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Pittsburgh Compound B and AV-1451 Positron Emission Tomography Assessment of Molecular Pathologies of Alzheimer's disease in Progressive Supranuclear Palsy

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Abstract

Introduction—Little is known about Alzheimer's disease molecular proteins, beta-amyloid and paired helical filament (PHF) tau, in progressive supranuclear palsy (PSP). Recent techniques have been developed to allow for investigations of these proteins in PSP. We determined the frequency of beta-amyloid deposition in PSP, and whether beta-amyloid deposition in PSP is associated with PHF-tau deposition pattern, or clinical features.

Methods—Thirty probable PSP participants underwent MRI, [¹⁸F]AV-1451 PET and Pittsburgh compound B (PiB) PET. Apolipoprotein (APOE) genotyping was also performed. A global PiB standard-uptake value ratio (SUVR) was calculated. AV-1451 SUVRs were calculated for a set of Alzheimer's disease (AD)-related regions and a set of PSP-related regions. Voxel-level analyses was conducted to assess for differences in AV-1451 uptake patterns and MRI atrophy between PiB(+) and PiB(−) cases compared to 64 normal PiB(−) controls. Statistical testing for correlations and associations between variables of interest were also performed.

Results—Twelve subjects (40%) showed beta-amyloid deposition. Higher PiB SUVR correlated with older age but not with AV-1451 SUVR in the AD- or PSP-related regions. Higher AV-1451 SUVR in AD-related regions was associated with higher AV-1451 SUVR in PSP-related regions.

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Disclosure

All authors have approved the final article and fulfill the requirements as stated by the journal for authorship. That is all authors have contributed to: (1) the Conception and design of the study or acquisition of data, or analysis and interpretation of data; (2) Drafting the article or revising it critically for important intellectual content and (3) given final approval of the version to be submitted.

We found little evidence for beta-amyloid related differences in clinical metrics, proportion of APOE e4 carriers, pattern of AV-1451 uptake, or pattern of atrophy.

Conclusion—Beta-amyloid deposition occurs in a relatively high proportion of PSP subjects. Unlike in Alzheimer’s disease, however, there is little evidence that beta-amyloid, and PHF-tau, play a significant role in neurodegeneration in PSP.

Keywords

Beta-amyloid; tau; AV1451; PiB; PSP; tau-PET

Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by the presence of tau isoforms with 4 repeats in the microtubule binding domain[1], and is hence considered a 4R tauopathy[2]. In contrast to PSP, Alzheimer’s disease shows deposition of paired helical filament (PHF) tau with both 3R and 4R isoforms, and is also characterized by the presence of another protein, beta-amyloid. Autopsy studies have identified the presence of concomitant Alzheimer’s disease proteins in the brains of subjects with PSP[3, 4] although little is known about Alzheimer’s disease proteins in PSP. Positron emission tomography (PET) ligands that bind to beta-amyloid, such as Pittsburgh Compound B (PiB) [5], have been available for a number of years and show excellent concordance with beta-amyloid deposition at autopsy[6]. Importantly, the presence of beta-amyloid deposition on PET imaging is considered a biomarker for the presence of underlying Alzheimer’s disease and beta-amyloid is believed to play a role in the neurodegenerative process of Alzheimer’s disease. Positron emission tomography ligands that can bind to tau have also recently been developed. One such ligand, [¹⁸F]AV-1451[7], has been shown to bind strongly to PHF-tau in Alzheimer’s disease in autoradiographic studies[8–10], and shows strong uptake in regions such as the temporal cortices on PET imaging in patients with Alzheimer’s disease[11, 12]. Studies have also shown that AV-1451 can detect PHF-tau uptake in temporal lobe regions in normal subjects that show beta-amyloid deposition on PET[11, 13], suggesting the presence of preclinical Alzheimer’s disease in such subjects and showing that the ligand is sensitive to early disease stages in Alzheimer’s disease. Elevated AV-1451 uptake has also been observed in patients with PSP. In contrast to Alzheimer’s disease, AV-1451 uptake in PSP is relatively minimal, observed predominantly in subcortical structures[14–19], and autoradiographic studies have shown little to no binding of AV-1451 to 4R tau in PSP[8–10]. Hence, while AV-1451 appears to be a very good biomarker of PHF-tau in Alzheimer’s disease, it is unclear whether AV-1451 does bind to 4R tau or whether the minimal binding observed in 4R tauopathies is even specific.

