**Abstract**

**Aim:** The aim of this study is to elucidate the patterns of characteristic hypometabolism on \(^{18}\)F-Fluoro Deoxy-glucose (\(^{18}\)F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) in the variants of Progressive supranuclear palsy (PSP) and its correlation with their core clinical features. **Material and Methods:** A retrospective analysis of 88 subjects with clinically suspected PSP was done. An institutional informed consent to participate in the study was taken from all the subjects. All the subjects had undergone a prior 99mTc-Trodat labeled Tropane derivative of dopamine transporter Single Photon Emission Computed Tomography (99mTc TRODAT-1 SPECT) study and had abnormal scans to confirm degenerative parkinsonism. The subjects were clinically examined by the neurologists using the Progressive Supranuclear Palsy Rating Scale proposed by the Movement Disorder Society and were further clinically segregated into eight subtypes. All the included subjects further underwent a detailed clinical analysis to obtain their individual Schwab and England activities of daily living scale and Modified Hoehn and Yahr staging by a neurologist. All the subjects underwent \(^{18}\)F-FDG PET/CT scan after adequate preparation. The scans were analyzed both qualitatively (visually) and quantitatively using Statistical Parametric Mapping. **Results:** The frontal, limbic, and sensorimotor cortices represented the common areas of hypometabolism among all the subtypes of PSP. The subcortical regions showing the most significant hypometabolism were the thalami, mid-brain, nucleus accumbens, caudate, globus pallidus, and putamen in descending order. Multiple cortical and subcortical regions of hypometabolism were identified in different subtypes of PSP. **Conclusion:** The characteristic patterns of hypometabolism observed in the different subgroups were more apparent on quantification and based on visual analysis alone, it may not be possible to differentiate the different subtypes of PSP. A good correlation was seen between some of the core clinical features and hypometabolic clusters.

**Keywords:** \(^{18}\)F-FDG PET/CT, progressive supranuclear palsy, Tc-99m TRODAT-1

**INTRODUCTION**

Progressive supranuclear palsy (PSP) is a sporadic, adult-onset neurodegenerative tauopathy, characterized by early postural instability with falls, supranuclear ophthalmoplegia, akinesia, frontal lobe dysfunction, and poor response to levodopa.\(^{[1‑4]}\) Although there are supportive findings documented on Magnetic Resonance Imaging (MRI),\(^{[5]}\) there are no pathognomonic diagnostic imaging findings, rather the role of anatomical imaging has more relevance in excluding other pathologies which may result in similar clinical phenotypes.

\(^{18}\)F-Fluoro Deoxy-glucose (\(^{18}\)F-FDG) is a glucose analog which serves as a competitive substrate of glucose within the human body and elucidates the topography of cerebral glucose metabolism in various physiological and pathological states. Since PSP, like other Parkinson plus syndromes, is characterized by abnormalities in the postsynaptic dopaminergic neurons,\(^{[6‑10]}\) \(^{18}\)F-FDG PET acts as a surrogate marker of mitochondrial activity and viability of the postsynaptic dopaminergic neurons.\(^{[11‑20]}\)

The clinical criteria proposed by the National Institute of Neurological Disorders and Stroke and Society for PSP,\(^{[4]}\) which was being used widely for the antemortem diagnosis of PSP, has shown very high specificity and sensitivity for the diagnosis of “probable,” “possible,” and classical PSP (Richardson’s syndrome).\(^{[4]}\) However, this criterion has shown limited sensitivity for the diagnosis at the first clinical visit and also in patients presenting with variant PSP syndromes.\(^{[4]}\) Recently, the Movement disorder society (MDS) has proposed new criteria to overcome the limitations of the former criterion. PSP is further subclassified into eight subgroups based on the four core clinical features (Ocular motor dysfunction, Postural instability, Akinesthesia, and Cognitive dysfunction), along with supportive imaging findings and clinical cues.\(^{[21]}\)
Although previous research on the role of FDG PET-CT in PSP has shown varying degrees of frontal, limbic, and brain stem hypometabolism predominantly involving the anterior cingulate cortex and the midbrain, which correlates more to the classical PSP with Richardson’s syndrome, there is a dearth of the functional imaging data in various subtypes and variants of PSP. This study is a retrospective analysis of the FDG PET findings in different clinical variants of PSP, as classified according to the MDS-PSP criteria.

Materials and Methods

A retrospective descriptive analysis of 88 patients with clinically suspected PSP was done. The study included retrospective cases from March 2016 to September 2020. An institutional informed consent to participate in the study was taken from all the subjects. All the subjects had undergone a prior 99mTc TRODAT-1 SPECT study and had abnormal scans to confirm degenerative Parkinsonism. All the patients were clinically examined by the neurologists using the Progressive Supranuclear Palsy Rating Scale proposed by the MDS and were further clinically segregated into the eight subtypes. A total of 106 subjects with abnormal TRODAT scans and clinical suspicion of PSP were analyzed [Flow chart 1]. Out of 106 subjects, 18 did not conform to the clinical criteria proposed by the MDS-PSP group either due to ambiguous history or co-existent neurological issues belonging to the mandatory exclusion criteria specified by the MDS-PSP group. The 88 patients who could give a proper chronological history and also met the mandatory inclusion criteria were further analyzed and based on core clinical features segregated into (1) PSP with Richardson’s syndrome, (2) PSP with predominant parkinsonism, (3) PSP with predominant gait freezing, (4) PSP with frontal presentation, (5) PSP with speech/language presentation, (6) PSP with postural instability, and (7) PSP with Cortico-basal syndrome. We could not recruit any subject in the eighth subtype, PSP with predominant ocular presentation (PSP-OM).

