In vivo [^{18}F]-AV-1451 tau-PET imaging in sporadic Creutzfeldt-Jakob disease

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Abstract

Objective

To determine whether specific patterns of [^{18}F]-AV-1451 tau-PET retention are observed in patients with autopsy-proven sporadic Creutzfeldt-Jakob disease (CJD).

Methods

In vivo [^{18}F]-AV-1451 PET neuroimaging was performed in 5 patients with sporadic CJD (median age, 66 years [63–74]), and results were compared to cognitively normal (CN) persons (n = 44; median age, 68 years [63–74]) and to participants with very mild Alzheimer disease (AD) dementia (n = 8; median age, 77 years [63–90]). Autopsy was completed in all patients with CJD, confirming the clinical diagnosis and permitting characterization of AD neuropathologic change (ADNC).

Results

All patients with CJD presented with rapidly progressive dementia, typical magnetic resonance brain imaging changes, and elevated CSF total tau (median = 6,519; range = 1,528–13,240 pg/mL). Death occurred within 9 months of symptom onset, with a median 1 month (0.2–3.3) interval from [^{18}F]-AV-1451 PET to autopsy. No unique pattern of [^{18}F]-AV-1451 retention was observed on visual inspection. Summary standardized uptake value ratios in patients with CJD (1.17, 1.08–1.36) were indistinguishable from CN persons (1.14, 0.84–1.54; $p = 0.6$), and well below those of participants with AD (2.23, 1.60–3.04; $p \leq 0.01$). [^{18}F]-AV-1451 retention in patients with CJD and CN persons was similar in brain areas frequently affected in AD and CJD. Neuropathologic analysis confirmed the clinical diagnosis in all patients with CJD. Four patients with CJD also had low-level ADNC (A1B1C0); one patient had intermediate-level ADNC (A2B2C1/2).

Conclusion

Increased [^{18}F]-AV-1451 retention was not observed in patients with rapidly progressive dementia due to sporadic CJD. The [^{18}F]-AV-1451 PET tracer maintains good specificity for paired helical tau filaments associated with AD dementia.

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Glossary

A β = β -amyloid; AD = Alzheimer disease; ADNC = Alzheimer disease neuropathologic change; CDR = Clinical Dementia Rating; CJD = Creutzfeldt-Jakob disease; CN = cognitively normal; NFT = neurofibrillary tangle; RPD = rapidly progressive dementia; SUVR = standardized uptake value ratio.

The discovery of radiopharmaceutical agents capable of binding hyperphosphorylated tau protein has facilitated quantification and characterization of in vivo tau deposition in individuals with typical^{1,2} and atypical Alzheimer disease (AD) dementia,^{3,4} Lewy body diseases,⁵ corticobasal syndrome,^{6,7} and frontotemporal dementia associated with select microtubule-associated protein tau mutations.^{8,9} [¹⁸F]-AV-1451 (flortaucipir) is reported to demonstrate good specificity for binding insoluble aggregates of paired helical filaments of tau protein—the building blocks of AD-associated neurofibrillary tangles (NFTs), neuropil threads, and dystrophic neurites of amyloid plaques.¹⁰ The tracer demonstrates lower affinity for tau in other non-AD tauopathies.¹⁰ These findings suggest that [¹⁸F]-AV-1451 may be used to improve the antemortem diagnosis of patients with slowly progressive neurodegenerative dementing diseases. However, it is unknown whether [¹⁸F]-AV-1451 PET imaging can be reliably applied to evaluate patients with rapidly progressive dementia (RPD).

Creutzfeldt-Jakob disease (CJD) represents one of the most common causes of RPD.^{11,12} While clinical algorithms and nonspecific diagnostic tests (e.g., diffusion-weighted magnetic resonance brain sequences) may be used to differentiate CJD from other common causes of RPD, disease-specific biomarkers capable of confirming or refuting the suspected diagnosis are needed to increase diagnostic accuracy, and facilitate counseling concerning treatment and prognosis. Accordingly, we sought to determine whether specific patterns of [¹⁸F]-AV-1451 PET retention are observed in patients with autopsy-proven sporadic CJD. These findings have potentially important implications concerning the specificity of [¹⁸F]-AV-1451 PET retention and the applications of this tracer in clinical practice.

