Original Article

FDG-PET in Autoimmune Encephalitis: Utility, Pattern of Abnormalities, and Correlation with Autoantibodies

Shreyashi Jha, Chandana Nagaraj[1], R. C. Mundlamuri, Suvarna Alladi, Saraswati Nashi, Raghavendra Kenchaiah, Anita Mahadevan[2], Maya Bhat[1], Jitender Saini[1], M. Netravathi

Departments of Neurology, [1]Neuroimaging and Interventional Neuroradiology (NIIR), and [2]Neuropathology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India

Abstract

Background: Fluorodeoxyglucose-positron emission tomography (FDG-PET) in autoimmune encephalitis (AE) as an adjunctive investigation helps in characterizing the type of AE based on characteristic metabolic patterns. **Objectives:** We aimed to study the following: (i) the sensitivity of FDG-PET in the diagnosis of AE, (ii) describe abnormal patterns of metabolism of various subtypes of AE, and (iii) correlate serum serology with FDG-PET abnormalities. **Materials and Methods:** This study was conducted at a tertiary university hospital in South India. The demographic profile, clinical features, and investigations (FDG-PET, magnetic resonance imaging (MRI) brain, electroencephalography (EEG), cerebrospinal fluid (CSF)) were reviewed. The nuclear medicine physician performed blinded qualitative visual and semi-quantitative analysis of the 18-FDG-PET (fluorine 18-FDG-PET) findings of these patients. **Results:** Twenty-nine (M:F: 11:18) patients were recruited; among them, 22 (75.8%) patients had autoimmune antibodies; the rest seven (24.1%) patients were seronegative. Among the 22 seropositive patients, 9 (31%) patients were positive for anti-N-methyl-D-aspartate receptor (NMDAR), 8 (28%) for anti-leucine-rich glioma inactivated 1 (LGI-1), 4 (14%) for anti-contactin-associated protein 2 (CASPR2), 1 (3%) for anti-glutamic acid decarboxylase (GAD)-65, and rest 7 (24%) patients were seronegative. The patterns most commonly observed were isolated hypermetabolism (41%), isolated hypometabolism (41%), and combined hypermetabolism with hypometabolism (18%). The fraction of abnormalities was lower for MRI (17/22; 73.9%) than for FDG-PET (27/29; 93.1%). FDG-PET correlated with serology in 10 (34%) cases [NMDAR: 6 (60%) and LGI-1: 4 (40%)]. The sensitivity of FDG-PET was 94.1% when compared with MRI. **Discussion and Conclusion:** FDG-PET correlated with serology in only one-third of patients. The most consistent pattern in both seropositive and seronegative AE is characterized by parieto-occipital hypometabolism and fronto-temporal with basal ganglia hypermetabolism.

Keywords: Autoimmune encephalitis, FDG-PET MRI

Introduction

Autoimmune encephalitis (AE) is an immune-mediated disorder affecting the central nervous system (CNS). It often poses a diagnostic challenge to the clinician because of its variable spectrum of clinical presentations, ranging from mild and gradually progressive cognitive impairment to more complex forms of encephalopathy with refractory seizures. Following the description of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis associated with ovarian teratoma in young females,[1] several auto-antibodies against cell surface synaptic antigens have been identified which result in a severe phenotype of limbic encephalitis, classically responsive to initiation of immunotherapy. They have been classified into antibodies against intracellular antigens and neuronal surface synaptic receptor antigens based on their location, pathophysiological mechanisms, and association with malignancies.[2] The antibodies against intracellular antigens are strongly associated with malignancy and respond poorly to immunotherapy while the neuronal surface autoantibodies have excellent outcomes with immunotherapy and have a minimal association with malignancies.[3,4] Early initiation of immunotherapy ensures a good outcome in AE associated with surface autoantibodies.[4]

A retrospective analysis of 15 patients with paraneoplastic neurological syndromes concluded that [18F] FDG-PET (fluorine 18-fluorodeoxyglucose-positron emission tomography) enabled localization of suspected malignancy in 53% of cases with previous unremarkable conventional radiological findings.[5] Imaging plays a crucial role in the evaluation of AE which includes brain magnetic resonance imaging (MRI) and malignancy screening with FDG-PET (18F-FDG-PET). Other investigations include cerebrospinal fluid (CSF) analysis, EEG (electroencephalography), and serum and/or CSF antibody testing.[6] The neuroimaging findings

Address for correspondence: Dr. M. Netravathi, Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru - 560029, Karnataka, India.
E-mail: sundernetra@yahoo.co.in

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in anti-NMDAR encephalitis, vary from involvement of the medial temporal regions and hippocampi of the brain to nonspecific involvement in the entire brain, including the striatum, diencephalon, or rhombencephalon.[7] Nearly 89% of the patients with anti-NMDAR encephalitis have no neuroimaging abnormalities at initial presentation as well as on follow-up.[7,8]