All the included subjects further underwent a detailed clinical analysis to obtain their individual Schwab and England activities of daily living scale (ADL) and Modified Hoehn and Yahr staging by a neurologist.

18F-FDG PET/CT scan of the brain was done, 45 to 60 min after intravenous injection of approximately 185 MBq (5 mCi) of 18F-FDG, provided the patients were fasting for 4 to 6 h and their blood sugar levels were less than 150 mg/dl. The subjects were imaged while they were on their usual medicines, in a quiet wakeful resting state, and with their eyes closed in dimmed ambient light. Foam padding and restraining straps were used for reducing head movements. The scan images were acquired on a dedicated PET-CT scanner (GE Discovery STE PET-CT with 16-slice CT). PET images were reconstructed by using the ordered subset expectation maximization algorithm and CT attenuation correction dead time correction and decay correction at the beginning of each scan. Images were interpreted independently by two experienced Nuclear Medicine physicians on an Advantage window workstation equipped with fusion software that enables the display of 18F-FDG PET images with and without attenuation correction, CT images, and PET/CT images.

On visual and semiquantitative analysis (Regional Quantification done using 3D-SSP regional hypometabolism (Z score) and comparison with the normal database on CORTEX-ID software, GE Discovery STE), the 18F-FDG PET images which were displayed as a series of 47 transaxial slices were scaled to a common maximum. The FDG uptake patterns were recorded and areas of hypometabolism that were two standard deviations from the mean were considered abnormal. The total regional hypometabolic areas were documented in the different variants of PSP.

After gross manual image reorientation and approximate definition of the image center point, the PET images were spatially processed using the Statistical Parametric Mapping toolbox (SPM 12.0, Wellcome Trust Centre for Neuroimaging, 2008) implemented within MATLAB 9.4.0.813654 (MathWorks, Natick, MA, USA). Further, the images were spatially normalized and smoothed by an isotropic 8 mm full-width half-maximum filter. Single-case SPM analysis which essentially compares regional differences in relative glucose metabolism was done to characterize individual patient scans using the general linear model. Each patient was compared statistically to the reference group of 15 healthy control subjects with a two-sample t-test. The measurements were assumed to be independent and had unequal variance between levels. Proportional scaling, which scales each image according to a reference count, which is the global brain activity to a physiologically realistic value of 50 ml/dl/min to the global mean, was used to minimize inter-subject variability. In the end, the SPM.mat file containing the specified design matrix was generated. Using this file, contrasts were defined, thus providing a map of voxels showing increased or decreased glucose metabolism in each patient as compared to the control group above the statistical threshold of P < 0.05. The results were further analyzed in the WFU Pick atlas toolbox to determine the regions of the brain involved. The clusters containing the maximum voxels with a peak at the given coordinate and their mean T-value clusters with a mean T-value of >2.0 was considered significant for cortical regions and >1.8 for subcortical regions and cerebellum. The total number of clusters and the number of significant clusters were calculated on all individual PET scans. The statistical t-maps, thus obtained, were overlaid onto the T1-weighted MRI template image provided by SPM 12 and saved as a portable document format (PDF) for further viewing and areas of reduced glucose metabolism represented in “winter” colors. The regions thus obtained were correlated with the different core clinical features and the clinical clues of the variants of PSP and an attempt at defining the features of each clinical variant of PSP was made.
RESULTS

A total of 88 subjects who could give a proper chronological history and also met the mandatory inclusion criteria were further analyzed and based on core clinical features and clinical clues segregated into (1) PSP with Richardson’s syndrome (n = 46), (2) PSP with predominant parkinsonism (n = 11), (3) PSP with predominant gait freezing (n = 7), (4) PSP with frontal presentation (n = 6), (5) PSP with speech/language presentation (n = 3), (6) PSP with postural instability (n = 9), and (7) PSP with Cortico-basal syndrome (n = 6). The demographic data along with scores on the PSP rating scale, ADL, and modified H and Y scores with the presence of signs and symptoms of Autonomic dysfunction are detailed in Table 1.

Out of the total 88 subjects, 55 were male and 33 belonged to the female gender. The age distribution in our subjects varied from 46 to 83 years with a mean age of 65.4 years and the duration of illness at the time of FDG PET scanning ranged from 1.4 to 3 years, with a mean of 1.25 years. The median score on the PSP rating scale was found to be 30 (range from 23 to 51.5). The median ADL score of our subjects ranged from 75 to 83.3 with a mean of 70 and the median score on the H and Y rating scale was 2.5 (range from 2.1 to 2.5) [Table 1].