Methods

Standard protocol approvals, registrations, and patient consents

[¹⁸F]-AV-1451 PET neuroimaging was performed on patients presenting to our tertiary care hospital with RPD attributed to sporadic CJD (*n* = 5). Neuroimaging data were obtained for comparison from participants with very mild AD dementia (Clinical Dementia Rating [CDR] 0.5¹³; *n* = 8) and CN persons (CDR 0; *n* = 44) who underwent [¹⁸F]-AV-1451 PET imaging as part of ongoing longitudinal studies of memory and aging at the Knight Alzheimer Disease Research Center in St. Louis, MO. Written informed consent was obtained from all participants or their delegates to review of

clinical records and completion of neuroimaging; patients with CJD (or their delegates) consented to brain-only autopsy. Study protocols were approved by the Washington University School of Medicine Human Research Protections Office.

Clinical assessment

Enrolled individuals were evaluated together with a knowledgeable collateral source by experienced clinicians (G.S.D., R.B., E.S.M., N.G., B.M.A.) using a semistructured interview and detailed neurologic examination. Patients with CJD were admitted to the neurology inpatient service at Barnes-Jewish Hospital (Washington University School of Medicine, St. Louis, MO) between November 2015 and August 2016 for evaluation and management of RPD. Sporadic CJD was diagnosed according to accepted criteria.¹⁴ CSF biomarkers known to correlate with CJD (e.g., total tau, 14-3-3, real-time quaking-induced conversion)^{15,16} were measured in all patients by the National Prion Disease Pathology Surveillance Center (Case Western Reserve University, Cleveland, OH). Additional investigations were ordered at the discretion of treating clinicians, including paraneoplastic autoantibody testing in all patients, and AD biomarker assessment in one patient (ADmark Alzheimer's Evaluation; Athena Diagnostics, Marlborough, MA). All clinical investigations were performed via Clinical Laboratory Improvement Amendments–approved laboratories, in accordance with established criteria. Patients with CJD were followed until death, and brain-only autopsies were completed.

CN persons and participants with very mild AD dementia were prospectively recruited and assessed within the Knight Alzheimer Disease Research Center longitudinal study of memory and aging. All participants with AD dementia presented with typical amnesic symptoms, met National Institute on Aging–Alzheimer's Association diagnostic criteria for AD dementia,¹⁷ and had elevated levels of cerebral β -amyloid (A β), as determined by [¹⁸F]-AV-45 (florbetapir) PET imaging.¹⁸ CN participants were devoid of cognitive symptoms (CDR 0) and substantial [¹⁸F]-AV-45 retention. PET imaging was completed between 2014 and 2016.

Neuroimaging

MRI data were acquired on Siemens 3T scanners (Biograph mMR *n* = 53, Trio *n* = 3, or Skyra *n* = 1; Siemens Medical Solutions, Erlangen, Germany). T1-weighted images were acquired using magnetization-prepared rapid-acquisition gradient echo sequences (appendix e-1, <http://links.lww.com/WNL/A216>). Images underwent cortical and subcortical

parcellation using FreeSurfer 5.3 (<http://freesurfer.net>),¹⁹ yielding 46 unique brain regions, corresponding to the Desikan atlas.

A β -PET imaging was performed following administration of a single IV injection of [¹⁸F]-AV-45 (7.2–11.3 mCi), with images acquired on a Biograph mMR (n = 48) scanner or Biograph 40 PET/CT (n = 4) (Siemens Medical Solutions). Data from the 50- to 70-minute postinjection window were converted to standardized uptake value ratios (SUVRs) using a cerebellar cortex reference region, and partial volume was corrected using a regional spread function technique.^{20,21} [¹⁸F]-AV-45 positivity was defined using an SUVR cutoff of 1.22.²² Previously defined regions of interest were used for processing, and a summary measure of A β deposition was generated using an average of the left and right lateral orbitofrontal, medial orbitofrontal, rostral middle frontal, superior frontal, superior temporal, middle temporal, and precuneus regions.¹⁸

