Original Article

Comprehensive Functional Evaluation of the Spectrum of Multi-System Atrophy with ^{18}F-FDG PET/CT and ^{99m}Tc TRODAT-1 SPECT: 5 Year's Experience from a Tertiary Care Center

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Abstract

Aim: To elucidate the patterns of characteristic hypometabolism on ^{18}F- fluorodeoxyglucose(^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in multisystem atrophy (MSA) and their correlation with the patterns of uptake on dopamine transporter imaging with ^{99m}Tc TRODAT-1 SPECT. **Material and Methods:** A retrospective analysis of 67 patients with clinically diagnosed MSA was performed. All the subjects underwent ^{99m}Tc TRODAT-1 SPECT and ^{18}F-FDG PET/CT scanning on two separate days. The ^{99m}Tc-TRODAT-1 scans were analyzed visually for asymmetry and rostro-caudal gradient. The FDG uptake patterns were recorded, and areas of hypometabolism that were two standard deviations from the mean were considered abnormal. **Results:** All the subjects had an abnormal pattern of FDG uptake on PET scan, both on a visual inspection and semiquantitative analysis. In MSA-P subjects (n = 29), diffuse predominant hypometabolism of the globus pallidus-putamen complex was noted, with relative sparing of the caudate nuclei. In MSA-C subjects (n = 25), characteristic hypometabolism was noted in the cerebellum and brainstem. In mixed subtypes (n = 13), variable involvement of the basal ganglia, cerebellum, and brainstem was noted with frontoparietal hypometabolism. A statistically significant difference between MSA-P and MSA-C for gradient reduction and asymmetry with gradient reduction was observed. **Conclusion:** Dopamine transporter imaging with ^{99m}Tc TRODAT-1 SPECT not only helps in confirmation of parkinsonian disorders but also demonstrates varying patterns of distribution in different subtypes of MSA. Characteristic patterns of hypometabolism in ^{18}F-FDG PET may help in the differentiation of the subtypes of MSA in the presence of clinically overlapping symptoms.

Keywords: ^{18}F-FDG PET/CT, ^{99m}Tc TRODAT-1 SPECT, multisystem atrophy

Introduction

Multisystem atrophy (MSA) is an adult-onset, sporadic, rapidly progressing neurodegenerative disorder manifesting with a variable combination of parkinsonism, autonomic dysfunction, cerebellar syndrome, and cortico-spinal abnormality with poor response to levodopa.[1,2] Pathologically, it is an alpha-synucleinopathy, a group of disorders characterized by abnormal deposition of the abnormally misfolded protein α-synuclein in the oligodendroglial cells forming glial cytoplasmic inclusions in the central and peripheral autonomic nervous system.[3] MSA is further classified as parkinsonian subtype - MSA-P, if parkinsonism is the predominant feature with predominant striatonigral degeneration, and MSA-C if cerebellar features predominate with olivo-ponto-cerebellar degeneration.[3,4] With its variable and heterogeneous clinical presentation MSA presents a major diagnostic challenge in neurology.

The dopamine transporter (DAT) is a sodium chloride–dependent trans-membrane protein on presynaptic nerve terminals. DAT density correlates with the density of the presynaptic dopaminergic neurons. ^{99m}Tc-TRODAT-1 is a specific ligand for DAT, which enables *in vivo* demonstration of striatal dopaminergic activity and integrity and is used as an imaging biomarker for the diagnosis of degenerative parkinsonian disorders.[5] ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a glucose analog that serves as a competitive substrate of glucose within the human body and can demonstrate the topography of cerebral glucose metabolism in various physiological and pathological states.[6] As MSA, like other Parkinson plus syndromes, is characterized by abnormalities in both the presynaptic and postsynaptic dopaminergic neuron, ^{18}F-FDG positron emission tomography (PET) acts as a surrogate marker of mitochondrial activity and viability of the postsynaptic dopaminergic neurons.[7]

The aim of the study was to elucidate patterns of characteristic hypometabolism on ^{18}F-FDG PET/computed tomography (CT)

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in various subtypes of MSA and to correlate the patterns of uptake on dopamine transporter imaging with ^{99m}Tc TRODAT-1.