In the criteria proposed by Graus *et al*.[9] in 2016, FDG-PET has been used in the criteria for diagnosis of definite autoimmune encephalitis only when the clinical, MRI, CSF, and EEG criteria are not met. The first case reports of FDG-PET include the case of anti-Hu AE in 1998, which demonstrated that abnormalities on FDG-PET were not concordant with MRI findings, with MRI showing unilateral temporal lobe involvement whereas FDG-PET showed bilateral temporal lobe involvement.[10] This is largely due to the low practicality and the uncertain specificity of FDG-PET in the evaluation of AE.[10] FDG-PET shows temporal abnormalities in the encephalitis caused by autoantibodies against intracellular antigens while autoantibodies against surface antigens are associated with either normal findings or diffuse abnormalities which are extra-temporal.[11] Apart from being used as a screening tool to detect malignancies, FDG-PET is more sensitive than MRI in possible confirmation of the diagnosis of AE.[11-13] Recently, many case series have shown that there is very poor agreement between FDG-PET and MRI.[11,14,15] The prognostic role of FDG-PET was evaluated in a case series of anti-NMDAR encephalitis which found that the severity of abnormalities on FDG-PET showed a positive correlation with the severity of clinical symptoms and showed normalization following clinical recovery.[16] Specific patterns of metabolism have been observed on FDG-PET in certain AE syndromes[14,15]; these patterns of metabolism are dependent on the differential distribution of the antigenic receptors in the brain and the degree of receptor dysfunction caused by the specific autoantibody.[16,17] In cases with autoantibodies to intracellular antigens, T-cell mediated inflammatory response leads to mesiotemporal hypermetabolism whereas cell surface antibodies lead to hypometabolism secondary to receptor internalization. In anti-NMDA receptor encephalitis, hypermetabolism of the basal ganglia with an "anteroposterior gradient" in the form of frontal and temporal hypermetabolism associated with occipital hypometabolism[16,18-20] has been observed.

In this study, we aim to do the following:

(i) Study the FDG-PET abnormalities in patients of AE and describe the abnormal patterns in various antibody subtypes, (ii) Assess the difference between visual qualitative analysis and semi-quantitative analysis of the FDG-PET abnormalities, (iii) Compare the sensitivity and degree of agreement of FDG-PET as an investigation with the available standardized investigations, and (iv) Correlate the autoimmune serology profile with FDG-PET.

Subjects and Methods

This study was conducted in the Department of Neurology at a tertiary university hospital in South India that included 29 patients who fulfilled the Graus criteria for AE from 2017 to 2019.[9] The clinical history of these patients, including their demographic profile, was obtained and investigations including MRI brain, EEG, and CSF findings were reviewed. The serum of all patients or both serum and CSF samples ($N = 22$) were tested for the available panel of autoantibodies associated with autoimmune encephalitis using the commercially available indirect immunofluorescence test. Ethics committee approval was obtained by (21/12/2019).

The nuclear medicine physician performed a blinded qualitative visual and semi-quantitative analysis of the 18-FDG-PET findings of these patients. The available literature on the pattern of abnormalities in FDG-PET was reviewed to correlate the visual analysis of the FDG-PET with the individual serology of the patients.[17,21,22] The semi-quantitative analysis data was used to validate the visual analysis. The median time between the onset of symptoms and FDG-PET was 12 weeks (range from 2 to 20 weeks). This delay was mostly because the patients had initially been evaluated in outside centers and were subsequently referred to our tertiary care hospital.

The study population was divided into two groups based on the serology status of the autoimmune profile: seropositive and seronegative AE. The seropositive cohort was further sub-grouped as per the individual serology, which was anti-NMDAR, anti-contactin-associated protein 2 (CASPR2), anti-leucine-rich glioma inactivated 1 (LGI-1), and anti-glutamic acid decarboxylase (GAD-65).

Image acquisition: All the patients fasted for 4–6 h before imaging. On the day of imaging, patients with random blood glucose levels were injected with 18F FDG intravenously in the secured iv access. All patients were injected between 259 and 370 megabequerel (MBq), and 45 min later, all underwent whole-body imaging (WB) on simultaneous Biograph mMR (Siemens, Erlangen, Germany) in 5-bed position (5 min/bed) from mid-canthus to mid-thigh, followed by dedicated brain imaging for 10 min with appropriate MR attenuation sequences (AC), DIXON for WB, and ultra-short echo time (UTE) for the brain. All the images were viewed in SYNGO Via and a semi-quantitative analysis of the brain was performed using molecular imaging (MI) neurology. MI neurology is a Software Project Management (SPM)-based software provided by SIEMENS. It calculates Z-score based on the normal database template incorporated in the software. Brain region mean Z-scores with magnitudes >2 were interpreted as significant. Comparisons were made to rates of abnormal initial brain MRI, abnormal initial EEG, and abnormal CSF.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. Appropriate statistical analysis on