At a dedicated visit, tau-PET imaging was performed following a single IV injection of [¹⁸F]-AV-1451 (6.8–10.8 mCi). Data were acquired on a Biograph 40 PET/CT (n = 54) or Biograph mMR (n = 3) scanner (Siemens Medical Solutions). CT brain images were obtained from participants scanned on the Biograph mMR permitting CT attenuation correction to be performed uniformly irrespective of scanner modality. Data for the 80- to 100-minute postinjection window were converted to SUVRs, using the cerebellar cortex as a reference, and partial volume corrected using a regional spread function technique. [¹⁸F]-AV-1451 retention was summarized using an average of the left and right inferior temporal cortex, amygdala, entorhinal cortex, and lateral occipital cortices.²² FreeSurfer regions, examined a priori, were selected to reflect CJD-specific regions defined via neuropathology, or those commonly demonstrating restricted diffusion on MRI. SUVRs from CJD-specific regions and regions previously reported to be sensitive to tau pathology in AD²² were compared across participants. Neuroimaging analysis was performed by study authors (B.G., H.B., S.M.) who were aware of the clinical diagnoses but blinded to the results of paraclinical testing and neuropathologic analyses.

Neuropathology

Neuropathologic analysis of brain tissue from patients with CJD was completed by study authors (R.P., N.C., K.S., C.F., N.S.) who were aware of the clinical diagnoses but blinded to the results of paraclinical testing and neuroimaging analyses. Macroscopic and microscopic analyses were performed according to standard techniques (appendix e-1, <http://links.lww.com/WNL/A216>), including immunohistochemistry using anti-A β (10D5; Eli Lilly, Indianapolis, IN) and anti-phosphorylated tau (PHF-1; a gift from Dr. P. Davies, Feinstein Institute for Medical Research, Manhasset, NY) antibodies. A neuropathologic diagnosis of prionopathy was confirmed by the National Prion Disease Pathology

Surveillance Center, in accordance with published criteria.²³ When present, AD neuropathologic change (ADNC) and aging-related tau astrogliopathy were assessed using established criteria.^{24–28}

Statistical analyses

Clinical data were analyzed using SPSS Statistics (version 24.0; IBM Corp., Armonk, NY). Comparisons across participant groups (CJD, CN persons, AD) were performed using the nonparametric Kruskal-Wallis test. Continuous and categorical measures were compared using the Mann-Whitney U test and Fisher exact test, respectively. Statistical significance was defined as $p < 0.05$ (Bonferroni-corrected for multiple comparisons, when appropriate).

Results

Specific demographic features, details of clinical presentation and disease course, and results of investigations for patients with sporadic CJD are summarized in table 1. All patients with CJD presented with typical clinical symptoms and signs associated with sporadic CJD, including RPD.¹⁴ No patient with CJD had a family history of CJD or risk factors associated with iatrogenic or variant CJD. Real-time quaking-induced conversion testing was consistent with CJD in 4/5 cases (80%). Total tau was elevated >1,500 pg/mL in the CSF of all patients, supporting the clinical diagnosis. Serum was tested for autoantibodies against CNS antigens in all patients, with low titers of voltage-gated P/Q calcium channel antibodies detected in cases C and E (2/5, 40%). Additional antibodies against thyroperoxidase and antinuclear antigens were identified in case C. In both cases, routine CSF analysis was bland (<5 white blood cells/mm³), and antibodies were deemed unlikely to contribute to the overall clinical picture. Patients with CJD (median 66 years, range 63–74; $p = 0.03$) and CN persons (median 68 years, range 63–74; $p < 0.001$) tended to be younger than participants with AD dementia (median 77 years, range 63–90; significant at $p < 0.017$). No differences were observed in the proportions of females included across groups (CJD = 2/5 [40%]; AD = 7/8 [88%]; CN = 24/44 [55%]; $p = 0.15$).

Diffusion-weighted MRIs demonstrated restricted diffusion within cortical and/or deep gray structures in all cases, corroborating the clinical diagnosis (figure 1, column II). [¹⁸F]-AV-1451 PET imaging was obtained following hospital admission in all patients with CJD, with a median time from symptom onset to imaging of 3.0 months (range, 1.4–4.5). No “CJD-specific” pattern of retention was evident on direct visual inspection of [¹⁸F]-AV-1451 images (figure 1, column III). Median (range) [¹⁸F]-AV-1451 PET SUVRs within regions comprising AD summary measures were indistinguishable between patients with CJD (1.17, 1.08–1.36) and CN persons (1.14, 0.84–1.54; $p = 0.6$) and were well below levels measured in participants with AD (2.23, 1.60–3.04; $p \leq 0.01$; figure 2). [¹⁸F]-AV-1451 PET retention was not increased in any of the 46 measured brain regions in

