18FDG PET-CT in sporadic Creutzfeldt-Jakob disease, correlated with MRI and histology

ABSTRACT
We present a case of sporadic Creutzfeldt–Jakob disease with profoundly abnormal 18fluoro-deoxy-glucose positron emission tomography with computed tomography (FDG PET-CT) at an early stage, and correlate this with the clear findings at magnetic resonance imaging and also postmortem histology. Prion diseases are rare but important causes of cognitive impairment. The role of FDG PET-CT is discussed, along with other investigations such as electroencephalography and cerebro-spinal fluid analyses.

Keywords: Dementia, magnetic resonance imaging, positron emission tomography, prion diseases

INTRODUCTION
Sporadic Creutzfeldt–Jakob disease (sCJD) is the most common prion disease. Although it is a very rare cause of cognitive impairment, it is an important diagnosis, particularly in the context of increasing use of positron emission tomography (PET) to characterize dementias. Clinical and radiological features are variable. Cerebral cortical 18F-fluorodeoxyglucose (FDG) uptake is affected and there can also be particular magnetic resonance (MR) features that may help establish the diagnosis, in addition to electroencephalography (EEG), cerebrospinal fluid (CSF) analysis, and histology.

CASE REPORT
A 66-year-old female retired cook and housekeeper presented with mild cognitive impairment and spatial agnosia that interfered with driving. Within 10 months, this had progressed to spatial disorientation causing disabling anxiety, with emotional lability and poverty of speech. Over the same time her Mini-Mental State score fell from 29 (out of 30) to 5. No motor features were present during this early phase. She was referred for radiology, including MR imaging (MRI) and FDG PET with computed tomography (PET-CT).

CT and structural MRI of her brain were unremarkable, with no significant parenchymal volume loss. However, MR diffusion-weighted imaging showed extensive cortical diffusion-restriction. FDG PET-CT showed a marked reduction of cerebral cortical uptake, with irregular and extensive distribution, showing some correspondence to diffusion restriction. The MRI findings and FDG-uptake in both the basal ganglia and cerebellum were normal.

In this case, the bilateral and extensive cortical abnormalities, in combination with the progressive subacute history were sufficient to diagnose prion disease. (The differential diagnosis for cortical diffusion-restriction includes focal

Nicholas C. D. Morley, Monika Hofer1, Philip Wilkinson2, Kevin M. Bradley
Departments of Radiology and 1Neuropathology, Oxford University Hospitals NHS Foundation Trust, 2Department of Psychiatry, University of Oxford, Oxford, United Kingdom

Address for correspondence: Dr. Nicholas C. D. Morley, Velindre Cancer Centre (X-Ray Department), Cardiff CF14 2TL, United Kingdom.
E-mail: morleyn1@cardiff.ac.uk

Submitted: 11-Jan-2021 Revised: 09-Feb-2021
Accepted: 07-Mar-2021 Published: 12-Oct-2021

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Morley NC, Hofer M, Wilkinson P, Bradley KM. 18FDG PET-CT in sporadic Creutzfeldt-Jakob disease, correlated with MRI and histology. World J Nucl Med 2021;20:411-3.
seizures, infarction, encephalitis and prion diseases, among others. Her EEG was abnormal but not diagnostic. CSF testing was not performed.

She was managed supportively until her death 3 years later, when her family agreed to postmortem examination and brain bank donation. Histopathology showed widespread spongiform change in the cerebral cortex associated with accumulations of abnormal prion protein in a perivascular distribution, diagnostic of CJD. The case was referred to the national surveillance unit for further characterization. Gene sequencing showed codon 129 heterozygosis (MV) and Western blot identified proteinase resistant prion protein Type 2A, i.e., MV2, a relatively rare subtype. There were no pathogenic gene mutations. Cerebellar "kuru-type plaques," described as characteristic in MV2 cases, were not seen, although cerebellar prion deposits were present.