different evaluations (clinical features, MRI, EEG, FDG-PET, and CSF abnormalities) was performed using SPSS version 20. The demographics and clinical characteristics of the patients were compared using unpaired t-tests. Results are reported as mean ± standard. Agreement in findings between MRI, EEG, and CSF abnormalities and FDG-PET abnormalities was measured using Cohen's kappa and McNemar's test. The correlation between findings on FDG-PET and serum or CSF autoantibody serology was reconnoitered by Chi-squared tests. Likelihood ratios were used to find the sensitivity of FDG-PET.

Data availability

The individual de-identified participant data will be shared if required on an SPSS sheet.

Results

Twenty-nine patients in the study cohort fulfilled the criteria of AE. Among them, 22 (75.8%) patients had autoimmune antibodies identified in the serum or CSF or both; the rest of the 7 patients (24.1%) were diagnosed as seronegative AE based on the clinical profile and imaging findings.[9]

Demographic profile of the study cohort

Among the 22 seropositive patients, nine (31%) patients were positive for anti-NMDAR, eight (28%) for anti-LGI1, four (14%) for anti-CASPR2, one (3%) for anti-GAD-65, and rest seven (24%) patients were seronegative. The demographic profile [Table 1] demonstrated that the mean ± SD age at presentation was higher in seronegative (44.8 ± 17.56 years) as compared to seropositive cases (34.9 ± 12.1 years) ($p = 0.28$). The mean ± SD duration of symptoms was 6.3 ± 11.3 months in seropositive AE and 20.4 ± 19.02 months in seronegative AE ($p = 0.01$). The cohort was women predominant (58.6%) compared to men (41.4%). Delay in diagnosis and further initiation of immunotherapy was within the range of 1–36 months (median-2 months). This delay was because of alternative diagnoses in four (13.7%) patients: post-infectious (1), vasculitis (1), and psychogenic (2) etiologies, which were considered by the first contact physicians before presentation to our center. Antecedent infection was seen in seven (24.1%) patients; six patients had a preceding history of fever and one patient had a preceding urinary tract infection before the onset of neurological symptoms. The median duration of the antecedent infection was seven days.

Clinical features

As seen in Table 2, Sleep disturbances (76%) and behavioral disturbances (66%) were the most common clinical manifestations observed in our cohort, followed by seizures (59%), cognitive impairment (52%), bladder and/or bowel incontinence (34%), movement disorders (30%), mutism (17%), autonomic disturbances (14%), and visual hallucinations (10%). Sleep disturbances in the form of insomnia were most commonly seen in the seronegative cohort in five (71.4%) patients. In the seropositive cohort, insomnia was seen in all patients with CASPR positivity (100%) followed by 75% of LGI-1 patients and 66.6% NMDAR positive patients. Behavioral disturbances were seen in all patients with NMDAR and LGI-1 positivity and 71.4% of seronegative patients. Seizures were seen in 87.5% of LGI-1-positive patients and 77.7% of NMDAR-positive patients. Status epilepticus was seen in two patients; one of whom was NMDAR positive and the other was seronegative. Cognitive impairment was seen in 75% of LGI-1, followed by 44.4% of anti-NMDAR positive patients, and 42.8% of seronegative patients. Incontinence was seen most commonly in the NMDAR cohort in 77.7% of patients. Mutism was exclusive to the NMDAR-positive cohort seen in nearly half (55.5%) of the patients. Visual hallucinations were seen in one patient in each of the NMDAR, CASPR, and LG1-1 populations. The movement disorders observed were tremors (1 patient each in the seronegative and CASPR positive cohort), dystonia (1 patient in the NMDAR cohort and 3 patients in the LGI-1 cohort), dyskinesias (1 patient in the NMDAR and 2 in the LGI-1 cohort), myoclonus (1 NMDAR positive patient), and ataxia (1 patient of NMDAR and 1 patient with seronegative status). Autonomic disturbances were seen only in the CASPR cohort in 75% of patients. Peripheral nerve hyperexcitability confirmed by electromyography was seen in 50% of the CASPR-positive patients.