The defining core clinical features and clinical clues are enumerated in Table 2. Among all the 88 subjects, 48 (54%) had ocular motor dysfunction, 73 (82%) had postural instability, 86 (97%) had akinesia/hypokinesia, 56 (63%) had history of Levodopa resistance, 69 (78%) had hypokinetic, spastic dysarthria, 19 (21%) had dysphagia, 14 (15%) had Photophobia, and 48 (54%) associated Autonomic dysfunction [Table 2].

In our study, the frontal, limbic, and sensorimotor cortices represented the common areas of cortical hypometabolism among all the subtypes of PSP. The frontal region had the highest number of significant hypometabolic clusters (n = 57), followed...
Table 1: Demographic data including age, gender, duration of illness, average H and Y, ADL (Activity of daily living), and PSP rating scale scores of different variants of PSP

| Variants | Age (years) | Numbers | Male | Female | PSP rating scale (median-30) | ADL (median-70) | H and Y (median-2.5) | Duration (years) (median-1.25) |
|----------|-------------|---------|------|--------|-------------------------------|-----------------|---------------------|-------------------------------|
| PSP-RS   | 65.6        | 46      | 30   | 16     | 32.6                          | 76.8            | 2.34                | 1.4                           |
| PSP-PGF  | 65.5        | 7       | 5    | 2      | 28.5                          | 83.3            | 2.5                 | 3                            |
| PSP-PI   | 65.7        | 9       | 4    | 5      | 23.3                          | 80              | 2.5                 | 1.1                           |
| PSP-SL   | 67.6        | 3       | 2    | 1      | 46                            | 80              | 2.2                 | 2                            |
| PSP-F    | 65          | 6       | 4    | 2      | 42                            | 75              | 2.3                 | 1.75                          |
| PSP-P    | 62          | 11      | 8    | 3      | 23                            | 83.3            | 2.1                 | 2                            |
| PSP-CBS  | 62.1        | 6       | 2    | 4      | 51.5                          | 75              | 2.2                 | 1.5                           |
| TOTAL    |             | 88      | 55   | 33     |                               |                 |                     |                               |

Table 2: Core clinical features of clinical rating scale for progressive supranuclear palsy, Golbe et al.[21]

| Variants | Number | O       | P       | A       | C       | CC1  | CC2  | CC3  | CC4  | AD |
|----------|--------|---------|---------|---------|---------|------|------|------|------|----|
| PSP-RS   | 46     | 39      | 44      | 45      | 31      | 32   | 39   | 15   | 13   | 29 |
| PSP-PGF  | 7      | 2       | 4       | 7       | 3       | 2    | 3    | 0    | 0    | 1  |
| PSP-PI   | 9      | 0       | 9       | 8       | 0       | 3    | 2    | 0    | 0    | 2  |
| PSP-SL   | 3      | 2       | 1       | 3       | 3       | 2    | 6    | 1    | 0    | 3  |
| PSP-F    | 6      | 1       | 3       | 6       | 6       | 2    | 5    | 0    | 0    | 5  |
| PSP-P    | 11     | 2       | 8       | 11      | 7       | 9    | 9    | 0    | 0    | 6  |
| PSP-CBS  | 6      | 2       | 4       | 6       | 6       | 4    | 5    | 3    | 1    | 2  |
| TOTAL    | 88     | 48      | 73      | 86      | 56      | 54   | 69   | 19   | 14   | 48 |

O=Ocular motor dysfunction, P=Postural instability, A=Akinessia, C=Cognitive dysfunction, CC1=Levodopa resistance, CC2=Hypokinetic, spastic dystarthis, CC3=Dysphagia, CC4=Photophobia, AD=Autonomic dysfunction

Table 3

Table 4

PSP with Richardson’s syndrome (PSP-RS)

Overall, male to female ratio was found to be 1.6, wherein the highest ratio was found to be in PSP-P patients (2.6) and the lowest in the PSP-CBS sub-group (0.5). The highest average score on the PSP rating scale was observed in the PSP-CBS subgroup (51.5) in accordance with multi-domain involvement in this group with overall reduced ADL (75) and the H and Y rating (2.2). The average mean duration of illness at the time of presentation was highest in the PSP-PGF subgroup (3 years) and the lowest in the PSP-PI subgroup (1.1 years) as multiple falls as a symptom is debilitating leading to earlier seeking of medical advice. Associated autonomic dysfunction was seen in 48 subjects (54.5%), brain stem involvement in 59 subjects (67%), and cerebellar involvement in 25 subjects (28.4%). The highest percentage of autonomic dysfunction was observed in the PSP-F subgroup (33.3%) and the lowest in the PSP-PGF subgroup (14%). Cerebellar involvement was most significant in the PSP-PGF subjects (42.8%) and least in the PSP-F subjects (0%). Brain stem involvement was the maximum in PSP-SL subgroup (100%) and the least in the PSP-PI subgroup (44%).

On analyzing the regional hypometabolic clusters in the different regions of the brain, 57 (64%) subjects had maximum hypometabolic clusters in the frontal region, 19 (21%) had the maximum clusters in the limbic cortices, and 11 (12.5%) subjects had maximum hypometabolic clusters in the subcortical regions; 59 (67%) subjects had associated hypometabolic clusters in the brain stem and 25 (28%) had hypometabolic clusters in the cerebellum [Figure 1]. The percentage involvement of the core clinical features, autonomic dysfunction (AD), cerebellar, and brain stem involvement in different variants of PSP are depicted in Table 4.