Table 1 Demographic features, details of clinical presentation and disease course, and results of investigations for patients with sporadic CJD

Case/age, y, sex	Duration, symptom onset to:		Clinical features		Cognitive impairment at time of imaging			CSF studies						Other investigations ^a
	Presentation, mo	Death, mo	Presenting symptoms	Exam findings	MMSE	gCDR	CDR-SB	Nucleated cells/mm ³	Protein, g/dL	Total tau, pg/mL	14-3-3	RT-QuIC		
A/63M	2.9	6.9	Confusion, word-finding difficulty	Cortical blindness, expressive aphasia, ataxia	18	1	6	0	27	2,517	Equivocal	–	Aβ = 340.65 pg/mL; p-tau = 46.45 pg/mL	
B/74M	4.5	4.7	Memory loss, disorientation	Cortical blindness, diffuse myoclonus	NA	3	16	15	40	1,528	–	+	—	
C/65F	1.3	2.2	Left-hand weakness, ataxia	Scanning dysarthria; left pyramidal weakness, hyperreflexia; left > right apraxia; apraxia of gait	26	0.5	2.5	0	26	12,443	+	+	Serum VGCC P/Q Ab = 0.04 nmol/L; TPO Ab = 668 IU/mL	
D/66F	2.7	4.0	Confusion, visual impairment	Dysconjugate gaze, poor visual tracking; cortical blindness; ataxia	21	2	14	5	64	13,240	+	+	—	
E/71M	1.7	4.1	Memory loss, ataxia	Saccadic smooth pursuit; ataxic gait	23	0.5	4	1	46	6,519	+	+	Serum VGCC P/Q Ab = 0.08 nmol/L	
Summary across participants, median (range)														
Age: 66 (63–74); sex: 40% F	2.7 (1.3–4.5)	4.1 (2.2–6.9)	—	—	22 (18–26)	1.0 (0.5–3)	6.0 (2.5–16)	1 (0–15)	40 (26–64)	6,519 (1,528–13,240)	—	—	—	

Abbreviations: Ab = antibody; Aβ = β-amyloid; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CJD = Creutzfeldt-Jakob disease; gCDR = global Clinical Dementia Rating; MMSE = Mini-Mental State Examination; NA = unable to assess because of level of cognitive impairment; p-tau = phosphorylated tau; RT-QuIC = real-time quaking-induced conversion; TPO = thyroperoxidase; VGCC = voltage-gated calcium channel.

^a Other investigations included screening for antibodies against neuronal nuclear, glial nuclear, Purkinje cell cytoplasmic, amphiphysin, CRMP-5, striated muscle, calcium channel, and acetylcholine receptor and voltage-gated potassium channel–associated antigens, with reflex testing for antibodies against cell-surface neuronal antigens if indicated. Only positive findings are reported.

Figure 1 Selected neuroimaging findings in patients with CJD

Structural magnetic resonance brain images (T2-FLAIR [column I] and DWI [column II]) and [¹⁸F]-AV-1451 PET images (axial and coronal orientation, column III) are shown for each patient with CJD, coregistered at the level of the thalamus (cases A–E; presented in radiologic convention). Restricted diffusion within the cortical ribbon and deep gray nuclei was commonly observed (arrowheads) in patients with CJD, without corresponding increases in [¹⁸F]-AV-1451 retention. [¹⁸F]-AV-1451 retention was frequently observed within the choroid plexus and deep gray structures. Such off-target binding may have contributed to the qualitative appearance of focal (subcortical) retention in cases A and E. CJD = Creutzfeldt-Jakob disease; DWI = diffusion-weighted image; FLAIR = fluid attenuated inversion recovery.

patients with CJD compared to CN persons or participants with AD.

All patients with CJD experienced rapid progression of dementia, with death due to CJD occurring within a median of 4.1 months (range, 2.2–6.9) after presentation to hospital. The median interval from [¹⁸F]-AV-1451 PET imaging to death was 1 month (range, 0.2–3.3). Neuropathologic analysis was performed in all cases (table 2 and figure 3). Characteristic spongiform changes, neuronal loss, and astrogliosis were the most prominent microscopic findings, corroborating the primary diagnosis of CJD. ADNC was a frequent but modest comorbidity (“low” ADNC in 4/5 cases [80%]; “intermediate” ADNC in 1 case²⁴ [20%]). No patient reported cognitive impairment preceding the onset of symptoms

attributed to CJD; thus, findings of ADNC were deemed compatible with “preclinical AD.” Additional findings included cerebral amyloid angiopathy in 3/5 cases (60%) and aging-related tau astrogliopathy within the mesial temporal lobe and basal forebrain of case E (1/5, 20%).