Investigations

Hematological parameters were normal in all patients. Hyponatremia (serum sodium concentration less than 135 mEq/L) was present in eight (27.5%) patients [Table 1]. The rest of the biochemical parameters were unremarkable. MRI was performed in 22 patients, of which 17 (73.9%) were abnormal; 16 (94%) had changes in the medial temporal lobes, hippocampi, and amygdala, whereas one patient with NMDAR positivity had white matter changes. Twenty-two had a prior MRI before PET was done. Rest seven had PET-MRI as the first MRI modality along with PET study in view of the clinical suspicion. Since we have simultaneous PET-MRI in our institute, all patients had the simultaneous acquisition of PET-MRI as a single study. EEG was available in 25 patients and was abnormal in 40% of patients. The diffuse slowing was the most common abnormality in 60%, followed by interictal discharges arising from the anterior temporal areas in 30%, and an electrographic seizure with right temporal lobe origin was seen in 10% of patients. CSF lymphocytic pleocytosis was observed in 43% of patients.

FDG-PET abnormalities

It was abnormal in all (93.1%) patients and the abnormalities detected are enumerated in Table 3. FDG-PET showed basal ganglia hypermetabolism in 79.3% and hypometabolism in 3.4% of patients. Isolated hypermetabolism was seen in 41%, isolated hypometabolism in 41%, and combined hypermetabolism with hypometabolism in 18% of patients. Hypermetabolism was common in the frontal (34.4%) and temporal (27.6%) regions. Our cohort demonstrated hypometabolism in frontoparietal regions (17.2%) and occipital regions (13.8%) although no hypometabolism was

Table 1: Demographic and investigative findings of the study population

Parameter	Anti-NMDAR	Anti-LGI-1	Anti-CASPR2	Anti-GAD-65	Seropositive	Seronegative
n (%)	9 (31.0)	8 (27.5)	4 (13.7)	1 (3.4)	22 (75.8)	7 (24.1)
M: F	2:7	5:3	2:2	0:1	9:13	2:5
Age at onset (years; Mean±SD)	24.6±8.3	57.1±13.9	37.7±19.4	31	34.9±22.1	43.2.1±17.8
Duration of symptoms (months; Mean±SD)	7.4±14.4	3.6±1.8	1.5±0.5	36	6.3±11.3	20.4±19.0
Antecedent infection	2 (22.2)	2 (25)	0	0	4 (18.1)	3 (42.8)
Serum sodium <135 mEq/L (*n*=8)	2 (22.2)	4 (50)	2 (50)	0	8 (36.3)	0
ANA profile positivity (*n*=3)	0	2 (25)	0	0	2 (9.0)	1 (14.2)
Anti-Ro-52 positivity	0	1 (12.5)	0	0	1 (4.5)	1 (14.2)
Anti Sm-nRNP positivity	0	1 (12.5)	0	0	1 (4.5)	0
CSF (N: 23)						
Elevated protein (>45 mg/dL)	2 (22.2)	3 (37.5)	2 (50)	1 (100)	8 (36.3)	2 (28.5)
Lymphocytic pleocytosis (>10 cells)	4 (44.4)	2 (25)	2 (50)	0	8 (36.3)	2 (28.5)
MRI abnormalities (*n*=17):						
Temporal lobes and amygdala	7 (77.7)	3 (37.5)	2 (50)	0	12 (54.5)	4 (57.1)
Supratentorial white matter	1 (11.1)	0	0	0	1 (4.5)	0
EEG abnormalities (*n*=10):						
Diffuse slowing	4 (44.4)	1 (12.5)	0	0	5 (22.7)	1 (14.2)
interictal discharges	1 (11.1)	0	0	0	1 (4.5)	2 (28.5)
Electrographic seizures	0	0	1 (25)	0	1 (4.5)	0

n=Number, ANA=Antinuclear antibody, CASPR2=Contactin-associated protein 2, CSF=cerebrospinal fluid, EEG=Electroencephalography, F=Female, Glutamic acid decarboxylase 65, LGI-1=leucine-rich glioma inactivated 1, M=Male, MRI=Magnetic resonance imaging, NMDAR=N-methyl-D-aspartate receptor, PNH=Peripheral nerve hyperexcitability

Table 2: Clinical features of the study population

Serology	Behavioral changes *n* (%)	Cognitive impairment *n* (%)	Mutism *n* (%)	Insomnia *n* (%)	Seizures *n* (%)	Autonomic Disturbances *n* (%)	Incontinence *n* (%)
NMDAR (*n*=9)	9 (100)	4 (44.4)	5 (55.5)	6 (66.6)	7 (77.7)		7 (77.7)
Seronegative (*n*=7)	5 (71.4)	3 (42.8)		5 (71.4)	6 (85.7)		
LGI-1 (*n*=8)	8 (100)	6 (75)		6 (75)	7 (87.5)		
CASPR2 (*n*=4)	3 (75)	3 (75)		4 (100)	1 (25)	3 (75)	
GAD-65 (*n*=1)		1 (100)			1 (100)		

n=Number, CASPR2=Contactin-associated protein 2, Glutamic acid decarboxylase 65, LGI-1=leucine-rich glioma inactivated 1, NMDAR=N-methyl-D-aspartate receptor

seen in 20.7% of patients. None of the patients in our cohort had any evidence of malignancy on whole-body FDG-PET.