PSP with Richardson’s syndrome (PSP-RS)

There were 46 subjects who fulfilled the proposed clinical criteria proposed by the MDS-PSP group. This subgroup was characterized by overall high scores on the PSP rating scale (32.6) and the H and Y scale (2.34) and a low score on ADL (76.8) with a shorter duration of illness at presentation (1.4 years). This group also showed significant autonomic dysfunction (63%), cerebellar (32.6%), and brain stem hypometabolism (71.5%). This subgroup also had the maximum number of hypometabolic clusters on metabolic mapping. Out of the 46 subjects, 26 showed the highest number of significant clusters in the frontal region, 11 in limbic, and 9 in subcortical regions. In our study, the most commonly involved subcortical regions were the thalamus, brain stem, nucleus accumbens, and the cedate regions [Figure 2a].

by limbic cortex (n=19) and subcortical regions (n=11). The region most frequently hypometabolic within the frontal cortex were the medial frontal, orbital frontal including the medial frontal orbital and the lateral frontal orbital regions, middle frontal, pre-central, superior frontal, and inferior frontal regions to varying degrees in the different variants. Within the limbic cortex, the regions more significantly hypometabolic were the cingulate, insular, uncus, hippocampus, and para hippocampal regions. The subcortical regions showing the most significant hypometabolism were the thalami, midbrain, nucleus accumbens, caudate, globus pallidus, and putamen in descending order. Within the parietal lobes, the most consistent hypometabolism was seen in the postcentral gyrual region, followed by precuneus, angular, and supramarginal gyrual regions and the superior pariatal lobule. The dominant cortical or subcortical regions of the brain which had the highest number of significant hypometabolic clusters along with the involvement of the brain stem including midbrain and the cerebellum are depicted in Table 3.

On analyzing the regional hypometabolic clusters in the different regions of the brain, 57 (64%) subjects had maximum hypometabolic clusters in the frontal region, 19 (21%) had the maximum clusters in the limbic cortices, and 11 (12.5%) subjects had maximum hypometabolic clusters in the subcortical regions; 59 (67%) subjects had associated hypometabolic clusters in the brain stem and 25 (28%) had hypometabolic clusters in the cerebellum [Figure 1]. The percentage involvement of the core clinical features, autonomic dysfunction (AD), cerebellar, and brain stem involvement in different variants of PSP are depicted in Table 4.

Overall, male to female ratio was found to be 1.6, wherein the highest ratio was found to be in PSP-P patients (2.6) and the lowest in the PSP-CBS sub-group (0.5). The highest average score on the PSP rating scale was observed in the PSP-CBS subgroup (51.5) in accordance with multi-domain involvement in this group with overall reduced ADL (75) and the H and Y rating (2.2). The average mean duration of illness at the time of presentation was highest in the PSP-PGF subgroup (3 years) and the lowest in the PSP-PI subgroup (1.1 years) as multiple falls as a symptom is debilitating leading to earlier seeking of medical advice. Associated autonomic dysfunction was seen in 48 subjects (54.5%), brain stem involvement in 59 subjects (67%), and cerebellar involvement in 25 subjects (28.4%). The highest percentage of autonomic dysfunction was observed in the PSP-F subgroup (33.3%) and the lowest in the PSP-PGF subgroup (14%). Cerebellar involvement was most significant in the PSP-PGF subjects (42.8%) and least in the PSP-F subjects (0%). Brain stem involvement was the maximum in PSP-SL subgroup (100%) and the least in the PSP-PI subgroup (44%).

PSP with Richardson’s syndrome (PSP-RS)

There were 46 subjects who fulfilled the proposed clinical criteria proposed by the MDS-PSP group. This subgroup was characterized by overall high scores on the PSP rating scale (32.6) and the H and Y scale (2.34) and a low score on ADL (76.8) with a shorter duration of illness at presentation (1.4 years). This group also showed significant autonomic dysfunction (63%), cerebellar (32.6%), and brain stem hypometabolism (71.5%). This subgroup also had the maximum number of hypometabolic clusters on metabolic mapping. Out of the 46 subjects, 26 showed the highest number of significant clusters in the frontal region, 11 in limbic, and 9 in subcortical regions. In our study, the most commonly involved subcortical regions were the thalamus, brain stem, nucleus accumbens, and the cedate regions [Figure 2a].
There were seven subjects who fulfilled the clinical criteria proposed by the MDS-PSP group. This subgroup was characterized by overall low average scores on the PSP rating scale (28.5), however showed high scores on ADL (83.3) and the H and Y rating (2.5) with a longer duration of illness at presentation (3 years). There was significant cerebellar (42.8%) and brain stem hypometabolism (85.7%) with relatively less autonomic dysfunction (14%). Out of the seven subjects who fulfilled the clinical criteria for inclusion in this subgroup, four had the highest number of significant hypometabolic clusters in the frontal region and three in the limbic regions. The most commonly hypometabolic regions were the cingulate, medial frontal, middle frontal, and insular regions along with significant striatal, thalamic, and brain stem hypometabolism [Figure 2b].

