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Case Report

^{18}FDG 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 ^{18}F-flourodeoxyglucose (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.[1] 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

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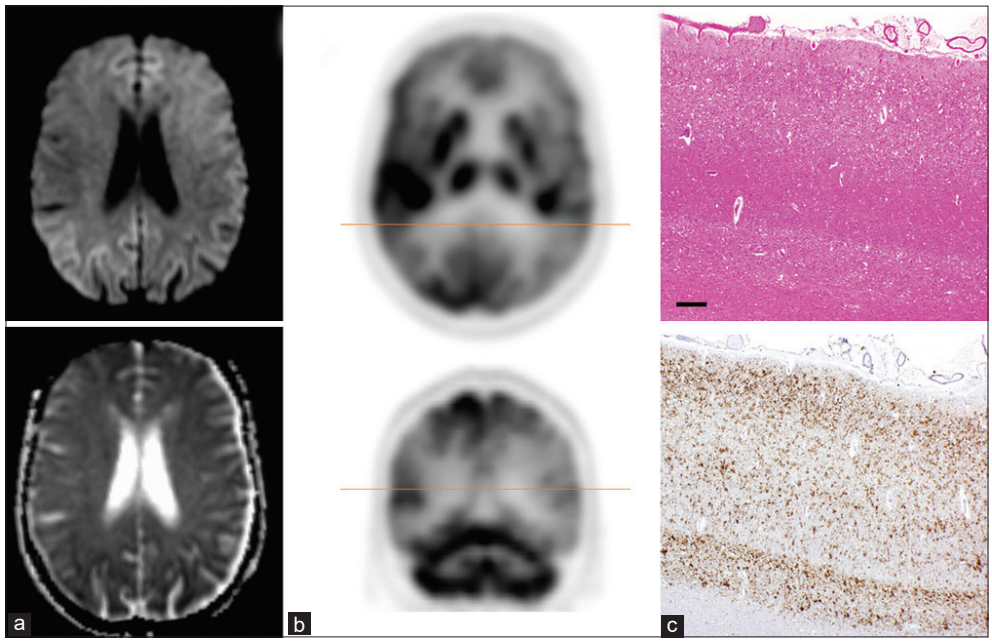

Figure 1: (a) Axial diffusion-weighted magnetic resonance imaging and apparent diffusion coefficient map, demonstrating increase in cortical signal on the diffusion-weighted sequence and corresponding decrease in apparent diffusion coefficient. This is cortical diffusion restriction. (b) Images from the 18fluoro-deoxy-glucose component of the positron emission tomography/computed tomography: An axial section at the level of the basal ganglia and a coronal section including the cerebellum. Both show heterogeneous marked reduction in cerebral cortical metabolism. 18Fluoro-deoxy-glucose uptake in cerebellar cortex is preserved (normally less avid than cerebral cortex). There is some more subtle hypometabolism affecting the left basal ganglia and thalamus. (c) Photomicrographs of sections of occipital cortex, the upper is stained with hematoxylin and eosin, and the lower with KG9 antibody following proteinase treatment. 20 μm scale bar. They show spongiform change in the striate cortex and proteinase resistant prion deposits

seizures, infarction, encephalitis and prion diseases, among others.[2,3] 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,[4] 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[5], 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,[6] 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.[7] Detection of protein 14-3-3 in the CSF can also be useful for diagnosis,[8] 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.[9,10]

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,[11-16] 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,[4] though they were preserved in this case. More generally, the imaging of prion diseases was well reviewed by Macfarlane *et al*., in 2007.[2] 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.

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Conflicts of interest

There are no conflicts of interest.

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