Patterns in anti-NMDAR encephalitis

Among the nine patients with encephalitis secondary to anti-NMDAR positivity, seven patients underwent FDG-PET in the acute phase within a median of four weeks from the MRI (range of 2 weeks to 20 weeks). Two patients underwent FDG-PET after two years and four years from the acute phase. The common pattern seen in 7/9 patients (77.7%) was basal ganglia hypermetabolism with preserved or hypermetabolism of the frontal lobes with occipital hypometabolism [Figure 1a and b] with normal MRI brain and EEG [Figure 1 c and d]. The other pattern which was seen in 2/9 (22.2%) of patients was basal ganglia hypermetabolism with temporo-parietal hypometabolism.

Patterns in anti-LGI-1 encephalitis

Among the eight patients with encephalitis secondary to anti-LGI-1 positivity, all patients underwent FDG-PET in the acute phase within a median of three weeks from the MRI (range of 2 weeks to 18 weeks). Basal ganglia hypermetabolism was seen in all patients. Temporal hypermetabolism was seen in 6/8 (75%) of patients [Figure 1e-h]. The other pattern was of frontal and occipital hypometabolism which was seen in 2/8 (25%) of patients.

Patterns in anti-CASPR2 encephalitis

Among the four patients with encephalitis secondary to anti-CASPR2 positivity, all patients underwent FDG-PET in the acute phase within a median of two weeks from the MRI (range of 2 weeks to 4 weeks). All four patients demonstrated basal ganglia hypermetabolism with frontal hypermetabolism and temporo-parietal hypometabolism [Figure 2e-h].

Patterns in seronegative encephalitis

Among the seven patients with seronegative encephalitis, seven patients underwent FDG-PET in the acute phase within a median of four weeks from the MRI (range of 2 weeks to 12 weeks). Two patients had global hypometabolism not suggestive of AE and five patients had frontal and temporal hypermetabolism [Figure 2].