PSP with postural instability (PSP-PI)

This subgroup had nine subjects and was characterized by overall low average scores on the PSP rating scale (23.3), however showed high scores on ADL (80) and the H and Y rating (2.5) with a short duration of illness at presentation (1.1 years). Cerebellar hypometabolism was seen in two subjects (22.2%), brain stem hypometabolism in four subjects (44.4%), and autonomic dysfunction in three subjects (33.3%).

The areas which showed the highest number of hypometabolic clusters were the medial frontal, middle frontal, pre-central, postcentral regions, cingulate gyri, and the thalami [Figure 2c].

PSP with Corticobasal syndrome (PSP-CBS)

The characteristics of this subgroup were overall high scores on the PSP rating scale (51.5) and the H and Y score (2) and a low score on ADL (75) with a smaller duration of illness at presentation (1.5 years) and a significant brain stem hypometabolism (50%) with relatively less degree of autonomic dysfunction (33.3%) and cerebellar (16.6%) hypometabolism. The cortical and subcortical hypometabolism was asymmetric unlike the other variants of PSP and the asymmetry was contralateral to the observed motor symptoms. There was significant asymmetric frontoparietal, basal ganglia, and thalamic hypometabolism in all subjects [Figure 2d]. The regions within the parietal lobe which showed the most consistent
hypometabolism were the postcentral gyrus (n = 7), superior parietal lobule, inferior parietal lobule, precuneus (n = 5), and posterior cingulate regions. Insular region was involved in all the subjects (n = 7). The regions within the frontal lobe showing significant hypometabolic clusters were the anterior cingulate, pre-central, and pre-frontal regions.

**PSP with predominant Parkinsonism (PSP-P)**

This subgroup was characterized by the lowest average scores on the PSP rating scale (23), however showed high scores on ADL (83.3) and the H and Y rating (2.1) with a relatively long average duration of illness at presentation (2 years). More than half of the subjects (54.5%) had a history of

| Variants   | Number | O     | P  | C     | A | AD | Cerebellum | Brain stem |
|-----------|--------|-------|----|-------|---|----|------------|------------|
| PSP-RS    | 46     | 84.7% | 95.6% | 67.3% | 97.8% | 63% | 32.6% | 84.6% |
| PSP-PGF   | 7      | 28%   | 57% | 42.8% | 100% | 14% | 42.8 | 85.7% |
| PSP-PI    | 9      | 0     | 100% | 0     | 88.8% | 33.3% | 22.2% | 44.4% |
| PSP-SL    | 3      | 66.6% | 33.3% | 100% | 100% | 33.3% | 100%  |
| PSP-F     | 6      | 16.6% | 50% | 100% | 100% | 83.3% | 0 | 83.3% |
| PSP-P     | 11     | 18.1% | 72.7% | 63.6% | 100% | 54.5% | 27.2% | 45.4% |
| PSP-CBS   | 6      | 33.3% | 66.6% | 100% | 100% | 33.3% | 16.6% | 50% |
| Total     | 88     |       |     |       |   |    |           |            |

Figure 2: (a) Patient with difficulty in walking, imbalance, tremors, more in the right lower limb, rigidity, bradykinesia, vertical gaze paresis, with speech disturbance and urinary incontinence, for 1 year, increasing since 6 months. The patient had a PSP rating scale ~ 65, H and Y ~ 4, and ADL ~ 50. SPM analysis of the FDG PET images shows hypometabolism in the bilateral basal ganglia, thalami, mid-brain, bilateral medial frontal, and anterior cingulate cortices, likely PSP with Richardson’s syndrome (PSP-RS). (b) Patient with progressive gait ataxia, bradykinesia, slurring of speech for 4 years with a recent history of falls, cognitive decline, and up gaze palsy. The patient had a PSP rating scale ~ 39, H and Y ~ 2.5, and ADL ~ 80. SPM analysis of the FDG PET images showed hypometabolism in the bilateral basal ganglia, thalami, mid-brain, bilateral medial frontal, middle frontal, insular, and anterior cingulate cortices, likely PSP-PGF. (c) Patient with bradykinesia, right-sided weakness, postural instability, and dysarthria for 2 years with a history of falls, on Levodopa for 2 years with no improvement in symptoms. The patient had a PSP rating scale ~ 18, H and Y ~ 2.5, and ADL ~ 80. SPM analysis of the FDG PET images showed hypometabolism in the bilateral superior frontal, medial frontal, middle frontal, pre-central, anterior cingulate, and bilateral caudate regions, likely PSP-PI. (d) Patient with bradykinesia, bilateral upper limb tremors, right more than left, slurring of speech, and history of imbalance for 1 year. The patient had a PSP rating scale ~ 36, H and Y ~ 2.5, and ADL ~ 80. SPM analysis of the FDG PET images showed hypometabolism in the bilateral pre-frontal and anterior cingulate cortices, left parietal, bilateral insular, midbrain, bilateral basal ganglia and bilateral thalamus (Left more than right), and left sensorimotor cortex, likely PSP-CBS. (e) Patient with bradykinesia, bilateral upper limb tremors, bobbing of head, rigidity, and slurring of speech with non-responsiveness to levodopa for 3 years with a recent history of falls. The patient had a PSP rating scale ~ 19, H and Y ~ 1.5, and ADL ~ 90. SPM analysis of the FDG PET images showed hypometabolism in the bilateral frontal and anterior cingulate cortices, bilateral basal ganglia, and thalamus, likely PSP-P. (f) Patient with bradykinesia, imbalance with history of falls, dysarthria, and postural hypotension with cognitive decline. The patient had a PSP rating scale ~ 41, H and Y ~ 3, and ADL ~ 60. SPM analysis of the FDG PET images showed hypometabolism in the bilateral pre-frontal, medial frontal, temporal, posterior parietal, and cingulate cortices, likely PSP-F. (g) The patient is being evaluated for slurring of speech with word-finding difficulty, difficulty in walking, and imbalance, for 2 years, with a history of falls and downward gaze palsy. The patient had a PSP rating scale ~ 42, H and Y ~ 2.5, and ADL ~ 70. SPM analysis of the FDG PET images showed hypometabolism in the bilateral inferior frontal, pre-central, superior frontal, and anterior cingulate cortices, midbrain, and bilateral thalamus, likely PSP-SL.
autonomic dysfunction and approximately one-third (27.7%) had cerebellar hypometabolism, whereas brain stem hypometabolism was seen in 45.4% of the subjects. Out of the 11 subjects, 6 had the maximum number of significant clusters in the frontal, 4 in the limbic, and 1 in the subcortical regions. All the subjects had significant striatal hypometabolism often with the involvement of the globus pallidus and nucleus accumbens which correspond to the increased propensity for tremors and rigidity in these subjects [Figure 2e].