While beta-amyloid PET has been studied in normal aging and Alzheimer’s disease, little is known about the frequency of beta-amyloid deposition on PET in PSP. It is also unknown whether beta-amyloid deposition is associated with PHF-tau (Alzheimer’s type tau) in PSP, or whether it modifies clinical outcomes or brain atrophy in PSP. In order to address these shortcomings in the PSP field, we designed a molecular PET study to address these questions. We hypothesized that beta-amyloid deposition on PET imaging would be present in approximately a third of the PSP subjects, similar to the frequency reported in normal subjects[20]. We also hypothesized that the presence of beta-amyloid would be associated with increased PHF-tau uptake, as measured by AV-1451, in Alzheimer’s disease-related

regions of brain, i.e. the temporal lobe, but not in regions related to PSP (PSP-related regions, as defined below). Understanding the relationship between beta-amyloid and PHF-tau in PSP could help to shed light on the neurodegenerative process of PSP, and could provide some information on similarities and differences between neurodegeneration in PSP and neurodegeneration in Alzheimer's disease.

Methods

Subject selection

Thirty subjects with probable PSP had been recruited into an NIH-funded study (Co-PI's Josephs/Whitwell) and underwent [^{18}F]AV-1451 PET imaging to assess tau[7, 21], Pittsburgh Compound B (PiB) PET to assess beta-amyloid deposition and a volumetric MRI. All 30 subjects had been identified from the Department of Neurology, Mayo Clinic, Rochester, MN. All clinical examinations and neuroimaging were performed within 72 hrs of each other. Of the 30 subjects, 23 met clinical criteria for PSP-Richardson's syndrome (PSP-RS), two PSP parkinsonism (PSP-P), two PSP corticobasal syndrome (PSP-CBS), and three progressive gait freezing (PSP-PGF)[22]. Three subjects have died; one with PSP confirmed at autopsy (hence definite PSP), and two without autopsy. All subjects underwent apolipoprotein E genotyping. The demographic features of the entire cohort are shown in Table 1. The study was approved by the Mayo Clinic IRB. All subjects had consented to research.

Neuroimaging methods

All PET scans were acquired using a PET/CT scanner (GE Healthcare, Milwaukee, Wisconsin) operating in 3D mode. For tau-PET, an intravenous bolus injection of 370MBq (range 333–407 MBq) of [^{18}F]AV-1451 was administered, followed by a 20-minute PET acquisition performed 80-minutes after injection. For PiB-PET, subjects were injected with approximately 628 MBq (range, 385–723 MBq) of PiB and after a 40–60 minute uptake period a 20-minute PiB scan was obtained consisting of four 5-minute dynamic frames following a low dose CT transmission scan. Emission data was reconstructed into a 256×256 matrix with a 30-cm FOV (Pixel size=1.0mm, slice thickness=1.96mm). Individual frames of the dynamic series were realigned if motion was detected, and then a mean image was created. AV-1451 and PiB PET scans were performed on the same day. All 32 subjects had a 3T magnetization prepared rapid gradient echo (MPRAGE) sequence[23] performed within 48 hrs of the PET scans.

All PET scans were co-registered to each subject's MPRAGE using SPM and the automated anatomical labeling (AAL) atlas[24] was transformed into the native space of each MPRAGE in order to calculate regional data. For PiB-PET, a global standard uptake value ratio (SUVR) was calculated as previously described[23]. Briefly, median uptake in prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions were calculated and divided by median uptake in the cerebellar grey matter. The global PiB SUVR was generated by combining uptake ratios from these six regions. A subject was considered beta-amyloid positive (PiB(+)) if the global PiB SUVR was >1.42[25].