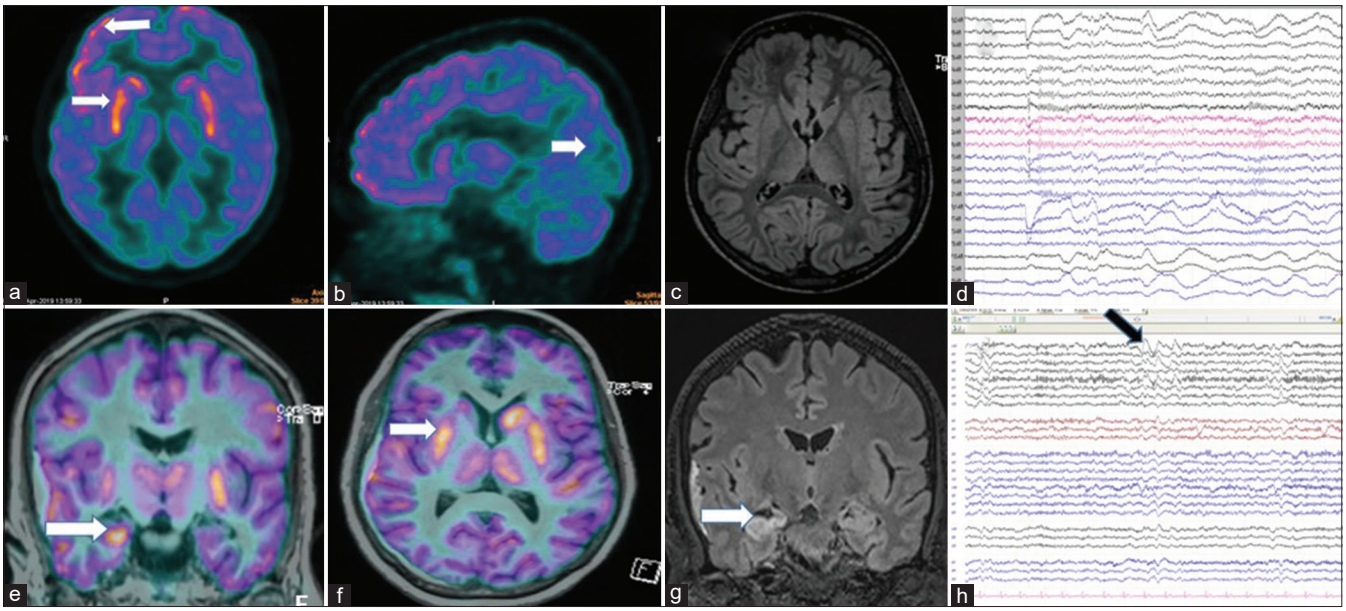

Figure 1: (a-d) A case of anti-N-methyl-D aspartate receptor (NMDAR) encephalitis: (a) shows fused FDG-PET axial section of brain with increased bilateral basal ganglia uptake with right frontal hypermetabolism (white arrows). (b) shows a fused FDG-PET sagittal section of the brain with severe parieto-occipital and medial temporal hypometabolism (white arrows). (c) Normal MRI brain. (d) Normal EEG. (e-h) A case of anti-leucine-rich, glioma inactivated-1 (LGI-1) encephalitis: (e) shows fused FDG-PET coronal section of brain with right temporal hypermetabolism (white arrows). (f) shows a fused FDG-PET axial section of the brain with increased bilateral basal ganglia uptake (white arrows). (g) shows an axial section of the MRI brain with right hippocampal T2 FLAIR hyperintensity (white arrows). Also, incidental finding of right fronto-temporal subdural hematoma is seen. (h) shows EEG with frontal intermittent rhythmic delta activity (FIRDA) (white arrows)

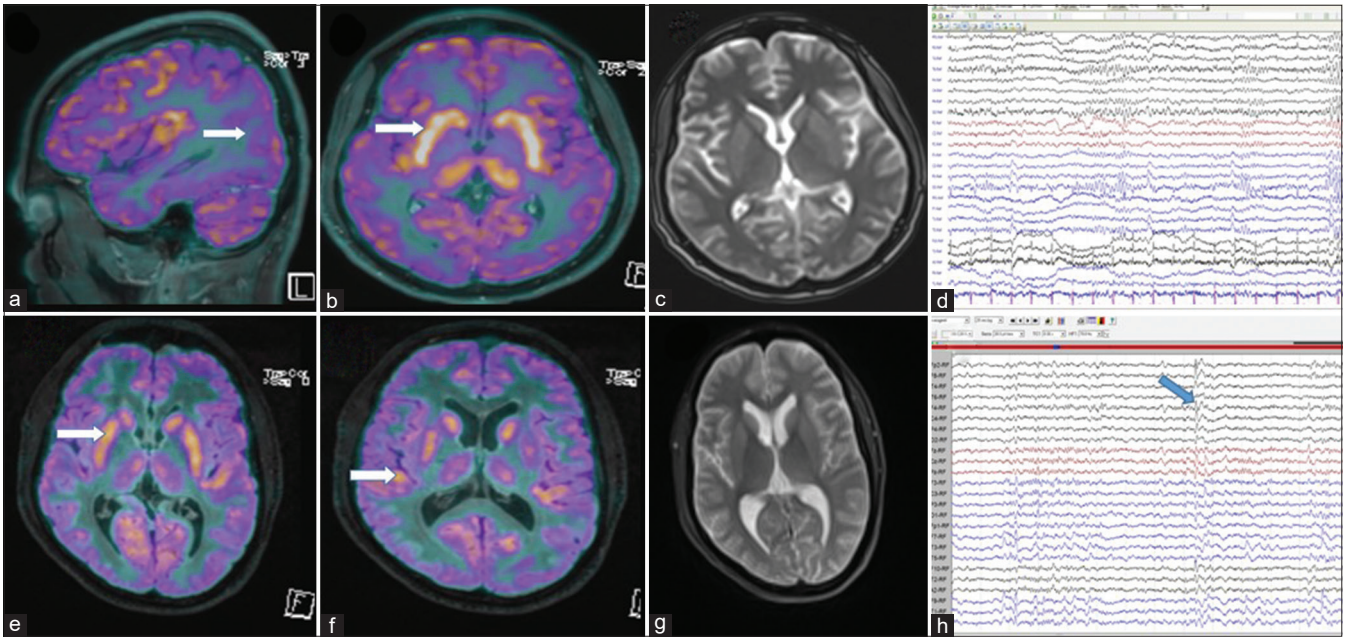

Figure 2: (a-d) A case of seronegative autoimmune encephalitis: (a) shows fused FDG-PET axial section of brain with increased bilateral basal ganglia uptake, (b) fused FDG-PET axial section of brain shows bilateral temporal hypermetabolism, (c) Normal MRI, (d) Bilateral independent spike and wave discharges across bilateral temporal regions seen. (e-h) A case of anti-contactin-associated protein 2 (CASPR2) encephalitis: (e) shows fused FDG-PET sagittal section of the brain with basal ganglia hypermetabolism. (f) shows a fused FDG-PET axial section of the brain with temporo-parietal hypometabolism. (g) Normal MRI brain. (h) Normal EEG

Pattern in anti-GAD 65 encephalitis

The only patient with anti-GAD-65 encephalitis had bilateral basal ganglia and temporal hypometabolism.