Discussion

No specific pattern of [¹⁸F]-AV-1451 retention was observed in patients with pathologically proven sporadic CJD. This finding is consistent with previous studies confirming that abnormal prion protein (PrP^{Sc}) deposition in sporadic CJD is not a risk factor for AD- or primary age-related tauopathy-like pathology²⁹ and with neuropathologic findings in patients

Figure 2 [^{18}F]-AV-1451 retention in AD- and CJD-specific regions of interest

Box/scatterplot showing [^{18}F]-AV-1451 SUVRs in AD- and CJD-specific regions of interest in patients with CJD (teal), CN persons (orange), and participants with AD dementia (blue). AD summary values were computed using an average of AD-specific regions of interest, including the left and right inferior temporal cortex, amygdala, entorhinal cortex, and lateral occipital cortices.²² CJD-specific regions of interest included areas commonly involved on neuropathology: the lateral occipital, caudal middle frontal, superior temporal, fusiform and pericalcarine cortices, and the thalami. AD = Alzheimer disease; CJD = Creutzfeldt-Jakob disease; CN = cognitively normal; SUVR = standardized uptake ratio value ratio.

with CJD reported in this study. This finding establishes that [^{18}F]-AV-1451 PET specificity is not compromised by profound elevations in soluble tau, or other alterations in cerebral metabolism (e.g., disruptions in MAO-B signaling reported to confound [^{18}F]-THK5351 PET tracer uptake³⁰) associated with rapidly progressive neurodegeneration, and further suggests that the [^{18}F]-AV-1451 PET tracer maintains good specificity for paired helical tau filaments observed in AD dementia.

AD features prominently in the differential diagnoses of patients with RPD who are referred to CJD surveillance centers.^{12,31} While the majority of CJD cases can be diagnosed using clinical algorithms and nonspecific diagnostic tests (e.g., diffusion-weighted magnetic resonance brain sequences), overlap may be observed in presenting symptoms, rates of progression, and clinical signs.³¹ Likewise, although the detection of marked elevations in CSF total-tau levels increases the likelihood of a CJD diagnosis,¹⁵ lower total-tau levels may be reported in patients with specific CJD molecular subtypes (e.g., MM-2, MV-2),³² while higher levels may be measured in patients with rapidly progressive AD.³³ In addition, elevations in phosphorylated tau may be found in the CSF of patients with CJD (beyond that expected in cognitively normal [CN] persons),^{34,35} impeding the interpretation of CSF tau measures in patients with RPD. Adding to the complexity, the high prevalence of AD in the elderly³⁶ increases the likelihood that ADNC may be incidentally detected in older patients with

RPD attributable to other causes, confounding interpretation of AD-specific biomarkers (i.e., A β -PET, and CSF A β and phosphorylated tau). Indeed, ADNC was identified in all patients with CJD in this study, and AD-specific CSF biomarkers were consistent with the preclinical stage of AD in the one patient (case A) in whom they were measured (i.e., low A β , normal phosphorylated tau). In vivo imaging of tau pathology has the potential to quantify the distribution and density of AD-associated tauopathy. In this way, tau-PET imaging may be used to distinguish patients with RPD attributable to AD from those with a more modest NFT burden, in whom AD is unlikely to account for the clinical presentation. This information may be even more helpful when interpreted together with other AD- and CJD-specific CSF biomarkers.^{34,37}

Recruitment of patients with RPD for specialized imaging studies presents numerous challenges, including the need to identify, characterize, and consent patients in a timely fashion, and the need to obtain investigations and maintain follow-up in patients with rapidly declining cognition and function. Nevertheless, imaging was completed according to established protocols in consecutively recruited CJD patients with very mild (CDR 0.5) to severe (CDR 3) dementia. All patients tolerated a minimal scan time of 20 minutes, affirming the tolerability of [^{18}F]-AV-1451 PET neuroimaging in patients with symptomatic dementia, and demonstrating that it is possible to enroll patients with RPD in neuroimaging studies.