For tau-PET, we calculated AV-1451 uptake across a set of Alzheimer's disease related regions (AD-related regions) that included the middle temporal gyrus, inferior temporal gyrus, fusiform, amygdala, entorhinal cortex and parahippocampal gyrus. We also calculated AV-1451 uptake across a set of PSP-related regions that included the midbrain, globus pallidum, thalamus, dentate nuclei of the cerebellum and motor cortex. AD-related and PSP-related regions were selected based on numerous pathological studies demonstrating pathology in these regions. Median values were calculated for each region which were then divided by median uptake in the cerebellar crus grey matter, and combined.

Voxel-level analyses

Voxel-level analyses were performed to assess patterns of AV-1451 uptake and brain atrophy in the PiB(−) and PiB(+) groups compared to a group of 64 age and gender matched PiB(−) controls. All MPAGE scans were spatially normalized to a customized template and segmented using the unified segmentation model[26], followed by the hidden Markov random field clean-up step. For the AV-1451 analysis, the AAL atlas was propagated to native MPAGE space and all voxels in the MPAGE-space AV-1451 images were divided by median uptake in cerebellar crus grey matter to create SUVR images. These images were then normalized to the customized template using the normalization parameters from the MPAGE normalization. Voxel-level comparisons were performed comparing SUVR across brain tissue (grey and white matter) using two-sided T-tests in SPM5, with results assessed at $p < 0.05$ after correction for multiple comparisons using the false discovery rate correction. For the MRI analysis, the template space grey and white matter segmentations were modulated and smoothed at 8mm full-width at half maximum. Voxel-level comparisons of grey matter and white matter were performed using two-sided T-tests in SPM5, with results assessed at $p < 0.05$ after correction for multiple comparisons using the false discovery rate correction. Age and gender were included in the analyses as covariates.

Statistical methods

Statistical analyses were performed in JMP (version 10.0). Group comparisons were performed using Wilcoxon signed rank tests for continuous variables and chi-squared tests/Fishers Exact test for categorical variables. Spearman rank correlations were assessed between 1) global PiB SUVR and AV-1451 uptake in AD- and PSP-related regions, 2) age at scan and the three neuroimaging metrics (global PiB SUVR, and AV-1451 uptake in AD- and PSP-related regions), 3) AV-1451 uptake in the AD-related and AV-1451 uptake in PSP-related regions, and 4) clinical scores and AV-1451 uptake in the AD and PSP-related regions. Linear regressions were used to determine associations while adjusting for potential confounders. All analyses were performed using the entire cohort ($n=30$) and also repeated in the large subject of PSP-RS subjects ($n=23$) to exclude any potential confounding effects of including multiple PSP variants that may have different relationships with the variables of interest.

Results

Clinical findings

Demographics and clinical characteristics of the entire cohort are shown in Table 1. Twelve (40%) of our PSP subjects were PiB(+) according to the PiB SUVR cutoff, i.e. $SUVR > 1.42$. The PiB(+) subjects were older at the time of PET. After adjusting for age at scan there were no differences in clinical characteristics between PiB(+) and PiB(−) subjects. The proportion of APOE e4 carriers in the whole cohort was 20% and this proportion did not significantly differ between the PiB(+) and PiB(−) subjects. After adjusting for age at scan, we did not find any associations between AV-1451 uptake in AD-related regions and the Montreal Cognitive Assessment of Cognitive Impairment (MoCA) ($p=0.41$), between AV-1451 uptake in AD-related regions and the PSP rating scale ($p=0.41$), between AV-1451 uptake in the PSP-related regions and the MoCA ($p=0.71$), or between AV-1451 uptake in the PSP-related regions and the PSP rating scale ($p=0.95$).

Within the PSP cohort the vast majority of subjects ($n=23$; 77%) were the PSP-Richardson's syndrome variant. Eleven of our PSP-Richardson's syndrome subjects (48%) were PiB(+) compared to only one (14%) of the other variant PSP syndromes. As with the whole cohort, the PiB(+) subjects were older at the time of PET scans. After adjusting for age at scan only the MoCA showed a difference, with a lower MoCA scores observed in the PiB(+) PSP-Richardson's syndrome variant (22 versus 26, $p=0.04$). There were no associations between AV-1451 uptake in the AD-related regions or PSP-related regions, and MoCA and PSP rating scale.