Semi-quantitative analysis revealed a significant metabolic change in at least one cortical region of the brain in all patients. Significant hypometabolism (Z-score <−2)

Table 3: Brain FDG-PET abnormalities in the study population

FDG-PET abnormality	Anti-NMDAR (*n*=9)	Anti-LGI-1 (*n*=8)	Anti-CASPR (*n*=4)	Anti-GAD-65 (*n*=1)	Seropositive (*n*=22)	Seronegative (*n*=5)
Basal Ganglia Hypermetabolism *n* (%)	6 (66.7)	7 (87.5)	4 (100)	1 (100)	18 (81.8)	5 (100)
Frontal hypermetabolism *n* (%)	6 (66.7)		1 (25)		7 (31.8)	3 (60)
Temporal hypermetabolism *n* (%)	1 (11.1)	4 (50)	1 (25)		7 (31.8)	2 (40)
Temporal hypometabolism *n* (%)				1 (100)		
Absent hypometabolism *n* (%)	1 (11.1)	4 (50)	1 (25)		6 (27.2)	
Unilateral Occipital hypometabolism *n* (%)	3 (33.3)	1 (12.5)			4 (18.1)	1 (20)
Bilateral Occipital hypometabolism *n* (%)	1 (11.1)	1 (12.5)	3 (75)		5 (22.7)	1 (20)

n=Number, CASPR2=Contactin-associated protein 2, FDG-PET=Fluorodeoxyglucose-positron emission tomography, Glutamic acid decarboxylase 65, LGI-1=leucine-rich glioma inactivated 1, NMDAR=N-methyl-D-aspartate receptor

was observed involving both parietal lobes and frontal lobes with median Z-score of −3.3 (R) and −3.7 (L) and −2.8 (R) and −2.6 (L), respectively. Significant hypometabolism (Z-score <−2) was also observed in temporal lobes. Significant hypermetabolism (Z-score >2) was not noted in the semi-quantitative analysis. Hypermetabolism was thus better appreciated on visual analysis only.

Comparison of MRI and FDG-PET findings

The fraction of imaging that was abnormal was lower for MRI (17/22; 73.9%) than for FDG-PET (27/29; 93.1%). However, this difference did not reach statistical significance (McNemar's test for 22 paired examinations, $P = 0.32$) and the overall agreement between MRI and FDG-PET in terms of scan abnormality was fair (Cohen's kappa = 0.33).

Comparison of other investigations and FDG-PET findings

At least one abnormal paraclinical finding consistent with AE was not in agreement with abnormalities on FDG-PET. This was transformed into a weak agreement when both CSF and EEG were abnormal with abnormal metabolism on FDG-PET (k = 0.19, *P* 0.01). All the investigations of MRI, CSF, and EEG with FDG-PET were abnormal only in six (20.6%) patients. One of the CSF, MRI, or EEG being abnormal did not agree with abnormal FDG-PET. Two or all three of the other paraclinical investigations needed to be abnormal to have an agreement with FDG-PET.

Correlation with serology

The serology demonstrated in serum or CSF was correlated with the probable serology estimated by the blinded nuclear physician based on FDG-PET abnormalities. FDG-PET correlated with serology in ten (34%) cases among which six (60%) were NMDAR and four (40%) patients were LGI-1 positive. The correlation was not found to be significant ($p = 0.667$).

Sensitivity

FDG-PET was compared with MRI and the sensitivity of FDG-PET was found to be 94.1%.

Discussion

In this study, we have described various patterns of FDG-PET abnormalities, agreement of FDG-PET with other ancillary investigations, and correlation of serology on FDG-PET with serum serology in 29 patients who met the consensus criteria for AE. Our study in a small group of patients yields important findings. FDG-PET was abnormal in 93.1% of AE patients and the abnormalities were more sensitive for the detection of AE compared with other ancillary investigations of MRI, CSF, or EEG. Further, this study demonstrated that temporo-parietal hypermetabolism with basal ganglia hypermetabolism is a common abnormality on FDG-PET, irrespective of the serological status of the patient. Abnormal patterns of metabolism occur in various subtypes of AE, which contributes, to making a definite diagnosis of AE. Visual analysis was concluded to be superior to semi-quantitiative analysis to estimate hypermetabolism. In a novel attempt, the serology estimated on FDG-PET was correlated with serum and/or CSF serology and both correlated in ten patients. Our results suggest that FDG-PET may be effective supporting evidence to diagnose and detect brain dysfunction in early AE especially in seronegative patients when no other investigations can detect any abnormality.