**PSP with predominant frontal presentation (PSP-F)**

The characteristics of this subgroup was overall relatively high average scores on the PSP rating scale (42) and the H and Y score (2.3) and a low score on ADL (75) with a relatively shorter duration of illness at presentation (1.75 years) and significant brain stem hypometabolism (83.3%) and autonomic dysfunction (83.3%). There was no significant hypometabolic cluster found in the cerebellum. Out of six subjects, five had the maximum number of dominant hypometabolic clusters in the frontal cortex and one in the limbic cortex. The regions predominantly hypometabolic were the superior frontal, medial frontal, middle frontal, medial and lateral orbital frontal, pre-central, cingulate, insular, hippocampal, parahippocampal, marginal gyral, and superior temporal regions [Figure 2f].

**PSP with predominant speech and language presentation (PSP-SL)**

The characteristics of this subgroup were overall high scores on the PSP rating scale (46) and the H and Y score (2.2) and high scores on ADL (80) with a relatively long duration of illness at presentation (2 years). Brain stem hypometabolism was seen in all the subjects (100%) with a relatively less degree of autonomic dysfunction (33.3%) and cerebellar (33.3%) hypometabolism. All the subjects had the maximum number of dominant clusters in the frontal cortex, predominantly involving the inferior frontal, pre-central gyral, and superior frontal regions [Figure 2g].

**DISCUSSION**

Multiple studies have been reported in the literature describing the pattern of cortical and subcortical hypometabolism on FDG PET-CT, predominantly involving the anterior cingulate and insular cortices, basal ganglia, and midbrain; however, there is a dearth of such data in the subtypes of PSP.[11-19]

In our study, the different PSP subtypes showed involvement of different cortical and subcortical regions which correlated with the known clinicopathological heterogeneity[25] of PSP. The frontal, limbic, and sensorimotor cortices represented the common areas of cortical hypometabolism among all the subtypes of PSP. The frontal region had the highest number of significant hypometabolic clusters followed by the limbic cortex and subcortical regions.

In **PSP-RS subjects**, the subjects who showed the highest number of significant hypometabolic clusters in the frontal region gave a history of significant cognitive dysfunction, speech abnormality, as well as signs of motor weakness. On further analysis, the majority had dominant hypometabolism in the inferior frontal, pre-central, and orbital frontal regions. The hypometabolism in the left inferior frontal region may correspond to the non-fluent aphasia demonstrated by most of these subjects. The orbital frontal hypometabolism may correspond to the cognitive dysfunction characterized by the loss of executive function, insight, and apathy as shown by most of these subjects. The rest of the frontal lobe hypometabolism may correspond to the primary motor, motor speech, and supplementary motor cortical dysfunction. The subjects, who showed the highest clusters in the limbic cortices, had significant emotional lability, pseudobulbar symptoms, autonomic dysfunction, and dominant axial symptoms including dysphagia and hypophonia.