Methodology

A retrospective analysis of 67 patients with a clinical suspicion of MSA, referred to us from our tertiary care neurology department of neurology, was conducted during 2014-2019. All patients included had clinically probable MSA according to Gilman *et al*.[1] consensus criteria, and had undergone both FDG PET and ^{99m}Tc-TRODAT-1 scanning. Other patients with clinically probable MSA, who had not undergone both studies, were excluded from admission to the study. An informed written consent to participate in the study was taken from all patients, and detail clinical history and examination was undertaken. All the subjects underwent ^{18}F-FDG PET/CT scan of the brain, and the studies were analyzed both qualitatively (visually) and semiquantitatively. The subjects also underwent dopamine transporter imaging with ^{99m}Tc-TRODAT-1 on a separate day. The scans were analyzed visually for asymmetry and rostrocaudal gradient on ^{99m}Tc-TRODAT-1 imaging. Asymmetry was noted on the ^{99m}Tc-TRODAT-1 scan when there was an asymmetrical reduction in ^{99m}Tc-TRODAT-1 binding in the bilateral striatum, and rostrocaudal gradient was noted when the reduction in the posterior striatum was greater than in the anterior striatum (putamen more than caudate). The FDG uptake patterns were recorded and areas of cortical and subcortical hypometabolism that were two standard deviations from the mean were considered abnormal. Quantification was performed using 3D-SSP regional hypometabolism (Z score) and compared with a normal age-matched database.

Image acquisition

Radiopharmaceutical preparation: ^{99m}Tc-labeled tropane derivative (TRODAT-1) was prepared from a preformulated lyophilized cold kit, and injected if the radiochemical purity was more than 90%. After the intravenous injection of 20 to 22 mCi, brain SPECT images were acquired using a low energy high-resolution collimator on a GE Discovery NM 630 dual-head camera (General Electronics Healthcare, Chicago, IL) at 4 h after injection. Iterative reconstruction (ordered subset expectation maximization) was performed, and images were reconstructed using back-projection with a Metz filter. The SPECT images were coregistered with each subject's corresponding CT image and then fine adjusted manually with a visual inspection of the overlaid images, using Multimodality software (Xeleris functional imaging workstation 4.0; General Electronics Healthcare, Chicago, IL).

^{18}F-FDG PET/CT was performed on a separate day following intravenous injection of 132-222 MBq (4-6 mCi) of 18F-FDG using a dedicated GE Discovery STE PET/CT scanner within 45 ± 15 min after injection of ^{18}F-FDG. A noncontrast CT scan was performed first (120 kV, 200 mA, 0.8 s per CT rotation, the pitch of 1.375:1, and a table speed of 27.55 mm/s). PET scanning was performed immediately after the acquisition of the noncontrast CT images, without changing the patient position. A single bed position was used for imaging with an acquisition time of 10 min. PET images were reconstructed by using the ordered set expectation maximization algorithm, CT attenuation correction, dead time correction, and decay correction to the beginning of each scan. CT data were used for attenuation correction. PET/CT images were interpreted at an advantage window workstation equipped with fusion software that enables the display of PET images with and without attenuation correction, CT images, and fused PET/CT images.

Statistical analysis

The data were entered into EXCEL and analyzed using SPSS (Statistical Package for the Social Science, version 16.0). $P < 0.05$ was considered statistically significant. The data were checked for normalcy using Shapiro-Wilk test, and the Z score for the two population proportions was applied between MSA-C and MSA-P groups, for variables asymmetry and rostrocaudal gradient.

Results

On demographic analysis, 58% of the subjects were female and 42% were male. Their average age was 60 (range 41–78) years. Their clinical symptoms are shown in [Figure 1]. All the subjects had an abnormal pattern of 18 F- fluorodeoxyglucose (FDG) uptake on PET scan, both on a visual inspection and semiquantitative analysis. In MSA-P subjects (n = 29), diffuse predominant hypometabolism of the globus pallidus-putamen complex was noted with relative sparing of the caudate nuclei [Figure 2]. In MSA-C subjects (n = 25), characteristic hypometabolism was noted in the cerebellum and brainstem [Figure 3]. In mixed (equally MSA-P and MSA-C subtypes (n = 13), there was variable involvement of the basal ganglia, cerebellum, and brainstem, with frontoparietal hypometabolism [Figure 2].

