Diagnosing Subtypes of Progressive Supranuclear Palsy: Can ^{18}F-FDG PET/CT Imaging Guide Our Way?

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder, characterized clinically by parkinsonian features, vertical supranuclear gaze palsy (VSGP), early falls along with behavioral and language abnormalities.[1,2] VSGP along with early falls was the first described phenotype of PSP, known as Richardson syndrome (PSP-RS).[3] Since then several other phenotypes have been reported, based on clinical presentation at disease onset, including those with initial oculomotor problems (PSP-OM), parkinsonism akin to idiopathic Parkinson's disease (PSP-P), frontal features (PSP-F), behavioral variant fronto-temporal dementia (PSP-FTD), progressive gait freezing (PSP-PGF), postural instability (PSP-PI), corticobasal syndrome (PSP-CBS), primary lateral sclerosis (PSP-PLS), cerebellar ataxia (PSP-C), and speech-language disorders (PSP-SL).[4]

National Institute of Neurological and Stroke and Society for PSP (NINDS-SPSP) criteria was widely used for diagnosing PSP till Movement Disorders Society (MDS) came up with the new criteria for PSP (MDS-PSP) in 2017.[5] NINDS-SPSP criteria had a high specificity and sensitivity in diagnosing PSP-RS, but it's low sensitivity in diagnosing PSP early and in detecting subtypes other than PSP-RS at disease-onset is a major disadvantage.[4,5] In fact, a recent study reported PSP variants other than PSP-RS in more than 3/4th of 100 autopsy-confirmed PSP cases, with a substantial proportion of them failing to satisfy the NINDS-SPSP criteria.[6] Although initial studies have highlighted the success of MDS-PSP criteria in clinicopathological correlation of PSP cases, there are concerns regarding its reliability in differentiating less progressive and rapidly progressive subtypes of PSP.[7,8]

Early diagnosis of PSP is of utmost importance, not only for understanding its prognosis, but also for recruiting appropriate patients in studies exploring diagnostic investigations or therapeutic strategies for PSP.[4] To standardize the utilization of MDS-PSP criteria, Grimm *et al.*[9] proposed the Multiple Allocation eXtinction (MAX) rules. In addition to improvement in the clinical diagnostic criteria, neuroimaging biomarkers may prove a great help in early diagnosis of PSP subtypes, although currently their primary role is limited to supporting its diagnosis and ruling out other differentials.[4,10] Because of its ability to highlight brain changes resulting from synaptic disturbances, neurodegeneration, and associated neuronal compensation following the primary pathology, F-18-fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET) imaging may reveal disease specific cerebral glucose metabolism disturbances, which may accurately differentiate Parkinson's disease (PD) from Parkinson-plus syndromes including PSP, multiple system atrophy (MSA), and corticobasal degeneration (CBD).[11-13]

^{18}F-FDG PET imaging in PD patients show hypermetabolism in striatum, thalamus, sensorimotor cortex, pons and cerebellum, and hypometabolism in temporoparietooccipital cortex. While, MSA patients have a hypometabolic striatum and cerebellum, those with PSP have a hypometabolic medial and dorsolateral prefrontal cortex, caudate, thalamus, and upper brainstem. CBD patients show asymmetric hypometabolism involving frontoparietal regions, striatum and thalamus.[11] On ^{18}F-FDG PET imaging in PSP patients, hypometabolism in the bilateral anterior cingulate gyrus, thalamus, midbrain, and left medial and dorsolateral frontal lobe has been linked to vertical gaze palsy, recurrent falls, freezing of gait, and non-fluent aphasia, respectively.[14-17] Unfortunately, there is a dearth of the functional imaging data in various subtypes of PSP.[18]