**DISCUSSION**

Cognitive impairment is a common presentation with a wide differential diagnosis. In addition to more common dementia syndromes, it can be a presenting feature of psychiatric disorder or as a secondary feature of conditions such as sepsis, hepatic failure, tumor, or hematoma. Prion diseases are a rare cause of cognitive impairment. Although they all feature the progressive and self-propagating denaturation of the prion protein, they are a heterogeneous set of diseases. CJD is the most common, affecting about one-per-million people worldwide and 85% of cases are sporadic (Variant CJD is perhaps better known, being related to zoonotic transmission in meat-products). sCJD cases have been subdivided on the basis of phenotype and molecular biology, specifically the common methionine or valine polymorphism at codon 129 in the PRNP gene (MM, MV, or VV), and by the electrophoretic mobility of pathological prion protein detected at Western blot (type 1 or 2). The clinical and neuropathological features can be diverse. Once clinical features are present, EEG is usually abnormal, and may include periodic sharp wave complexes that can be diagnostic. Detection of protein 14-3-3 in the CSF can also be useful for diagnosis, while other biomarkers such as tau, neuron-specific enolase, S100B, α-synuclein and neurofilament light chain protein may also be abnormal but are less specific. There are exciting reports of greater sensitivity and specificity with the newly available real-time quaking-induced conversion assay (RT-QuIC), to detect the misfolded prion protein itself (PrPSc) including detection from olfactory mucosa and skin samples.

In keeping with the complexity of the clinical features, radiological findings are also variable and sometimes lack typical...
features. Irregular deficits of cortical FDG uptake are described in case-series,[11‑18] and prior studies have also discussed the sometimes discordant FDG and MRI findings[12,17‑19] although histopathological confirmation is often incomplete. These studies also report basal ganglia lesions in many cases. The MV2 subtype of sCJD is recognized as particularly difficult, and the basal ganglia are commonly affected on MRI,[14] though they were preserved in this case. More generally, the imaging of prion diseases was well reviewed by Macfarlane et al., in 2007.[25] There are also more recent reports of imaging with other PET tracers such as translocator protein (TSPO) ligands, dueterodeprenyl PET for microglial activation, florbetaben for amyloid deposition and oxygen-15 water for blood flow,[20‑23] and a report correlating FDG PET with cerebral blood flow measured by MR arterial spin labeling.[24]

As in this case, multimodal neuroimaging can form an important part of the investigation of suspected prion disease, by detecting the combination of cortical diffusion-restriction and hypometabolism. Although treatments are currently limited, improvement in diagnosis may help to identify candidates for therapeutic trials. It is also important to consider sCJD as a rare but important differential diagnosis when investigating cognitive impairment with FDG PET-CT.

Financial support and sponsorship Nil.

Conflicts of interest There are no conflicts of interest.