Frontal and limbic cortical involvement has been reported in various neuroimaging and neuropathological studies in the literature in the form of a distinct pattern of frontal lobe atrophy in voxel-based morphometry in PSP by Brenneis et al.,[21] significantly decreased Fractional anisotropy (FA) and increased apparent diffusion coefficient in the frontal part of inferior fronto-occipital fasciculus using diffusion tensor imaging and tractography by Pia Kvickström et al. and increased tau deposition in the frontal lobes with typical autopsy findings in PSP-RS.[23,24]

In our study, significant subcortical hypometabolism was seen involving the basal ganglia, thalami, brain stem, and nucleus accumbens regions. The subjects who had dominant hypometabolic clusters in the brain stem, especially midbrain had gaze palsy as the dominant clinical clue. The subjects who had dominant hypometabolic clusters in the thalamic and basal ganglia regions gave truncal imbalance with multiple falls as the dominant presenting complaint and also exhibited a significant degree of extrapyramidal symptoms; 32% of subjects had cerebellar hypometabolism which corresponded to the presence of ataxia and dysarthria in these subjects. In subjects with significant brain stem hypometabolism, there was significantly associated hypometabolism in the medial and lateral temporo-occipital, parahippocampal regions, and the cuneus which may be associated with the visual processing deficits in the presence of ocular motor dysfunction. Across the literature, PSP-RS shows the maximum degree of subcortical involvement with the highest density of neurofibrillary tangles (NFTs), neuritipil threads, and tau deposition in the various parts of basal ganglia and brainstem. Widespread NFTs associated with neuronal cell loss and gliosis were also observed in the basal ganglia, sub-thalamic nucleus, and various brain stem nuclei, on neuropathologic examination.[25,26]

In a recent study by Whitwell et al.,[27] evidence of volume loss and flortaucipir uptake was reported in the midbrain (including the red nucleus and substantia nigra), striatum, and subthalamic nucleus, with volume loss of the superior cerebellar peduncle and increased flortaucipir uptake in the globus pallidus, thalamus, and dentate nucleus of the cerebellum, which concurs with our findings of extensive subcortical hypometabolism.
In our study, the subjects corresponding to the **PSP-PGF** subgroup had a relatively indolent clinical presentation with predominant limiting motor features along with unresponsiveness to levodopa. This subgroup was characterized by significant cingulate, medial frontal, middle frontal, and insular hypometabolism along with significant striatal, thalamic, brain stem, and cerebellar hypometabolism with relatively less autonomic dysfunction. As basal ganglia, supplementary motor cortices along with the limbic cortices are responsible for amplitude, motor sets, and motor cues for normal gait generation, and the corresponding frontal, cingulate, striatal, and insular hypometabolism seen in our study may contribute to the episodes of gait freezing and other gait abnormalities. The majority had some degree of gaze involvement which corresponded well with the involvement of midbrain and brain stem. Two of the subjects had truncal ataxia, dysarthria, and gait apraxia which corresponded to the cerebellar hypometabolism in these subjects.

Similar findings were reported by Whitwell et al.,[27] wherein they showed that the PSP-PGF variants showed much more restricted involvement of subcortical circuits as compared to PSP-RS subjects with evidence of volume loss and elevated flortaucipir uptake in the striatum, globus pallidus, and thalamus, and PSP-PGF along with PSP-P showed the highest flortaucipir uptake in the putamen and globus pallidus of all the PSP variants after correcting for age.

**PSP-PI** subgroup was characterized by early onset of postural instability with a history of unprovoked falls and absence or delayed cognitive and ocucomotor dysfunction. The areas which showed the highest number of hypometabolic clusters were the medial frontal, middle frontal, pre-central, postcentral regions, cingulate gyri, and thalamus. Despite all the subjects having the highest number of significant clusters in the frontal region, none showed any significant degree of cognitive dysfunction. The frontal regions consistently involved were the medial frontal, middle frontal, and pre-central regions which execute the motor and supplementary motor cortical functions. There was relative sparing of the orbital frontal and pre-frontal cortices which may correspond to the absence of cognitive dysfunction seen in these subjects. None of the subjects had any significant midbrain involvement, which corresponded to the absence of clinical motor gaze deficits. The thalami were consistently hypometabolic in all the subjects in accordance with the studies reported in the literature which describe the significant role of thalami in the maintenance of stance and cerebral postural network with thalamic dysfunction resulting in deficits in the thalamic postural control.[28] Since the cingulate cortex receives input from the thalamus, the cingulate hypometabolism, along with thalamic hypometabolism, may contribute to the imbalance and multiple falls in these subjects.

The subjects corresponding to the **PSP-CBS subgroup** showed early onset of progressive asymmetric oro-buccal or limb apraxia and cortical sensory deficits with asymmetric limb rigidity. The cortical and subcortical hypometabolism was asymmetric unlike the other variants of PSP and the symmetry was contralateral to the observed motor symptoms. There was significant asymmetric fronto-parietal, basal ganglia, and thalamic hypometabolism in all subjects. The significant pre-central, postcentral, anterior parietal, and insular hypometabolism noted in our subjects were concordant with similar findings reported by Pardini et al.[29] in the CBS variant PSP. A previous study done on PSP-CBS patients also reported flortaucipir imaging showing elevated uptake in the dentate nucleus of the cerebellum, midbrain, subthalamic nucleus, globus pallidus, and putamen, with abnormal subcortical circuitry on MRI.