^{99m}Tc-TRODAT-1 scan was abnormal in all patients and showed pronounced asymmetry with a prominent rostrocaudal gradient with putamen being more affected than the caudate nucleus in the MSA-P subtype. A Z score for two population proportions applied between MSA-C and MSA-P groups, for variables asymmetry and rostro-caudal gradient revealed a statistically significant difference between MSA-P and MSA-C for gradient reduction ($P < 0.007$) and asymmetry with gradient reduction ($P < 0.005$). Table 1 shows the results of the patients.

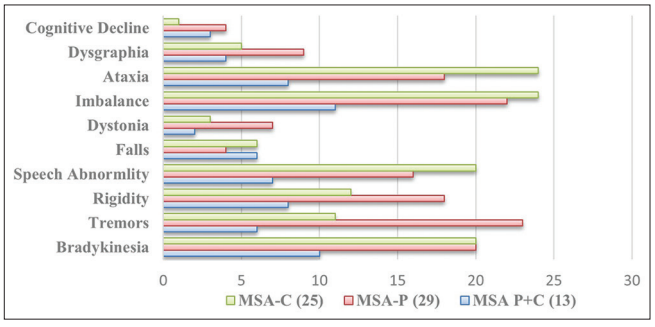

Figure 1: Clinical symptoms of MSA patients

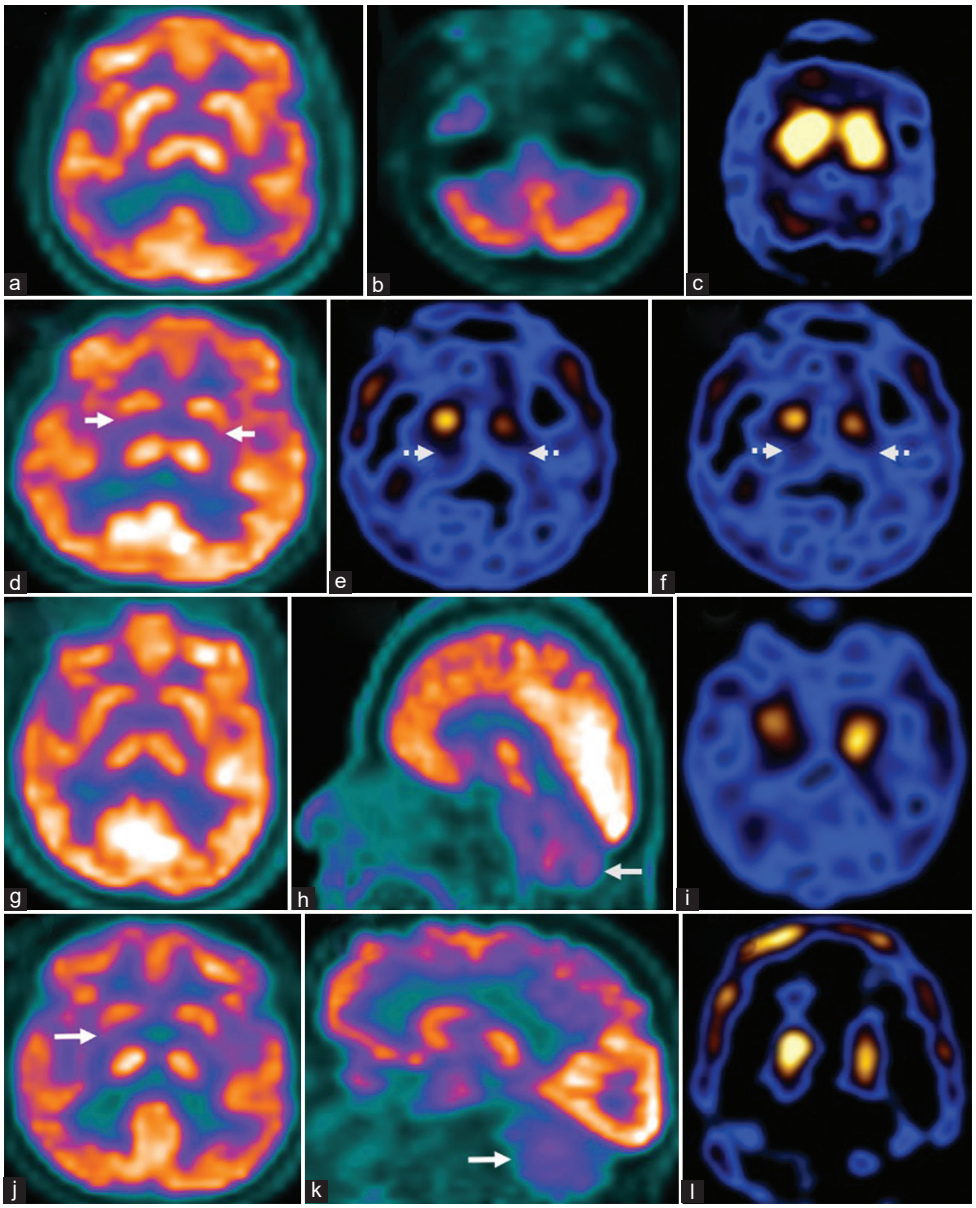

Figure 2: Normal FDG PET brain (a and b) showing homogenous tracer distribution with normal TRODAT scan (c) FDG PET scan in MSA-P (d) shows hypometabolism (arrow) in bilateral posterior striatum with reduced TRODAT uptake (e and f) with a rostro-caudal gradient (Dotted arrows). FDG PET scan in MSA-C shows normal metabolism in bilateral striatum (g) with hypometabolism (arrow) in the cerebellum (h) with reduced TRODAT uptake (i). FDG PET scan in MSA-P+C (j and k) shows hypometabolism (arrows) in the bilateral basal ganglia and cerebellar hemispheres with reduced TRODAT uptake (l).

Discussion

