Fluorodeoxyglucose Positron Emission Tomography in Richardson’s Syndrome and Progressive Supranuclear Palsy-Parkinsonism

Karin Srulijes, MD,1,2 Matthias Reimold, MD,3 Rajka M. Liscic, MD, PhD,1,2 Sarah Bauer,1,2 Elisabeth Dietzel,1,2 Inga Liepelt-Scarfone, PhD,1,2 Daniela Berg, MD,1,2 and Walter Maetzler, MD1,2,4*

1Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany; 2German Center for Neurodegenerative Diseases, DZNE, University of Tuebingen, Tuebingen, Germany; 3Nuclear Medicine and PET Center, University of Tuebingen, Tuebingen, Germany; 4Robert-Bosch-Hospital, Department of Clinical Gerontology, Stuttgart, Germany

ABSTRACT

Background: We hypothesized that postural instability and cognitive decline in patients with Richardson’s syndrome could be a consequence of reduced thalamic and frontal metabolism. Severe Parkinsonian signs in patients with progressive supranuclear palsy-parkinsonism may be reflected by alterations in putaminal metabolism. Methods: Eleven patients with Richardson’s syndrome, 8 patients with progressive supranuclear palsy-parkinsonism, 12 with Parkinson’s disease, and 10 controls underwent clinical assessment and fluorodeoxyglucose positron emission tomography (PET). Results: Richardson’s syndrome patients showed pronounced thalamic hypometabolism, and patients with progressive supranuclear palsy-parkinsonism pronounced putaminal hypometabolism, compared to all other investigated groups. The putamen/thalamus uptake ratio differentiated progressive supranuclear palsy-parkinsonism from Richardson’s syndrome (area under the curve = 0.86) and from Parkinson’s disease (area under the curve = 0.80) with acceptable accuracy. Conclusions: Richardson’s syndrome, progressive supranuclear palsy-parkinsonism and Parkinson’s disease showed different metabolic patterns in fluorodeoxyglucose PET.

Key Words: hypometabolism; parkinsonism; positron emission tomography; postural instability; progressive supranuclear palsy

Progressive supranuclear palsy (PSP) has recently been divided into several subgroups.1 The 2 most common subgroups are Richardson’s syndrome (RS), covering the “classical” PSP patient, and PSP-parkinsonism (PSP-P), resembling an idiopathic Parkinson’s disease (PD)-like phenotype particularly at early disease stages.1,5 Postmortem findings6,7 argue for the usefulness of this classification.

Using [18F]Fluorodeoxyglucose–positron emission tomography (FDG-PET), hypometabolism has been described in the prefrontal cortex, caudate nucleus, putamen, thalamus, and mesencephalon of PSP patients compared to PD and controls. Until now, no reports about glucose metabolism in the abovementioned PSP subtypes are available. According to clinical and neuropathological differences between RS and PSP-P and PD we hypothesized that these disorders show distinct metabolic patterns.

First, we hypothesized that RS patients have thalamic hypometabolism. Clinically, RS patients show a high frequency of falls. It has recently been shown that thalamic acetylcholine esterase activity is reduced in PD patients suffering from falls.12 A similar finding has been observed in PSP and was interpreted as a consequence of disrupted cholinergic fibers ascending from brainstem nuclei (pedunculopontine and laterodorsal tegmental nuclei) to the thalamus.13 There is some evidence that regions with reduced acetylcholine esterase activity show impaired glucose metabolism.13,14 This has recently been substantiated by Zwergal et al.,15 who showed by use of FDG-PET that imbalance and falls in PSP are closely associated with thalamic dysfunction.

Second, we hypothesized that putaminal hypometabolism is predominantly found in the PSP-P subgroup, due to severe Parkinsonism in these patients. Lozza et al.16 found that more severely affected PD patients with executive dysfunction (potentially including PSP-P subjects) show basal ganglia hypometabolism.
Third, we explored whether the well-known PSP-related pattern of frontal hypometabolism can primarily be attributed to 1 of the investigated subgroups.