Spearman correlation analyses

Scatter-plots showing relationships between the different neuroimaging metrics, and with age, for the entire cohort are shown in Figure 1. Global PiB SUVR did not correlate with AV-1451 SUVR in the AD-related regions (Spearman $\rho=0.12$, $p=0.53$) or in the PSP-related regions (Spearman $\rho=0.09$, $p=0.65$). We found that older age at the time of PET scan correlated with greater global PiB SUVR (Spearman $\rho=0.49$, $p=0.006$). There were trends for older age to correlated with higher AV-1451 uptake in the AD-related regions (Spearman $\rho=0.34$, $p=0.07$) and for higher AV-1451 uptake in the PSP-related regions (Spearman $\rho=0.35$, $p=0.07$). A strong positive correlation was also observed between AV-1451 SUVR in the AD-related regions and AV-1451 SUVR in the PSP-related regions (Spearman $\rho=0.84$, $p<0.0001$). Linear regression analysis adjusting for age showed that AV-1451 SUVR in the PSP-related regions remained a predictor of AV-1451 SUVR in the AD-related regions ($p<0.0001$). These relationships remained the same when the analysis was restricted to subjects with PSP-Richardson's syndrome, with the exception that no correlations were identified between age and AV-1451 uptake in the AD-related regions (Spearman $\rho=0.25$, $p=0.27$) or in the PSP-related regions (Spearman $\rho=0.19$, $p=0.39$).

Voxel-level AV-1451 results

Patterns of AV-1451 uptake in the PiB(−) and PiB(+) PSP subjects compared to controls are shown in Figure 2. Elevated uptake was observed in midbrain, dentate nucleus of the

cerebellum, thalamus, subthalamic nucleus, pallidum, putamen, caudate nucleus and frontal lobe in PiB(−) PSP compared to controls. The PiB(+) group also showed elevated uptake in the midbrain, thalamus, subthalamic nucleus, putamen, and pallidum compared to controls. No differences were observed between the PiB(−) and PiB(+) subjects when compared directly. Results were the same when restricted to only subjects with PSP-Richardson's syndrome.

Voxel-level MRI results

Patterns of grey and white matter atrophy in the PiB(−) and PiB(+) PSP subjects compared to controls are shown in Figure 3. The PiB(−) group showed white matter atrophy in midbrain and superior cerebellar peduncles, and grey matter atrophy in frontal regions and striatum. The PiB(+) group also showed white matter atrophy in midbrain and grey matter atrophy in frontal regions and striatum. No differences were observed between the PiB(−) and PiB(+) subjects when compared directly. Results were the same when restricted to only the subjects with PSP-Richardson's syndrome.

Discussion

In this study we demonstrate that beta-amyloid deposition on PET occurred in 40% of a cohort of PSP subjects, the majority of which had PSP-Richardson's syndrome. We show that its deposition is related to age. In addition, we demonstrate that beta-amyloid is not associated with PHF-tau, with little evidence that it modifies clinical features, in PSP.

Forty percent of our PSP subjects had a global PiB SUVR greater than 1.42[25]. One study estimated the frequency of beta-amyloid positivity in cognitively normal subjects to be 12.9% at age 55, increasing to 32.6% at age 80 years, with 23.1% expected at age 70 years[27]. Another study found a frequency of 34.9% in cognitively normal subjects in the age range 70–79 years[20]. Our frequency was, therefore, somewhat higher than expected given the median age of our cohort is 70 years. The frequency of APOE e4 carriers in our cohort was 20%, in line with estimates of APOE e4 carrier frequency in cognitively normal subjects[27]. This suggests that the higher frequency of beta-amyloid positivity in the PSP cohort is not due to a higher frequency of APOE e4 carriers. Similarly, a previous pathological study of 143 PSP cases found an APOE e4 frequency of 21% with 28% having beta-amyloid deposition[3], and a previous study assessing cerebrospinal fluid found a reduction in Aβ-42 in PSP compared to controls but the Aβ-42 levels were not related to APOE genotype[28]. The frequency of beta-amyloid deposition was, in fact, slightly higher in the PSP-Richardson's syndrome subjects, with 48% showing beta-amyloid positivity compared to 14% in the variant syndromes of PSP. The reason for this is unclear but was not due to age, since the median age at PET was identical between the PSP-Richardson's syndrome and variant syndrome PSP cases.