Table 2 Histopathologic findings in sporadic CJD cases

Area	Neuronal loss	Gliosis	Spongiform change	Diffuse plaques	Cored plaques	Neuritic plaques	NFT	CAA	Final diagnoses
Case A									Sporadic CJD (MM-2 subtype); low ADNC (A1B1C0) ²⁴ ; mild-moderate CAA
Frontal	3	3	3	2	0	0	0	2-3	
Temporal	3	3	4	3	0	0	0	0	
Occipital	2-3	2-3	3	2	0	0	0	2-3	
MTL									
AH	0	0	0	0	0	0	1	0	
PHG	2	2	2	0	0	0	1	0	
Isocortex	2	2	3	2	0	0	3	2	
Striatum	0	0	2	0	0	0	1	0	
Thalamus	0	2	2	0	0	0	0	0	
Cerebellum	0	0	0	0	0	0	0	0	
Case B									Sporadic CJD (MM-2 subtype); intermediate ADNC (A2B2C1/2) ²⁴ ; mild-moderate CAA
Frontal	2-3	3	3-4	4	0	1	0	2	
Temporal	2-3	2-3	2	4	focal 3	2	2	0	
Occipital	3	3	4	4	0	0	0	2	
MTL									
CA4	0	0	0	2	0	1	1	0	
CA1/ subiculum	0	0	0	4	3	4	3-4	0	
PHG	0	0	0	4	2	3	3	0	
Isocortex						2-3	2-3		
Striatum	0	0	2	4	4	1	1	0	
Thalamus	2-3	3	2	focal 4	4	0	0	0	
Cerebellum	0	0	0	0	0	0	0	0	
Case C									Sporadic CJD (MM-1 subtype); low ADNC (A1B1C0) ²⁴
Frontal	3	3-4	3	3-4	0	0	1	0	
Temporal	2-3	2-3	3	3-4	0	0	1	0	
Occipital	2-3	2-3	2-3	3-4	0	0	0	0	
MTL									
AH	3	2	0	1	0	0	0	0	
PHG	3	3	2	4	0	0	1	0	
Striatum	3	4	3	0	0	0	1	0	
Thalamus	3	4	3	0	0	0	0	0	
Cerebellum	0	0	1	0	0	0	0	0	

Continued

Table 2 Histopathologic findings in sporadic CJD cases (*continued*)

Area	Neuronal loss	Gliosis	Spongiform change	Diffuse plaques	Cored plaques	Neuritic plaques	NFT	CAA	Final diagnoses
Case D									Sporadic CJD (VV-2 subtype); low ADNC (A1B1C0) ²⁴
Frontal	0	0	1	1	0	0	0	0	
Temporal	0	0	1	0	0	0	1	0	
Occipital	0	0	0	0	0	0	1	0	
MTL									
CA1	1	2–3	3	0	0	0	2 (focal 3)	0	
PHG	1–2	2	2	0	0	0	2 (focal 3)	0	
Striatum	3	4	4	0	0	0	1	0	
Thalamus	1	3	3	0	0	0	1	0	
Cerebellum	Gr 2	WM 2	Mol 2	0	0	0	0	0	
Case E									Sporadic CJD; low ADNC (A2B1C0) ²⁴ ; moderate CAA; mild ARTAG ^a
Frontal	2	3	3	4	3	0	0	2–3	
Temporal	2	2	2	2	3	1	1	2–3	
Occipital	1	1	1	2	3	0–1	0	3–4	
MTL									
CA4	0	2–3	1	0	0	0	0	0	
CA1/ subiculum	2–3/3	3	4	0	0	0	1	0–1	
PHG	3–4	3–4	4	4	2	0–1	1–2	0	
Striatum	3–4	3–4	3–4	0	0	0	0–1	0	
Thalamus	3	4	3	3	0	0; grains 2	0	0	
Cerebellum	Gr 2–3, DN 3	WM 3	Mol 2–3	0	0	0	0	0	

Abbreviations: ADNC = Alzheimer disease neuropathologic change; AH = Ammon's horn; ARTAG = aging-related tau astroglipathy; CA4/CA1 = cornu ammonis areas 4 and 1; CAA = cerebral amyloid angiopathy; CJD = Creutzfeldt-Jakob disease; DN = dentate nucleus; Gr = granular layer; Mol = molecular layer; MTL = mesial temporal lobe; NFT = neurofibrillary tangle; PHG = parahippocampal gyrus; WM = white matter.