Patients and Methods

Eleven RS patients meeting criteria proposed by Williams et al.1 and Litvan et al.,3 and 8 patients meeting criteria for PSP-P1 were prospectively recruited for this study17 by movement disorders specialists. As PSP-P patients show “classical” PSP symptoms (eg, falls, supranuclear gaze palsy, cognitive decline) at later disease stages, we abstained from applying the criterion “in the first year of the disease.”4 This adaption has also been used by others recently.18 Clinical and demographic data, the motor subscore of the Unified Parkinson’s Disease Rating Scale (UPDRS-III),19 and the PSP rating scale20 were assessed (Supporting Table 2). Supporting Table 2 gives information about frequency of PSP-associated symptoms in the investigated PSP patients at early disease stages, and at study inclusion.

Clinical and FDG-PET datasets of 12 PD patients meeting the UK Parkinson’s Disease Society Brain Bank (UK PD SBB) criteria21 and of 10 healthy volunteers, assessed for recent PET studies22–24 were included in the analyses.

FDG-PET Acquisition and Image Reconstruction

Within 1 month of clinical assessment, individuals underwent FDG-PET according to the locally established standard acquisition protocol; the same protocol was used for PD patients and controls (for detailed technical aspects we refer to Ref. 22).

A Priori Region of Interest Analysis

A priori region of interest (ROI) analysis was performed using predefined, locally established 3-dimensional ROIs for the putamen (2 \( \times \) 0.7 mL), the thalamus (2 \( \times \) 1.0 mL), and the cerebellum (2 \( \times \) 9.2 mL). From these ROIs, we calculated the putaminal and thalamic uptake ratio (UR, putaminal and thalamic FDG concentration, respectively, divided by cerebellar FDG concentration), and the putamen/thalamus ratio (putaminal FDG concentration divided by thalamic FDG concentration).

Voxelwise Analysis and Frontal ROI Definition

Prior to Statistical Parametric Mapping (SPM; www.fil.ion.ucl.ac.uk/spm) analysis, voxelwise FDG uptake was normalized to cerebellar FDG uptake and SPM’s “proportional scaling” was disabled.

Cortical hypometabolism was assessed calculating a voxelwise group comparison between the combined PSP group (n = 19) and the control group (SPM2, voxel-level threshold of significance P < .001). Subsequently, a mask, comprising all cortical regions with reduced FDG uptake in PSP, was applied to all participants to assess the individual degree of hypometabolism in cortical regions typically affected in PSP (ie, particularly in the frontal cortex).

In addition, we calculated an exploratory voxelwise comparison of PSP-P versus RS patients. The same voxel-level threshold was used. Clusters with a false discovery rate (FDR)-corrected P value < 0.05 were considered significant. In both SPM analyses, age was used as a covariate to improve statistical power.

Statistical Analysis

Data were analyzed using the JMP 8.0.2 program (SAS Institute, Inc., Cary, NC). We tested the hypothesis that thalamic and frontal uptake (UR) is reduced in RS as compared to PSP-P, and that putamen UR is reduced in PSP-P as compared to RS, using 2-sample t tests, correcting for multiple (three) comparisons with the method of Bonferroni and Holm (significant at corrected P < .05). Significantly reduced FDG uptake was confirmed by comparison with healthy controls. Descriptive statistics, including receiver operating characteristic (ROC) curve analysis, were calculated to explore the diagnostic potential of the defined ROI to delineate PSP-P from PD, and from RS.

Results

Demographic and clinical features as well as FDG uptake were summarized in Supporting Table 1. Age, gender, disease duration, age at onset of disease, and PSP rating score did not differ significantly between the groups. Median UPDRS-III sum scores were significantly higher in PSP-P compared to PD subjects (P = .003).

ROI Analysis (Putamen and Thalamus)

Thalamic UR (Supporting Table 1; Fig. 1; right part of Fig. 2) was lower in the RS group than in the PSP-P group (P = .006) and in controls (P < .0001).

Putaminal UR (Supporting Table 1; Fig. 1; right part of Fig. 2) was lower in the PSP-P group than in the RS group, though not statistically significant (P = .08; cf. P = .005 if compared to healthy controls).

The putamen/thalamus ratio, being independent from reference tissue uptake, differentiated well between both PSP subgroups; ROC curve analysis yielded a diagnostic accuracy (area under the ROC curve [AUC]) of 0.86; post hoc cutoff 1.15 yields 100% sensitivity and 75% specificity for detection of RS subtype; cf. 2-sample t test P = .001.