Our study demonstrated that FDG-PET becomes abnormal early in AE, in line with previous studies, and there is poor concordance between MRI, CSF, and FDG-PET.[13,23,24] In cases of autoimmune encephalitis, FDG-PET commonly shows hypermetabolism but focal areas of hypometabolism may also be observed.[14] Previous studies have shown hypometabolism in the brain to be the most common pattern of FDG-PET in AE.[17,25] Our study demonstrated equal proportions of isolated hypometabolism and hypermetabolism patterns, while combined patterns of both hypermetabolism and hypometabolism were less commonly seen. Semi-quantitative analysis was concluded to be noninferior to visual analysis of FDG-PET abnormalities. Furthermore, we found visual analysis to be superior in detecting hypermetabolism. Cortical dysfunction and autoantibody-mediated cellular changes altering the synapses and densities of receptors are postulated to be reflected in the altered metabolism on FDG-PET.[22] Specific metabolic patterns on FDG-PET correlate with the presence of a specific antibody[26,27] and there were distinct patterns of abnormal metabolism among the seropositive group.

NMDAR encephalitis is the most common form of AE[18]; in our series of NMDAR antibody encephalitis, increased

basal ganglia uptake with increased frontal metabolism with parieto-occipital hypometabolism was seen. Although the resolution of this pattern of hypometabolism is associated with improved outcomes as previously reported,[24,28] two patients who underwent FDG-PET in the chronic phase showed similar imaging abnormalities, which correlated with persistent antibody positivity even though the patient was clinically asymptomatic. Hypometabolism in our patients with NMDAR antibody encephalitis showed a parieto-occipital gradient. Another feature noted was that the abnormality on FDG-PET involved both cortical and subcortical regions while the abnormality on MRI was restricted to the mesial temporal regions.

Basal ganglia hypermetabolism was a classical feature seen in anti-CASPR2 and anti-LGI1 encephalitis, both being cell surface antigens, similar to previous observations,[29] while basal ganglia hypometabolism was seen in the intracellular anti-GAD65 encephalitis, probably related to the longer disease duration.

In line with a few studies from India, we observed parieto-occipital hypometabolism with basal ganglia hypermetabolism common in AE.[21,23,29] In addition, we also explored the FDG-PET findings in seronegative AE, which were found to be predominantly fronto-temporal hypermetabolism and global hypometabolism.

A recent systematic review and meta-analysis of 444 patients with AE found 18F-FDG PET to have an overall detection sensitivity performance of 87% with similar patterns of mixed hypermetabolism and hypometabolism in various AE subtypes, hypometabolism being more predominant in the later stages of the disease. The parieto-occipital gradient remained a consistent finding, and hypometabolism in these areas is an important marker towards the diagnosis of anti-NMDAR AE.[27]

LGI-1 is highly expressed in the hippocampus,[19] and hence, frontal and temporal hypermetabolism pattern was observed in voltage-gated potassium channel (VGKC)-associated syndromes. Furthermore, asymmetrical abnormality due to differential expression of the LGI-1 receptor was also noted in our study in the FDG-PET and MRI abnormalities, unlike other subtypes of AE. Interestingly, the "anteroposterior gradient" described in anti-NMDAR encephalitis earlier, was also described in all four patients with anti-CASPR2 encephalitis in our study. A salient feature seen in seronegative patients was that they demonstrated characteristic patterns of hypermetabolism in the frontal and temporal lobes, which aided in the diagnosis when other ancillary investigations were normal.

Among the seropositive group, serum serology correlated in ten patients, and these serologies belonged to the subtypes of anti-NMDAR and anti-LGI-1 encephalitis. To our knowledge, this has not been attempted previously in the available literature.

Early therapeutic intervention improves long-term outcomes in AE[12] and FDG-PET can form an important diagnostic armamentarium in early diagnosis, especially in seronegative patients. Our study is limited by the small number of cases, which does not allow the description of new patterns associated with autoantibodies. However, the patterns we found are in line with what has been described in literature characteristic or more frequent for each autoantibody,[12,15-17] along with few new patterns which have been described. We also aimed to correlate the serum serology with the serology on FDG-PET, which has not been attempted before. Consequently, better standardization of FDG-PET reading could help to establish the role of FDG-PET in the diagnostic workup of autoimmune encephalitis.

Although the study has a small patient population, it adds to the sparse literature on FDG-PET in AE from India and would need validation with larger prospective trials.

Conclusions

Our results in a small group of antibody-positive AE patients show much greater sensitivity for detection of an underlying abnormality with 18-FDG-PET than with MRI, CSF, or EEG. Temporal hypermetabolism with increased basal ganglia uptake is a common finding seen in AE, better appreciated on qualitative visual analysis. FDG-PET further also has a fair correlation with serum/CSF serology. Because early intervention is needed for optimal clinical outcome, our results suggest that 18F-FDG-PET be added to the clinical workup of patients with suspected AE, particularly in those with normal or nonspecific MRI findings.

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Conflicts of interest

There are no conflicts of interest.

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