We found no evidence for an association between beta-amyloid and the presence of PHF-tau in the AD-related regions in PSP, but instead showed that beta-amyloid deposition was related to age. These findings would suggest that beta-amyloid deposition in PSP is an age-related phenomenon (so called pathological aging) as opposed to representing preclinical Alzheimer's disease. Autopsy cases of PSP with pathological aging, characterized by the

presence of numerous senile plaques but with a low Braak neurofibrillary tangle stage, have indeed been published[3, 29, 30], and the frequency of pathological aging in PSP (18%) is higher than the frequency of concomitant Alzheimer's disease (10%)[3]. Although another autopsy study found that 36% of PSP cases had concomitant Alzheimer's disease by the time they died[4]. The frequency of beta-amyloid positivity we observed on PET, compared to autopsy frequencies, may suggest that some of the patients with beta-amyloid deposition do have preclinical Alzheimer's disease but we are capturing them early before they develop tau in AD-signature regions. Regardless, our finding has implications for the interpretation of beta-amyloid PET scans in PSP subjects, and suggests that the presence of a positive beta-amyloid scan may not necessarily be an indication of underlying Alzheimer's disease; particularly in older PSP subjects.

We had hypothesized that beta-amyloid deposition would be associated with PHF-tau deposition in the AD-related regions in PSP. Instead, we found that AV-1451 uptake in AD-related regions strongly correlates with uptake in the PSP-related regions. Given the high confidence from autoradiographic studies that AV-1451 does bind strongly to PHF-tau, it is possible that the observed correlation of uptake between the AD and PSP-related regions is driven by some low level of PHF-tau that may be present in PSP. Another possibility is that uptake in both regions is related to off-target binding to some other aspect of neurodegeneration. Whatever AV-1451 is binding to in PSP, it is likely occurring in both AD and PSP-related regions.

When we compared clinical and voxel-level imaging between PiB(+) and PiB(-) PSP subjects, we found little evidence for any difference. In fact, with the exception of a slightly lower MoCA score in the PiB(+) PSP-Richardson syndrome subjects compared to the PiB(-) PSP-Richardson syndrome subjects there were no clinical differences. The patterns of AV-1451 uptake were similar in the PiB(+) and PiB(-) subjects with both groups showing elevated uptake predominantly in subcortical structures compared to controls, concurring with patterns previously published in PSP[14–19]. Similarly, on MRI both groups showed expected patterns of atrophy[18], with involvement of midbrain, striatum and frontal lobes. No differences were observed between the PiB(+) and PiB(-) groups, suggesting that the presence of beta-amyloid deposition does not influence patterns of AV-1451 uptake or brain atrophy in PSP. The lack of clinical and imaging differences between those with and without beta-amyloid may argue against beta-amyloid, and PHF-tau playing a striking role in PSP neurodegeneration, as they do in Alzheimer's disease.

The strengths of this study are the large number of subjects and its novelty, being the first study to assess association of beta-amyloid with PHF-tau and clinical features in PSP using molecular imaging. Limitations were the lack of autopsy confirmation and the fact that our cohort was predominantly represented by subjects with PSP-Richardson's syndrome. Future studies will be needed to assess the influence of beta-amyloid deposition on the other variant PSP syndromes, such as PSP-Parkinsonism. The smaller number of subjects in the PiB(+) compared to the PiB(-) group may have reduced power to assess regional abnormalities in this group in the voxel-based analyses.

In summary, our data shows that beta-amyloid deposition occurs in PSP predominantly as an age-related phenomenon, with little evidence that beta-amyloid and PHF-tau play a significant role in neurodegeneration in PSP.

