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Sporadic CJD in association with HIV

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Introduction

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive fatal neurodegenerative disorder. There are four subtypes: sporadic, familial, iatrogenic and variant. Most cases are sporadic (sCJD) due to spontaneous accumulation of abnormal prion protein, neuronal loss and spongiform changes (1,2). With an annual incidence of one per million (3), we report an unusual case of pathologically confirmed sCJD developing in a human immunodeficiency virus (HIV) positive patient but presenting with clinical and radiological features suggestive of variant CJD (vCJD).

Case presentation

A 63-year-old married black Zimbabwean moved to the United Kingdom in 2004. He was diagnosed with HIV in 2007 and immediately commenced on combination anti-retroviral therapy (cART) resulting in persistently undetectable viral load (HIV RNA < 40 copies/mL) and CD4 counts above 400 cells/ μ L. The patient was treated for hypertension, hypercholesterolaemia and type-2 diabetes mellitus, and had no significant family history.

Earliest symptoms date to August 2010 when he suffered from transient episodes of dizziness. By September he noticed difficulties with day-to-day episodic memory, decision making and driving. In November, paranoid delusions and vivid nightmares became apparent. His symptoms progressed over the subsequent 3 months to include obsessive-compulsive behaviour and visual hallucinations, such as seeing relatives who were still resident in Zimbabwe. One day in February 2011 he locked himself at home with extreme fear he was being chased. He continued to decline over the following month becoming doubly incontinent, somnolent and Zimmer-frame dependent. He was admitted to hospital in April 2011 following a tonic-clonic seizure.

He was disorientated in time and place and scored 7/30 on the Mini-Mental State examination (4). Eye movement examination revealed bilateral gaze evoked horizontal nystagmus. Rooting and grasp primitive reflexes were present. He had bradykinesia worse on the right, mild bilateral leg weakness, symmetrically present reflexes and extensor plantar responses. There were no signs of chorea, myoclonus or sensory disturbance. His gait was ataxic and apraxic.

Extensive investigations excluded an underlying autoimmune, endocrine, paraneoplastic or infective encephalitic process, including progressive multifocal leukoencephalopathy and HIV dementia complex (Table 1).

Blood tests revealed a mild iron deficient anaemia. Cerebrospinal fluid examination detected a slightly raised protein at 540 mg/dL, normal glucose, weakly positive 14-3-3 protein, elevated S-100 protein, and significantly elevated total-Tau protein at >1000 pg/ml. Electroencephalogram showed diffuse excess of slow activity. Magnetic resonance imaging (MRI) of brain revealed bilateral abnormal signal within the posterolateral thalami compatible with pulvinar sign and suggestive of vCJD (Figure 1) (5,6).

Further investigations at the MRC National Prion Unit-UCL revealed a negative tonsillar biopsy and positive blood test consistent with vCJD (7). Prion protein genotyping detected MV heterozygosity at codon 129.

He was eventually transferred to a nursing home and died from aspiration pneumonia 10 months after disease onset.

Post-mortem histopathological examination was consistent with sCJD, particularly in the absence of abnormal prion proteins in somatic organs including the spleen and lymphoreticular tissue in the appendix.

Conclusion

We describe an unusual presentation of CJD in a HIV-positive patient. Although MRI findings were suggestive of vCJD, the short residence in the UK and MV heterozygosity at codon 129 are atypical and the histopathological examination was consistent with sCJD (8,9).

A recent case was reported of a patient with chronic stable HIV developing sCJD (10). With only 2 cases reported so far, the association of CJD with HIV remains unclear. With estimated 36.7 million people currently living with HIV worldwide and annual incidence rate of CJD at one per million, the 2 reported cases do not raise concern about a causal link (11). With HIV becoming more controlled on ARV's, non-HIV related neurological presentations become more common.