Multiple system atrophy (MSA) is characterized by varying degrees of parkinsonism, cerebellar ataxia, and autonomic dysfunction.[8-12] As per the revised consensus criteria, autonomic dysfunction is mandatory for the diagnosis of MSA.[1] MSA is further classified based on the predominant symptomatology and phenotype into MSA-P and -C. At present, the diagnosis of MSA relies on clinical criteria.[1] However, the clinical distinction between MSA, Parkinson's disease (PD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), and spinocerebellar ataxias (SCAs) is often difficult and challenging,[13,14] especially in the early stage of MSA owing to the lack of specific diagnostic tests.[15]

The imaging features of MSA include 1) magnetic resonance imaging (MRI), with evidence of atrophy in the putamen, pons, or cerebellum, 2) hypometabolism on ^{18}F-FDG PET in the putamen and brainstem, and 3) evidence of presynaptic nigro-striatal dopaminergic dysfunction on single-photon emission computed tomography (SPECT) or PET as measured by ^{99m}Tc-TRODAT-1 or ^{18}F-F-DOPA PET scans.[1]

In patients with MSA-P, ^{18}F-FDG PET scan shows significant hypometabolism in the striatum, more severe in the posterior

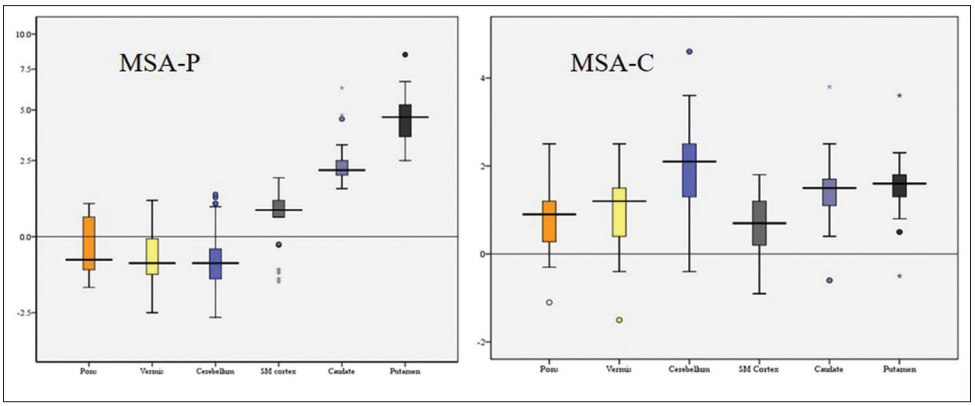

Figure 3: Box plot of patients with MSA-P and MSA-C showing Z scores on Y-axis and different cortical and sub-cortical regions on the X-axis. Putamen-globus pallidus complex consistently showed diffuse hypo-metabolism as compared to healthy controls ($P < 0.001$) in MSA-P. Diffuse hypometabolism was seen in the cerebellum in MSA-C as compared to healthy controls ($P < 0.001$)

