18}F -FDG PET/CT can reveal abnormalities in other areas such as brainstem, cerebral cortex, or cerebellum, some of them clinically silent [5].

Our first patient, despite two negative follow-up MRI exams, presented an uncommon ^{18}F -FDG brain mixed metabolic pattern as described by Fisher [2] showing hypometabolism involving the primary visual cortex, left associative visual cortex, left parahippocampal gyrus, and thalamus, associated with hypermetabolic foci in lateral parietotemporal cortex bilaterally, orbitofrontal cortex, cerebellar tonsillae, and culmen. However, in this patient, ^{18}F -FDG PET/CT documented few additional findings including increased metabolism in pallidus, midbrain, and brainstem. Whereas basal ganglia [6] as well as brainstem [5] hyperactivity has been separately demonstrated, this is the first time that midbrain hypermetabolism is documented in a patient affected by autoimmune encephalitis. MRI abnormalities in midbrain along with imaging abnormalities in medial temporal lobes have been reported in case of LE related to antibodies against Ma2

(a protein playing a role in the biogenetic pathway of messenger RNA and hyperexpressed in patients with various types of tumors) [7]. However, there are no reports regarding increased FDG uptake in the midbrain of such patients. Another peculiarity of our first case is the positivity to two different types of antibodies (GAD and NMDAR auto-antibodies), unlike many previous reports.

Moreover, to the best of our knowledge, only one case of autoimmune encephalitis analyzed by SPM has been reported in literature [8]. Finally, in our patient, MRI evidenced fluctuating signs. In particular, a week after the start of therapy, MRI was negative, but 2 weeks later, it showed diffuse abnormalities (right temporal cortex, bilateral frontal cortex, occipital regions, and basal ganglia).

The second patient presented areas of brain hypometabolism involving temporomesial regions, posterior cingulate, and precuneus not correlating with any clinical symptom. The further sequential ^{18}F -FDG PET/CTs surprisingly showed migrating foci of hypermetabolism, one of which turned into hypometabolism at a later examination.

FDG hypermetabolism converting to hypometabolism on a follow-up examination has already been described, but in a case of herpetic encephalitis [9]. Anyway, this possibility has been excluded in our patient by HSV serology, and a possible epileptic activity was excluded as well. The lack of evident antibodies also seems to exclude an autoimmune-mediated locally increased neuronal activity caused by direct alteration of synaptic and neuronal properties. Therefore, it could be reasonably maintained that these hypermetabolic