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Highlights

- Forty percent of PSP subjects have beta-amyloid deposition on PET
- Beta-amyloid deposition in PSP was not associated with tau uptake on PET, or clinical features
- There is little evidence that beta-amyloid, and paired helical filament tau, play a significant role in neurodegeneration in PSP

Figure 1.
Scatter-plots showing the relationships between global PiB SUVR, AV-1451 uptake and age.
The only significant correlation identified was between PiB SUVR and age at scan.

Figure 2. Voxel-level maps showing elevated AV-1451 tau uptake in PiB(-) and PiB(+) PSP subjects compared to matched controls. Results are shown after correction for multiple comparisons using the false discovery rate correction at $p < 0.05$.

Figure 3. Voxel-level maps showing grey matter (shown in red) and white matter (shown in green) volume loss in PiB(-) and PiB(+) PSP subjects compared to matched controls. Results are shown after correction for multiple comparisons using the false discovery rate correction at $p < 0.05$.

Table 1

Demographic and clinical features of the total PSP cohort, divided by PiB status

	Total (n=30)	PiB – (n=18)	PiB + (n=12)	P-value PiB – vs +
Demographic features				
% female	18 (60 %)	11 (56%)	8 (67%)	0.54
Age at scan (years)	70 (65, 73)	66 (64, 71)	71 (71, 73)	0.03
Disease duration (years)	3 (3, 5)	3 (3, 5)	4 (2, 5)	0.75
% PSP - Richardson syndrome	23 (77 %)	12 (63%)	11 (92%)	0.11
% APOE e4 carriers	5 (20%)	2 (12%)	3 (38%)	0.13
Global PiB SUVR	1.39 (1.30, 1.53)	1.32 (1.29, 1.36)	1.59 (1.52, 1.72)	<0.001
Tau SUVR in AD - signature	1.18 (1.13, 1.24)	1.20 (1.16, 1.23)	1.17 (1.10, 1.24)	0.46
Tau SUVR in PSP - signature	1.25 (1.17, 1.30)	1.27 (1.17, 1.30)	1.20 (1.18, 1.29)	0.55
Clinical features				
FAB/18 *	14 (13, 15)	14 (13, 16)	14 (12, 14)	0.60 [†]
PSIS/5	3 (2, 4)	3(2, 4)	3.5 (2, 4)	0.18
PSPRS total/100	44 (42, 49)	43 (36, 49)	46 (42, 49)	0.44 [†]
PSPRS gait_midline/20	14 (13, 16)	14 (13, 16)	14 (13, 15)	0.67 [†]
MDS - UPDRS I/52	11 (9, 16)	12 (10, 18)	9 (8, 13)	0.66 [†]
MDS - UPDRS II/52	24 (17, 28)	24 (16, 26)	28 (21, 31)	0.48 [†]
MDS - UPDRS III/120	41 (35, 48)	41 (34, 47)	43 (36, 49)	0.75 [†]
TULIA/12 *	11 (11, 12)	12 (11, 12)	11 (10, 11)	0.31 [†]
MoCA/30	25 (22, 26)	26 (23, 27)	23 (19, 25)	0.40 [†]
GRS/10	0 (0, 1)	0 (0, 0)	1 (0, 2)	0.51 [†]
Schwab and England/100% *	70% (40%, 80%)	80% (40%, 80%)	70% (60%, 80%)	0.26 [†]
GDS/15	5 (4, 8)	5 (4, 8)	5 (3, 8)	0.46 [†]

Data shown as median and interquartile range;

[†] p-values are age-adjusted

* Lower number = poorer performance/worse score

APOE = apolipoprotein E; FAB = frontal assessment battery; GDS = Geriatric Depression Scale; GRS = Global rating scale for dystonia; MDS-UPDRS = Movement Disorder Society sponsored revision of the Unified Parkinson's disease Rating Scale; MoCA = Montreal Cognitive Assessment Battery; PiB = Pittsburgh Compound B; PSIS: PSP saccadic impairment scale; PSPRS = progressive supranuclear palsy rating scale; SUVR = standard uptake value ratio; TULIA = Test of upper limb apraxia. Results shown as median (IQR) or N (%)