In this issue of the journal, XYZ *et al.*[19] performed a single-center cross-sectional, retrospective evaluation of ^{18}F-FDG PET imaging findings in 88 PSP patients and correlated them with the clinical features. Included patients had an abnormal 99mTc-TRODAT scan and were diagnosed with the different clinical variants of PSP using MDS-PSP criteria. The mean age of the included patients was 65.4 years, and the mean duration of illness at ^{18}F-FDG PET imaging was 1.25 years. Males predominated with male: female ratio being 1.67. While PSP-RS, PSP-PGF, PSP-PI, PSP-SL, PSP-F, PSP-P, and PSP-CBS comprised 52.3%, 7.9%, 10.2%, 3.4%, 6.8%, 12.5%, and 6.8%, respectively, none of the patients had PSP-OM subtype of PSP. The authors have suggested that failure to identify eye signs early along with development of dominant motor and/or non-motor symptoms when the patient reaches the neurologist may be the major reasons for lack of PSP-OM cases in their cohort.

Amongst all the patients, the most common brain regions showing hypometabolism on ^{18}F-FDG PET imaging included frontal, limbic, and sensorimotor cortices. Patients with PSP-RS subtype showed the highest number of hypometabolic clusters. Affection of cortical and subcortical structures varied with the PSP subtypes and correlated with their primary clinical features. In PSP-RS subtype, hypometabolism was seen in frontal and limbic cortices, brainstem, thalamus, basal-ganglia (BG), and cerebellum. While frontal cortex hypometabolism correlated with the cognitive decline and non-fluent aphasia, hypometabolic limbic cortices was associated with pseudobulbar symptoms, autonomic dysfunction along with axial features including swallowing and speech abnormalities. Patients with VSGP had mibdrain hypometabolism, those with recurrent falls showed thalamic and BG hypometabolism, and those having ataxia and dysarthria exhibited cerebellar hypometabolism. Frontal and limbic cortical involvement was supported by previous

neuroimaging and neuropathological studies,[20-23] and the extensive subcortical involvement was similar to that reported on flortaucipir analysis in a recent study.[21]

Patients with PSP-PGF had hypometabolism in frontal, cingulate, striatum and insula which correlated to the gait dysfunction including freezing of gait. Cerebellar hypometabolism in this subtype was associated with ataxia of trunk and speech along with gait apraxia. Whitwell *et al.*[21] has previously reported similar findings of a highly restricted subcortical involvement in PSP-PGF as compared to PSP-RS patients.[21]

Involvement of medial frontal, middle frontal, pericentral, cingulate regions, and thalami in patients with PSP-PI subtype correlated to their predominant clinical feature of early postural instability with recurrent unprovoked falls. While the intact cognition in this subtype correlated to normo-metabolic orbitofrontal and pre-frontal cortices, sparing of midbrain explained the absence of VSGP. Asymmetric hypometabolism of fronto-parietal cortex, BG, and thalamus was seen in PSP-CBS patients, contralateral to the side of motor dysfunction, as has been described previously.[24] PSP-P patients showed remarkably hypometabolic striatum, correlating with tremor and rigidity, with similar results being available in literature.[21,25]

While pre-frontal and medial frontal hypometabolism in PSP-F was associated with dysfunction in frontal cognitive domain, hypometabolic temporal, limbic, and parietal lobes correlated with decline in memory, autonomic functions, and visual-spatial orientation, respectively. Hypometabolic frontal cortices especially involving the primary and supplementary motor speech regions in PSP-SL patients correlated to the non-fluent progressive aphasia or speech apraxia. Similar neuroimaging findings have previously been reported in patients with progressive speech apraxia.[21]

Single-centre study, retrospective design, small sample size, inability to include patients of PSP-OM subtype along with lack of pathological confirmation of diagnosis are the major limitations of this study. Moreover, the authors have not mentioned if they have used the MAX rules before finalizing the PSP subtypes using the MDS-PSP criteria. However, this study has highlighted a subtype-specific ^{18}F-FDG PET imaging findings in PSP patients, more early in the disease. Multicentre prospective studies with a larger sample size in future may help define a clear role of ^{18}F-FDG PET imaging in supplementing clinical diagnosis of PSP subtypes.

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