1 = rare/minimal; 2 = sparse/mild; 3 = moderate; 4 = frequent/severe; all histologic samples are from the right hemisphere.

^a Case E also had mild ARTAG in the MTL and basal forebrain²⁸ and a rare ballooned neuron in the MTL (compatible with VV1 subtype of CJD).

An obvious advantage of the enrollment of patients with a universally fatal and rapidly progressive disease is the potential for a remarkably brief imaging-to-autopsy interval. Such a brief interval may allow detailed radiologic–pathologic correlations to be investigated under physiologic conditions, circumventing the theoretical limitations associated with autoradiographic studies using postmortem tissue. In vivo [¹⁸F]-AV-1451 PET retention patterns have previously been shown to recapitulate Braak histopathologic stages in individuals with and without symptomatic AD.³⁸ However, this finding (in vivo) has yet to be corroborated with neuropathology. Although regional increases in [¹⁸F]-AV-1451 PET retention in our small sample did not reliably identify neuropathologic regions of increased NFT deposition, future

studies enrolling larger numbers of older patients with RPD could establish the sensitivity of in vivo [¹⁸F]-AV-1451 PET imaging for the detection of ADNC in individuals with the earliest (preclinical) stages of AD.

This study was limited by the small sample size of patients with CJD and the even smaller number of patients with quantifiable tauopathy. As a result, it was not possible to rigorously evaluate the association between in vivo [¹⁸F]-AV-1451 retention and NFTs at autopsy. In addition, as sporadic CJD was identified as the primary cause of RPD in all cases, the utility of [¹⁸F]-AV-1451 PET imaging in differentiating patients with *other* causes of RPD could not be

Figure 3 Selected neuropathologic findings in patients with CJD

H&E stained sections (column I) show spongiform change (arrows, panel G)—coarse in case A (panel A, temporal cortex), fine in case B (panel D, occipital cortex), case C (panel G, striatum), case D (panel J, cerebellum), and case E (panel M, H&E $\times 40$, subiculum)—and astrogliosis (arrowheads, panel G) with variable anatomical distributions. Very rare neocortical balloon cells are present only in case E (arrow, panel M). IHC for β -amyloid peptide (column II; antibody 10D5) reveals diffuse amyloid plaques (arrowhead, panel E) and cored amyloid plaques (arrow, panel E); case A shows moderate diffuse plaques (panel B, temporal cortex); case B shows frequent diffuse and cored plaques (panel E, striatum); case C shows frequent diffuse plaques and no cored plaques (panel H, temporal cortex); case D shows only very rare diffuse plaques (panel K, temporal cortex); and case E shows frequent diffuse plaques and moderate cored plaques (panel N, frontal cortex). IHC for phosphorylated tau protein (column III; antibody PHF-1) highlights features of tauopathy: neurofibrillary tangles (arrows, panels C, F, and I), neuropil threads (arrowhead, panel C), and neuritic plaques (arrowhead, panel F). Tauopathy is modest in case A (panel C, inferior temporal isocortex), focally robust in case B (panel F, subiculum), almost absent in case C (panel I, parahippocampal gyrus); focally sparse to moderate in case D (panel L, CA1 area), and focally sparse in case E (panel O, parahippocampal gyrus). Scale bar (panel A) is equivalent to approximately: 40 μ m (panel G); 100 μ m (panels E and M); 200 μ m (panels C, D, F, and J); 400 μ m (panels A, I, L, and D); and 1,000 μ m (panels B, H, K, and N). CJD = Creutzfeldt-Jakob disease; H&E = Hematoxylin & eosin; IHC = immunohistochemistry.

considered. [^{18}F]-AV-1451 PET imaging may be especially useful in the evaluation of patients with more slowly progressive variants of prion disease (e.g., variably protease-sensitive prionopathy³⁹ and specific subtypes of familial CJD⁴⁰), in whom the absence of restricted diffusion and predominance of cortical atrophy may mimic findings in AD dementia.

In conclusion, increased [^{18}F]-AV-1451 retention was not observed in patients with RPD due to sporadic CJD. Our results contribute to the emerging understanding that [^{18}F]-AV-1451 tau-PET is specific for paired helical tau filaments. Case series recruiting patients with additional causes of RPD are required to evaluate the clinical applications of in vivo [^{18}F]-AV-1451 PET imaging in patients with RPD.