ROC analysis of putaminal UR yielded an AUC of 0.80 for detection of PSP-P. A post hoc cutoff of 1.0...
FIG. 1. Putaminal, thalamic, and frontal uptake ratios in RS, PSP-P, PD, and controls. Putaminal uptake ratio (UR), thalamic UR, putamen/thalamus ratio, and frontal UR in Richardson's syndrome (RS, n = 11), progressive supranuclear palsy-parkinsonism (PSP-P, n = 8), Parkinson's disease (PD, n = 12), and healthy controls (n = 10). See also Supporting Table 1.

FIG. 2. Voxelwise group comparison. (Left column) Progressive supranuclear palsy (PSP) patients (PSP-parkinsonism [PSP-P] and Richardson's syndrome [RS]) show widespread hypometabolism particularly in the frontal cortex, but also in the bilateral insula, striatum, thalamus, and midbrain. A mask comprising all cortical clusters from this analysis (cyan) was used to extract the frontal uptake ratio (ΔUR, glucose uptake normalized to cerebellum; for details see Voxelwise Analysis and Frontal ROI Definition). P < .001 was used as voxel-level threshold; all depicted clusters survived correction for multiple comparisons (positive false discovery rate [pFDR] < 0.01). (Right column) Analysis of PSP subgroups revealed a similar pattern of regions in which RS showed lower uptake than PSP-P, except for the putamen where uptake was lower in PSP-P. Differences between subgroups did not survive correction for multiple comparisons; for illustration purpose, we used a liberal voxel-level threshold (P < .05). Color codes reflect the group difference in ΔUR.
yields 75% sensitivity, and 100% specificity; cf. 2-sample t test $P = .004$.

Voxelwise Analysis and Frontal Mask

In the combined PSP group (PSP-P and RS), voxel-based analysis revealed widespread hypometabolism particularly in the frontal cortex (cingulate gyrus, particularly anterior cingulate, large portions of the medial frontal gyrus and upper parts of the middle and inferior frontal gyrus), bilateral insula, striatum (particularly caudate, but also dorsal putamen), thalamus, and midbrain (left part of Fig. 2). All cortical voxels from these clusters were combined in a mask of which more than 90% belonged to the frontal lobe and the anterior cingulate (“frontal UR”).

Frontal UR (Supporting Table 1; Figs. 1 and 2) was significantly lower in RS than in PSP-P ($P = .02$). Frontal and thalamic UR correlated highly ($R^2 = 0.72$, $P < .0001$).

Discussion

In RS, we found that thalamic hypometabolism was in line with our first hypothesis, which may be explained by a cholinergic deficit in this region. Early occurrence of falls and postural instability are most likely the clinical correlate to this finding.

In accordance with our second hypothesis, PSP-P patients showed pronounced putaminal hypometabolism, which is clinically reflected by severe parkinsonism, but not relevantly reduced thalamic metabolism. Our ROC curve analysis between RS and PSP-P revealed an AUC of 0.86. Therefore, the putamen/thalamus ratio may be a useful parameter in clinical differential diagnosis of these PSP subgroups. In addition, PSP-P is clinically similar to PD, especially at early disease stages, and differentiation is a diagnostic challenge. Our result of the ROC curve analysis between these 2 cohorts (AUC = 0.80) indicates that putaminal hypometabolism may be of diagnostic value for discriminating PSP-P from PD.

We found that the typical pattern of frontal hypometabolism was mainly attributed to the RS subgroup. This is not surprising as RS patients have an increased risk for dementia, and regularly show cognitive dysfunction early in the disease course. The strong positive correlation between frontal and thalamic metabolism makes it tempting to speculate that this represents the disturbance of one functional network.

Possibly most interesting, most of the PSP-P patients showed normal frontal metabolism. The lack of “PSP-typical” cortical hypometabolism in these patients should lead to a cautious interpretation of FDG-PET results in patients with a possible PSP-P in clinical practice.

A limitation of this study is the small sample size. Future studies may not only focus on the reproduction of our preliminary finding in a larger cohort but may also include further PSP subtypes.

In summary, we found pronounced frontal and thalamic hypometabolism in RS, and pronounced putaminal hypometabolism in PSP-P. These findings may have implications for the differentiation of these 2 PSP subgroups, but also for the differentiation of these 2 subgroups from PD.

Acknowledgment: We thank all patients who took part in the study.

References