Table 1: Statistical analysis of the group of patients

TRODAT uptake in basal ganglia	MSA-C ($n=25$)	MSA-P ($n=29$)	*Z* score (*P*)
Asymmetry	14	20	-0.98 (0.32)
Gradient	9	21	-2.68 (0.007*)
Asymmetry + Gradient	7	19	-2.75 (0.005*)

putamen than anterior putamen and caudate. In patients with MSA-C, hypometabolism is seen in the brainstem and cerebellum.[16] In patients with overlapping clinical profiles of both parkinsonism and cerebellar dysfunction, hypometabolism has been reported in both the putamen–pallidal complex as well as in the cerebellum. In other studies, in patients with advanced MSA, the degree of hypometabolism on ^{18}F-FDG PET in the striatum and cerebellum has been found to positively correlate with clinical measurements of parkinsonism and ataxia.[17,18] Studies have also shown hypometabolism in the cerebral cortex, predominantly involving the frontal region,[16-18] which correlated with the duration of illness.[19]

In our patients, we found statistically significant hypometabolism in the striatum, more in the putamen and sensory-motor cortices, in MSA-P subjects, and the cerebellum and brain stem in MSA-C patients, respectively. In patients with clinical features of both MSA-P and MSA-C, hypometabolism was noted in both striatum and cerebellum, similar to findings in the literature [Figure 3].

Various authors have evaluated the role of ^{99m}Tc-TRODAT-1 scan in the evaluation of patients with MSA and whether it can differentiate MSA from PD patients.[5,20] Randel *et al*.[20] used the binding ratio of ^{99m}Tc-TRODAT-1 in the striatum in patients with MSA-P and PD and compared it with a control population. They found that, as a group, MSA-P patients had statistically higher ^{99m}Tc-TRODAT-1 binding in the striatum compared with PD patients, and both patient groups had significantly lower binding as compared to controls. However, they were not able to individually differentiate between MSA-P and PD patients based on ^{99m}Tc-TRODAT-1 scan findings. They also found a marked reduction in ^{99m}Tc-TRODAT-1 binding in MSA-P, whereas a smaller reduction was found in MSA-C. MSA-C in turn can usually be differentiated from other hereditary ataxias such as SCAs, which show predominantly normal ^{99m}Tc-TRODAT-1 scans.

In our study, we also found reduced ^{99m}Tc-TRODAT-1 binding in both MSA-P and MSA-C patients. However, when these patients were further characterized for variables of asymmetry and rostrocaudal gradient of ^{99m}Tc-TRODAT-1 binding, we found that asymmetry can be a feature of both groups, seen more often in the MSA-P group. However, this difference was not statistically significant. The presence of a gradient in the reduction of ^{99m}Tc-TRODAT-1 putaminal, versus caudate, uptake was a significant feature of the MSA-P group. Also, the occurrence of both asymmetry and gradient together in the same patient was also predominantly seen in MSA-P, with a highly significant *P* value of 0.005.

In the present study, we found fundamental differences in the striatal ^{99m}Tc-TRODAT-1 binding between the MSA-P and MSA-C subtypes in a small group of MSA patients, based on asymmetry and gradient reduction in binding. However, in conventional diagnostic settings for evaluation of MSA patients both ^{18}F-FDG PET and ^{99m}Tc-TRODAT-1 brain scan could be used to differentiate it from PD, DLB, or PSP, or to distinguish between the MSA-P and MSA-C subtypes.

Our study has some limitations. Firstly, the retrospective nature of the study. Secondly, the diagnosis of MSA was based on clinical evaluation as pathological confirmation was not available. However, all the patients included in the study were evaluated by movement disorder specialists and we applied Gilman clinical diagnostic criteria[1] so as to achieve as accurate diagnosis as possible. Finally, our study had a relatively small patient cohort. We nonetheless were able to demonstrate a clear and highly significant difference between MSA-C and MSA-P on ^{99m}TRODAT-1and ^{18}F-FDG PET scan.

Conclusion

Dopamine transporter imaging with ^{99m}Tc-TRODAT-1 alone cannot reliably distinguish between MSA, PD, DLB, and PSP. It is not possible to differentiate MSA-P from PD or MSA-C on the basis of ^{99m}Tc-TRODAT-1 scan alone. Characteristic patterns of hypo-metabolism on ^{18}F-FDG PET-CT may help in the differentiation of the subtypes of MSA in the presence of clinically overlapping symptoms.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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