REFERENCES

1. Folstein MF, Folstein SE. Mini-mental state. A grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189‑98.
2. Macfarlane RG, Wroe SJ, Collinge J, Yousry TA, Jäger HR. Neuroimaging findings in human prion disease. J Neurol Neurosurg Psychiatry 2007;78:664‑70.
3. Sheerin F, Pretorius PM, Briley D, Meagher T. Differential diagnosis of restricted diffusion confined to the cerebral cortex. Clin Radiol 2008;63:1245‑53.
4. Krasnianski A, Schulz-Schaeffer WJ, Kallenberg K, Meissner B, Collie DA, Roebert S, et al. Clinical findings and diagnostic tests in the MV2 subtype of sporadic CJD. Brain 2006;129:2288‑96.
5. Liao YU, Lebo RV, Clawson GA, Smuckler EA. Human prion protein cDNA: Molecular cloning, chromosomal mapping, and biological implications. Science 1986;233:364‑7.
6. Parchi P, Giese A, Capellari S, Brown P, Schulz-Schaeffer W, Windl O, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol 1999;46:224‑33.
7. Steinhoff BJ, Räcker S, Herrendorf G, Poser S, Grosche S, Zerr I, et al. Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Arch Neurol 1996;53:162‑6.
8. Sanchez-Juan P, Green A, Ladogana A, Cuadrado-Corrales N, Sánchez-Valle R, Mitrová E, et al. CSF tests in the differential diagnosis of Creutzfeldt-Jakob disease. Neurology 2006;67:637‑43.
9. Green AJ. RT-QuIC: A new test for sporadic CJD. Pract Neurol 2019;19:49‑55.
10. Ascari LM, Rocha SC, Gonçalves PB, Vieira TC, Cordeiro Y. Challenges and advances in antemortem diagnosis of human transmissible spongiform encephalopathies. Front Bioeng Biotechnol 2020;8; https://doi.org/10.3389/fbioe.2020.585896.
11. Henkel K, Zerr I, Hertel A, GratzKF, Schröter A, Tschampa HJ, et al. Positron emission tomography with [18F] FDG in the diagnosis of Creutzfeldt-Jakob disease (CJD). J Neurol 2002;249:699‑705.
12. Renard D, Castelnovo G, Collombier L, Thouvenot E, Boudouss V. FDG-PET in Creutzfeldt-Jakob disease: Analysis of clinical-PET correlation. Prion 2017;11:440‑53.
13. Prieto E, Dominguez-Prado I, Riverol M, Ortega-Cubero S, Ribelles MJ, Luquin MR, et al. Metabolic patterns in prion diseases: An FDG PET voxel-based analysis. Eur J Nucl Med Mol Imaging 2015;42:1522‑9.
14. Kim EJ, Cho SS, Jeong BH, Kim YS, Seo SW, Na DL, et al. Glucose metabolism in sporadic Creutzfeldt-Jakob disease: A statistical parametric mapping analysis of (18) F-FDG PET. J Eur Neurol 2012;19:488‑93.
15. Hamaguchi T, Kitamoto T, Sato T, Mizusawa H, Nakamura Y, Noguchi M, et al. Clinical diagnosis of MM2-type sporadic Creutzfeldt-Jakob disease. Neurology 2005;64:643‑8.
16. Kilic AK, Kaymakamzade B, Saka E, Tan E. The sole initial imaging finding in Creutzfeldt-Jakob disease: Focal FDG-PET hypometabolism. Noro Psikiyatr Ars 2019;56:226‑8.
17. Mente KP, O’Donnell JK, Jones SE, Cohen ML, Thompson NR, Bizzi A, et al. Fluorodeoxyglucose positron emission tomography (FDG-PET) correlation of histopathology and MRI in prion disease. Alzheimer Dis Assoc Disord 2017;31:1‑7.
18. Xing XW, Zhang JT, Zhu F, Ma L, Yin DY, Jia WQ, et al. Comparison of diffusion-weighted MRI with 18F-fluorodeoxyglucose-positron emission tomography/CT and electroencephalography in sporadic Creutzfeldt-Jakob disease. J Clin Neurosci 2012;19:1354‑5.
19. Renard D, Vandenberghe R, Collombier L, Kotzki PO, Pouget JP, Boudouss V. Glucose metabolism in nine patients with probable sporadic Creutzfeldt-Jakob disease: FDG-PET study using SPM and individual patient analysis. J Neurol 2013;260:3055‑64.
20. Iaccarino L, Moresco RM, Presotto L, Bugiani O, Iannaccone S, Giaccone G, et al. An in vivo 11C-(R)-PK11195 PET and in vitro pathology study of microglia activation in Creutzfeldt-Jakob disease. Mol Neurobiol 2018;55:2856‑68.
21. Engler H, Lundberg PO, Ekborn K, Nennesmo I, Nilsson A, Bergström M, et al. Multitracer study with positron emission tomography in Creutzfeldt-Jakob disease. Eur J Nucl Med Mol Imaging 2003;30:85‑95.
22. Engler H, Nennesmo I, Kumlien E, Gambini JP, Lundberg PO, Savictheva I, et al. Case report imaging astrocytosis with PET in Creutzfeldt-Jakob disease: Case report with histopathological findings. J Clin Exp Med 2012;5:201‑7.
23. Matias-Guiu JA, Guerrero-Márquez C, Cabrera-Martin MN, Gómez-Pinedo U, Romeral M, Mayo D, et al. Amyloid- and FDG-PET in sporadic Creutzfeldt-Jakob disease: Correlation with pathological prion protein in neuropathology. Prion 2017;11:205‑13.
24. Yuan J, Wang S, Hu W. Combined findings of FFDG-PET and arterial spin labeling in sporadic Creutzfeldt-Jakob disease. Prion 2018;12:310‑4.