Table 1. Results of relevant investigations

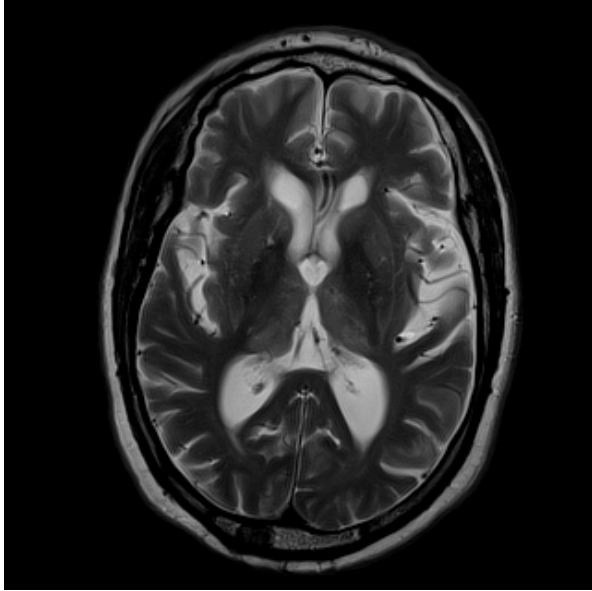
Test	Result (reference range)
Blood	
Ammonia	29 (16 - 60)
ANA (Hep2)	Negative
Anti-neuronal antibodies Hu, Ri, Yo	Negative
Anti-cardiolipin IgG	14.7 (0 - 15)
Caeruloplasmin	345 (220 - 400)
c ANCA	Negative
CD4 count	433
Copper	25 (11 - 20)
Creatinine Kinase	287 (30 - 170)
C-reactive protein	<5 - 61.8 (0 - 5)
Cryptococcal antigen	Negative
DRVVT Lupus Inhibitor	Not Demonstrated
Erythrocyte sedimentation rate	47 (0 - 15)
Haemoglobin A1c, %	7.6 (4 - 6)
Homocysteine	14.3 (5 - 15)
LDH	334 (240 - 480)
Lead	0.1 (0 - 1.4)
Mercury	4.0 (0 - 30)
NMDA receptor antibodies	Negative
p ANCA	Negative
Plasma porphyrins	Not detected
Prion blood test for vCJD	Positive
PRNP genotype	Codon 129 genotype was MV heterozygous
Prostate specific antigen	2.25 (0 - 4)
Red-cell porphyrins	Not in excess
Rheumatoid factor	10 (0 - 14)
Serum Protein Electrophoresis	
Paraprotein band	Not detected
Serum Total Protein	79 (66 - 87)
Immunoglobulin G	19.6 (6 - 16)
Immunoglobulin A	<0.1 (0.8 - 4)
Immunoglobulin M	0.3 (0.5 - 2)
Syphilis serology (VDRL)	Negative
T.brucei IFAT	Negative
Thiamine	418 (275 - 675)
Toxoplasma status	Negative
Vitamin B12	200 (197 - 866)
Voltage gated Ca ²⁺ channel antibodies	Negative
Voltage gated K ⁺ channel antibodies	Negative
Cerebrospinal fluid	
Acid fast bacilli	Not seen
Cryptococcal antigen	Negative
Cytology	No cells
Cytomegalovirus	Not detected
Enteroviruses	Not detected
Epstein Barr Virus	Not detected
Glucose	5.6 (2.2 - 3.9) (serum glucose 10.4)
Herpes simplex virus type 1	Not detected

Herpes simplex virus type 2	Not detected
JC Virus	Not detected
Microscopy and culture	No organisms seen
Mumps	Not detected
Nigrosin stain	No encapsulated yeast seen
Oligoclonal bands	Negative
Protein	540.8
Syphilis serology	Negative
Toxoplasma gondii	Negative
Varicella Zoster Virus	Not detected
Viral load	<40
WCC/RBC	<1
14-3-3	Weakly positive
S100 protein	1.17 (<0.38)
Tau protein	>1000
<hr/>	
Imaging	
Chest x-ray	No focal pulmonary collapse or consolidation.
CT Head	Mild ventricular and sulcal enlargement.
CT chest/abdomen/pelvis with contrast	No mass or significant adenopathy. Mild ureteric dilatation.
PET CT scan	No uptake consistent with hidden malignancy
MRI Head with gadolinium	A small amount of periventricular T2 FLAIR and T2 high signal within the central pons. Symmetrical abnormal high signal within the medial aspects of the thalami and the pulvinar. Appears confluent with the periventricular high signal extending into the centrum semi ovale. The mamillary bodies also appear hyperintense with signal changes within the tectal plate, central pons and peri aqueductal regions. These areas demonstrate high signal on the diffusion weighted images. These appearances are consistent with the pulvinar sign.
Scrotal ultrasound scan	Multiple small calcifications. No masses or evidence of a tumour.
Urinary tract ultrasound scan	No evidence of renal masses or obstruction.
Electroencephalography	Diffuse excess of slow activity.

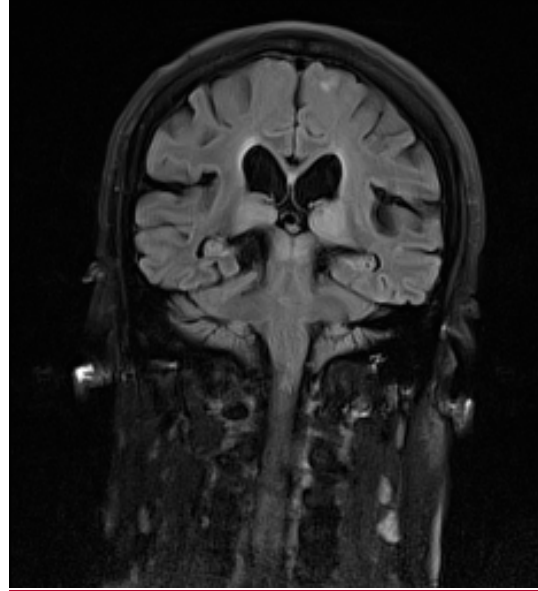
ANA, Antinuclear antibody; ANCA, Anti-Neutrophil Cytoplasmic Antibody; LDH, Lactate Dehydrogenase; M, C & S, Microscopy, Culture & Sensitivity; WCC, White Cell Count; RBC, Red Blood Cell count; CT, computed tomography; MRI, magnetic resonance imaging; PET, Positron Emission Tomography

Figure 1. MRI revealed high signal on FLAIR, diffusion weighted and T2 weighted imaging in the posterior and medial thalamus. There is abnormal signal in the caudate and posterior brain stem consistent with the pulvinar sign in CJD.