Clinically, the **PSP-P** subjects showed predominant extrapyramidal motor symptoms mimicking idiopathic Parkinson’s disease and some also showed an initial partial response to Levodopa. All the subjects had significant striatal hypometabolism often with the involvement of the globus pallidus and nucleus accumbens which correspond to the increased propensity for tremors and rigidity in these subjects. Pathological studies largely confirm our neuroimaging results, finding a more restricted distribution of tau pathology in PSP-P compared to PSP-RS involving the subthalamo-nigral-pallidal system (Jellinger, 2008).[30] with PSP-P showing similar striatal tau burden but lower tau burden in the frontal lobe and cortex compared to PSP-RS (Schofield **et al.**, 2011)[31] and higher flortaucipir uptake in the putamen (J.L. Whitwell, **et al.**).[32]

**PSP-P** subjects presented with frontal cognitive or behavioral dysfunction along with a varying degree of ocular motor deficits and postural instability. The significant pre-frontal and medial frontal hypometabolism may correspond to the behavioral, personality, and cognitive dysfunctions in these subjects. Temporal, limbic, and inferior parietal hypometabolism may correspond to the associated derangements in memory, geographical disorientation, imbalance, and significant autonomic dysfunction found in this subgroup. Although there was significant brain stem hypometabolism, only one subject had apparent ocular vertical motor deficits. The thalamic and brain stem hypometabolism observed in the rest of the subjects may be secondary to functional de-afferentation from the hypometabolic frontal and parietal cortices.

**PSP-SL** subjects presented with Non-fluent/Agrammatic progressive aphasia or progressive apraxia of speech with or without vertical ocular motor dysfunction. Since all the subjects had the maximum number of dominant clusters in the frontal cortex, predominantly corresponding to the primary and supplementary motor speech areas which may explain the dominant symptomatology of the subjects. Similarly, in the study by Whitwell **et al.**, the PSP-SL variant showed striking atrophy and flortaucipir uptake in premotor and pre central (motor) cortex, with the degree of involvement of the supplementary motor area and pre-central cortex differentiating PSP-SL from all the other PSP variants, except for PSP-CBS. This pattern of pre-motor and motor atrophy and flortaucipir uptake has been described in patients with a progressive...
apraxia of speech (Josephs et al., 2012[25]; Utianski et al., 2018[26]; Whitwell et al., 2013).[27]

In our study, the brain stem involvement was found to be the highest in this group; however, this is in contrast to the findings reported in the literature, according to which, the PSP-SL variant tends to show less involvement of the infratentorial structures, including midbrain, superior cerebellar peduncle, and dentate nucleus of the cerebellum.[27,33] Thus, there may be a false bias in our study owing to the least number of subjects in this group.

**PSP-OM:** We could not identify any patient in this category. The reason for this might be the failure of such patients to identify the eye signs early, as one tends to compensate for slight ocular movement abnormality and if at all inconvenienced, may approach an eye specialist rather than a neurologist. By the time, a neurophysician’s advice is sought, the patient usually develops other motor or non-motor abnormalities which dominate over the eye symptoms and the actual chronology may be masked.

**Summary**

Overall, the PSP-RS subgroup had the maximum number of hypometabolic clusters involving the cortical, subcortical, and cerebellar regions, which corresponded to the widespread clinical complaints in these subjects comprising early onset axial symptoms, non-fluent aphasia, and pseudo bulbar phenomenon along with oculomotor and cognitive dysfunction. The PSP-PI group had the least degree of clinical ocular motor and cognitive dysfunction which correlated with relatively less brain stem and pre-frontal hypometabolism.

Cerebellar hypometabolism showed a strong correlation with dysarthria, truncal ataxia, and gait apraxia. PSP-PGF subgroup showed the highest degree of cerebellar hypometabolism followed by the PSP-RS group, in concordance with the dysarthric speech and gait apraxia observed in these subjects. Postural instability and falls correlated with thalamic hypometabolism were seen predominantly in the PSP-PI and PSP-RS subgroups. Limbic hypometabolism correlated with autonomic dysfunction as well as the presence of axial symptoms and was seen predominantly in the PSP-RS, PSP-CBS, and PSP-SL subgroups. The presence of significant frontal hypometabolism may be suggestive of PSP-RS, PSP-F, or PSP-CBS, and the lack of significant frontal hypometabolism may be suggestive of PSP-P or PSP-PGF.

Overall, across all the subgroups, brain stem hypometabolism was found to be much more than the manifested ocular motor deficits. There was significantly associated hypometabolism in the medial and lateral temporo-occipital, parahippocampal regions, and the cuneus which may be correlated with the visual perceptual deficits. In the subjects with significant imbalance and extrapyramidal symptoms, there was associated involvement of the subcortical regions, namely the thalami, basal ganglia, and the nucleus accumbens.

**Conclusion**

In the presence of clinically overlapping symptoms, 18F-FDG PET CT scan may not only help in the early diagnosis of PSP but may also shed a light on the possible subgroup. The characteristic pattern of hypometabolism observed in the different sub-groups was more apparent on quantification. Based on visual analysis alone, it may not be possible to differentiate the different subtypes of PSP. Although, there was a good correlation between some of the core clinical features and hypometabolic clusters; however, more volume of data and longitudinal studies are required in the different subtypes for establishing the characteristic pathognomonic pattern of a particular subtype of PSP on the 18F-FDG PET scan.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/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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**Conflicts of interest**

There are no conflicts of interest.

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