Background

Mutations in the \textit{MAPT} gene are associated with the depostion of pathological tau protein in the brain. The [\textsuperscript{18}F]AV-1451 PET radioligand was developed as an \textit{in vivo} biomarker of tau accumulation. The ligand has been consistently shown to be bound to paired helical filaments (PHF) of tau in individuals with Alzheimer’s disease\textsuperscript{1}, but the effectiveness of this ligand has not been widely explored in other tau-related diseases. There is evidence to show that the [\textsuperscript{18}F]AV-1451 ligand is useful in characterising some Frontotemporal dementia (FTD) causing \textit{MAPT} mutations that also show tau PHF pathology e.g. V337M and R406W. Here we present [\textsuperscript{18}F]AV-1451 binding in a patient with a behavioural variant FTD who has a Q351R \textit{MAPT} mutation.

Clinical Details

A 65-year-old female presented with a 20 year history of slowly progressive behavioural change and memory impairment. Her first symptom was episodic memory loss at age 45 and she reported poor memory for both words and faces. She subsequently became disinhibited, apathetic, developed a change in appetite, and displayed impaired problem-solving, orientation, and attention. Visuoperceptual and visuospatial functions were normal and all aspects of language were well preserved. Her family history indicated that her father had a similar presentation, with onset in his late 40s.

Genetic screening revealed a novel Q351R mutation in the \textit{MAPT} gene (a single heterozygous nucleotide change on exon 12 c.1052 A>G).

Investigations

The Q351R \textit{MAPT} carrier underwent [\textsuperscript{18}F]AV-1451 PET and T1 weighted MRI imaging at baseline and 1 year follow-up. Five healthy controls underwent the same procedure cross-sectionally.

<table>
<thead>
<tr>
<th>Q351R \textit{MAPT} patient</th>
<th>Healthy controls (n=5)</th>
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<tbody>
<tr>
<td>Baseline (Age)</td>
<td>Follow-up (Age)</td>
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<tr>
<td>65.2</td>
<td>66.3</td>
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Table 1. Demographics of Q351R \textit{MAPT} carrier and 5 healthy controls.

Participants were scanned on a Siemens Biograph 6 PET-CT scanner. Data was acquired following intravenous bolus injection of [\textsuperscript{18}F]AV-1451 for 120 minutes in 3D-mode. Dynamic images were reconstructed using a filtered back projection algorithm (direct inversion Fourier transform), with isotropic voxel size of 2 x 2 x 2 mm\(^3\). Correlations for decay and random counts, were performed, and attenuation and scatter were corrected based on a low-dose CT scan acquired preceding PET acquisition. Rigid head motion correction was performed to align the reconstructed dynamic PET frames using image registration for each scan. Frames affected by mismatched attenuation correction were identified by visual inspection and excluded from kinetic analysis.

Results

Visual inspection of the PET images (Figure 1) shows that [\textsuperscript{18}F]AV-1451 binding is high in the anterior medial temporal lobe and basal ganglia in the carrier at baseline compared to controls, with increased binding at follow-up. Differences were assessed through the calculation of \textit{t}-scores for binding potential (BP) values between the carrier and controls, using standard single case methodology\textsuperscript{2} (Table 2). Spearman correlation coefficients were used to test the relationship between BP and cortical volume in the carrier.

Significant differences in BP between the carrier and control group were found in the insula (baseline \(p=0.037, \text{follow-up } p=0.009\), putamen (\(p=0.011, p=0.004\), pallidum (\(p=0.009, p=0.009\)) and the medial-temporal region (\(p=0.003, p=0.002\)), and additionally the temporal cortex (\(p=0.016\), caudate (\(p=0.009\), and thalamus (\(p=0.040\)) at 1 year follow-up. The Spearman correlation coefficient revealed a significant negative correlation between BP and cortical volume in the patient at baseline (\(r=-0.886, p=0.019\)).

Conclusion

The study shows binding of [\textsuperscript{18}F]AV-1451 in a Q351R \textit{MAPT} mutation carrier is consistent with her clinical syndrome and neuroanatomical involvement. Mutations nearby to Q351R in the \textit{MAPT} gene (V337M and R406W) have PHF pathology, and the strong binding in this single case is also suggestive of PHF pathology. The [\textsuperscript{18}F]AV-1451 ligand may be a useful biomarker in at least a subset of \textit{MAPT} mutations that result in PHF pathology in FTD.


\textsuperscript{4}Swieten, J. C. M., ... & Hansson, O. (2016). 18F\textsuperscript{3}AV-1451 PET imaging in a patient with frontotemporal dementia with the V337M \textit{MAPT} mutation. \textit{Brain Pathology}, 27(1), 88-100.