Author contributions

G.S. Day participated in study design, provision of patient care, acquisition and interpretation of clinical and neuroimaging data, statistical analysis, and drafting, revision, and finalization of the manuscript. B.A. Gordon participated in interpretation of neuroimaging data, statistical analysis, and drafting, revision, and finalization of the manuscript. R.J. Perrin participated in acquisition and interpretation of neuropathologic data, and drafting, revision, and finalization of the manuscript. N.J. Cairns participated in acquisition and interpretation of neuropathologic data, and revision and finalization of the manuscript. H. Beaumont participated in interpretation of neuroimaging data, and revision and finalization of the manuscript. K. Schwetye participated in acquisition and interpretation of neuropathologic data, and revision and finalization of the manuscript. C. Ferguson participated in acquisition and interpretation of neuropathologic data, and revision and finalization of the manuscript. N. Sinha participated in acquisition and interpretation of neuropathologic data, and revision and finalization of the manuscript. R. Bucelli participated in patient care, acquisition of clinical data, and revision and finalization of the manuscript. E.S. Musiek participated in patient care, acquisition of clinical data, and revision and finalization of the manuscript. N. Ghoshal participated in patient care, acquisition of clinical data, and revision and finalization of the manuscript. M.R. Ponisio participated in patient care, acquisition of imaging data, and revision and finalization of the manuscript. B. Vincent participated in acquisition and interpretation of neuropathology data, and revision and finalization of the manuscript. S. Mishra participated in interpretation of neuroimaging data, and revision and finalization of the manuscript. K. Jackson participated in acquisition of neuroimaging data, and revision and finalization of the manuscript. J.C. Morris participated in interpretation of clinical and neuroimaging data, and revision and finalization of the manuscript. T.L.S. Benzinger participated in acquisition and interpretation of neuroimaging data, and revision and finalization of the manuscript. B.M. Ances participated in study design, interpretation of clinical data, acquisition and interpretation of neuroimaging data, and revision and finalization of the manuscript. Dr. Ances had full

access to all of the data and takes responsibility for the integrity of the data and the accuracy of the conclusions.

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In vivo [^{18}F]-AV-1451 tau-PET imaging in sporadic Creutzfeldt-Jakob disease

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Study question

Do patients with sporadic Creutzfeldt-Jakob disease (CJD) have a specific pattern of [^{18}F]-AV-1451 tracer retention?

Summary answer

Patients with sporadic CJD do not have a distinctive pattern of [^{18}F]-AV-1451 retention.

What is known and what this paper adds

[^{18}F]-AV-1451 PET is useful for the antemortem diagnosis of slowly progressing neurodegenerative dementing disorders such as Alzheimer disease (AD). However, this study shows that it lacks similar utility for CJD, a common cause of rapidly progressing dementia.

Participants and setting

The study examined five patients with sporadic CJD who presented to the Barnes-Jewish Hospital in St. Louis between November 2015 and August 2016. The study also obtained data for eight participants with very mild AD and 44 healthy controls who participated in longitudinal studies at another institution in St. Louis.

Design, size, and duration

All subjects underwent [^{18}F]-AV-1451 PET. CJD diagnoses were confirmed via autopsy.

Primary outcomes

The primary outcome was the average [^{18}F]-AV-1451 standardized uptake value ratio (SUVR) within regions comprising AD summary measures.

Main results and the role of chance

Visual inspection of [^{18}F]-AV-1451 PET images revealed no CJD-specific pattern of [^{18}F]-AV-1451 retention. [^{18}F]-AV-1451 SUVRs in patients with CJD (median, 1.17; range, 1.08–1.36) were indistinguishable ($p = 0.6$) from those in healthy controls (median, 1.14; range, 0.84–1.54) but significantly ($p < 0.01$) lower than those in individuals with AD (median, 2.23; range, 1.60–3.04). The patients with CJD did

not have significantly greater [^{18}F]-AV-1451 retention than the healthy controls in any of 46 measured brain regions.

Bias, confounding, and other reasons for caution

The study's major limitation was that it included very few patients with CJD. This precluded any analysis of the association between [^{18}F]-AV-1451 retention and specific tauopathic features in CJD, and subtle differences between patients with CJD and controls may not have been detected.

Generalizability to other populations

Rapidly progressing dementia can result from conditions other than sporadic CJD, and this study's results may not be generalizable to persons with the other subacute progressive conditions.

Study funding/potential competing interests

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