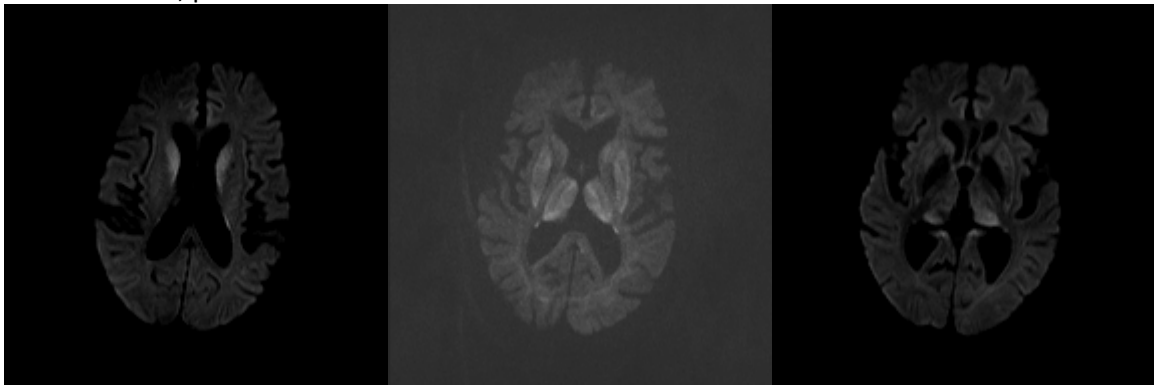
a) MRI head with Gadolinium: Axial T2 showing abnormal signal in the basal ganglia including the typical 'pulvinar' sign.



b) MRI head Coronal FLAIR sequence confirms signal change in the thalamic regions ('pulvinar' sign)



c) MRI diffusion weighted sequence depicts the extent of diffuse signal changes within the caudate nuclei, putamina and thalami.



References

1. The National CJD Research & Surveillance Unit. Creutzfeldt-Jakob Disease in the UK. <http://www.cjd.ed.ac.uk/documents/figs.pdf> (accessed on the 28th of September).
2. WHO: global surveillance, diagnosis, and therapy of human transmissible, spongi-form encephalopathies: report of a WHO consultation. World Health Organisation (WHO): emerging and other communicable disease, surveillance and control; February 9-11, 1998; Geneva, Switzerland. <http://www.who.int/csr/resources/publications/bse/whoemczdi989.pdf>
3. Ladogana A, Puopolo M, Croes EA, Budka H, Jarius C, Collins S, et al. Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. *Neurology*. 2005; 64(9):1586-1591.
4. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189–98.
5. Collie DA, Summers DM, Sellar RJ, Ironside JW, Cooper S, Zeidler, et al. *ANJR*. Diagnosing Variant Creutzeldt-Jakob Disease with the Pulvinar Sign: MR Imaging Findings in 86 Neuropathologically Confirmed Cases. 2003; 24:1560-1569.
6. Heath CA, Cooper SA, Murray K Diagnosing variant Creutzfeldt-Jakob disease: retrospective analysis of the first 150 cases in the UK. *J Neurol Neurosurg Psychiatry*. 2011; 82:646.
7. Jackson GS, Burk-Rafel J, Edgeworth JA, Sicilia A, Abdilahi S, Korteweg J, et al. A highly specific blood test for vCJD. *Blood*. 2014; 123(3): 452-453.
8. Knight R. Differential diagnosis of rapidly progressive dementia. *J Neurol Neurosurg Psychiatry*. 2010; 81:10.
9. The Revision of the Surveillance Case Definition for Variant Creutzfeldt-Jakob Disease (vCJD). World Health Organisation. WHO/CDS/CSR/EPH/2001.5. Geneva, Switzerland. 2001. whqlibdoc.who.int/hq/2002/WHO_CDS_CSR_EPH_2001.5.pdf
10. Babi MA, Kraft BD, Sengupta S, Peterson H, Orgel R, Wegermann Z, et al. Related or not? Development of spontaneous Creutzfeldt-Jakob disease in a patient with chronic, well-controlled HIV: A care report and review of the literature. *SAGE Open Medical Case Reports*. 2016; 4:1-6.
11. World Health Organisation – HIV Department. (2016) *Global summary of the AIDS epidemic*. Available at: http://www.who.int/hiv/data/epi_core_2016.png?ua=1 [Accessed on 4th of April 2017].