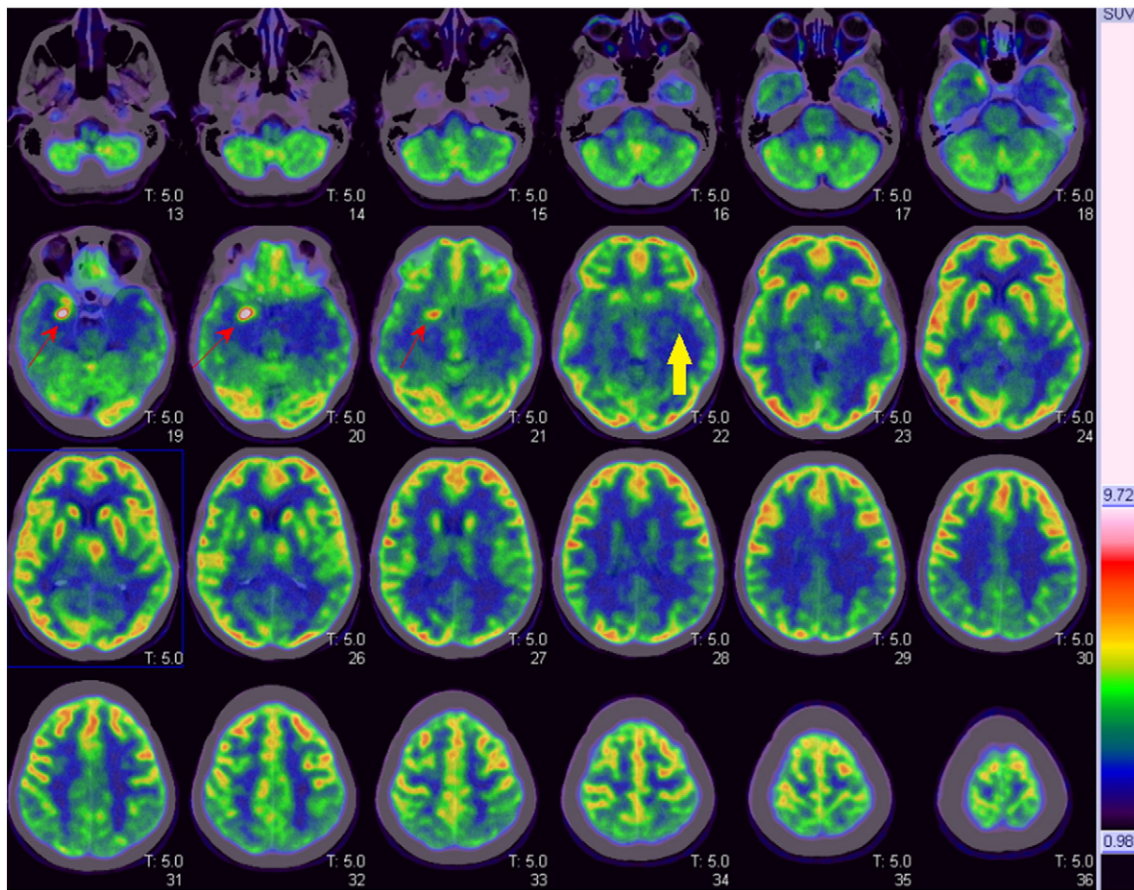


Fig. 4. On the third follow-up ^{18}F -FDG brain PET/CT, the previously noted hypermetabolic focus is not evident anymore and turned into hypometabolism (yellow arrow). There is evidence of a new hypermetabolic focus in the right temporal lobe (red arrows). The color scale has been toned up in order to evidence the relative intense hypermetabolism in the affected area.

areas are most likely due to inflammatory status, whose origin could not be properly explained and which have never been described before.

The absence of any antibodies in our second case represents an unusual finding and may indicate a subtype of LE whose response to therapy appears to be partial and more similar to what was observed in patients without antibodies directed toward cell membrane antigens. This seems to be in contrast to what was observed by Bataller et al. [10], who described three patients with LE of unclear etiology or without antibodies showing an optimal response to corticosteroids. It could be hypothesized that a further still-unknown cause underlies the onset of migrating brain inflammatory process. ^{18}F -FDG PET/CT demonstrated great specificity in the detection of inflammatory areas and was also more useful than MRI in evaluating therapy response in the second patient.

In conclusion, we support the use of ^{18}F -FDG brain PET/CT in the management of patients with LE. Some atypical metabolic patterns, such as the ones described in our cases, should be recognized and not confused with cerebral metastases, as it might be suspected in the presence of a paraneoplastic syndrome.

References

- [1] Anderson NE, Barber PA. Limbic encephalitis — a review. *J Clin Neurosci* 2008;15:961–71.
- [2] Fisher RE, Patel NR, Lai EC, Schulz PE. Two different ^{18}F -FDG brain PET metabolic patterns in autoimmune limbic encephalitis. *Clin Nucl Med* 2012;37:e213–8.
- [3] Mohr BC, Minoshima S. ^{18}F fluorodeoxyglucose PET/CT findings in a case of anti-NMDA receptor encephalitis. *Clin Nucl Med* 2010;35:461–3.
- [4] Basu S, Alavi A. Role of FDG-PET in the clinical management of paraneoplastic neurological syndrome: detection of the underlying malignancy and the brain PET–MRI correlates. *Mol Imaging Biol* 2008;10:131–7.
- [5] Ances BM, Vitaliani R, Taylor RA, Liebeskind DS, Voloschin A, Houghton DJ, Galetta SL, Dichter M, Alavi A, Rosenfeld MR, Dalmau J. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain* 2005;128:1764–77.
- [6] Maeder-Ingvar M, Prior JO, Irani SR, Rey V, Vincent A, Rossetti AO. FDG-PET hyperactivity in basal ganglia correlating with clinical course in anti-NDMA-R antibodies encephalitis. *J Neurol Neurosurg Psychiatry* 2011;82:235–6.
- [7] Dalmau J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, Saiz A, Meneses P, Rosenfeld MR. Clinical analysis of anti-Ma2-associated encephalitis. *Brain* 2004;127:1831–44.
- [8] Kassubek J, Juengling FD, Nitzsche EU, Lücking CH. Limbic encephalitis investigated by ^{18}F -FDG-PET and 3D MRI. *J Neuroimaging* 2001;11:55–9.
- [9] Meyer MA, Hubner KF, Raja S, Hunter K, Paulsen WA. Sequential positron emission tomographic evaluations of brain metabolism in acute herpes encephalitis. *J Neuroimaging* 1994;4:104–5.
- [10] Bataller L, Kleopa KA, Wu GF, Rossi JE, Rosenfeld MR, Dalmau J. Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. *J Neurol Neurosurg Psychiatry* 2007;78:381–5.