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SHORT COMMENTARY

Sporadic CJD in association with HIV

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Abstract

Background Creutzfeldt-Jakob disease (CJD) is a rapidly progressive fatal neurodegenerative disorder. We report an unusual case of pathologically confirmed sporadic CJD developing in a HIV-positive patient but presenting with clinical and radiological features suggestive of variant CJD.

Case presentation A 63-year-old man with chronic stable HIV developed progressive difficulties with decision-making, obsessive compulsive disorder and visual hallucinations over 3 months. CSF examination detected a weakly positive 14-3-3 protein, elevated S-100 protein, and siginificantly elevated total-Tau protein. Brain MRI revealed bilateral abnormal signal within the posterolateral thalami compatible with pulvinar sign. Further investigations revealed a negative tonsillar biospy and positive blood test consistent with variant CJD. However, prion protein genotyping detected MV heterozygosity at codon 129 and post-mortem histopathological examination was consistent with sporadic CJD.

Conclusion Although MRI findings were suggestive of variant CJD, the short residence in the UK and MV heterozygosity are aytpical, and the histopathological examination was consistent with sporadic CJD. With only two cases of HIV and sporadic CJD reported so far, the association of CJD with HIV remains unclear.

Keywords Creutzfeldt–Jakob disease · Human immunodeficiency virus

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 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).

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Case presentation

A 63-year-old married black Zimbabwean moved to the United Kingdom (UK) in 2004. He was diagnosed with HIV in 2007 and immediately commenced on combination antiretroviral therapy (cART) resulting in persistently undetectable viral load (HIV RNA < 40 copies/mL) and CD4 counts above 400 cells/μL. 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 walking-frame dependent. He was admitted to hospital in April 2011 following a tonic–clonic seizure.

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

Table 1 (continued)

Test	Result (reference range)
JC virus	Not detected
Microscopy and culture	No organisms seen
Mumps	Not detected
Nigrosin stain	No encapsulated yeast seen
Oligoclonal bands	Negative
Protein	54 (15–45)
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
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 periaqueductal 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 and sensitivity, *WCC* white cell count, *RBC* red blood cell count, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET* positron emission tomography

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 54 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 (Fig. 1) [5, 6].

Further investigations at the MRC National Prion Unit-UCL revealed a negative tonsillar biopsy and positive blood-based assay for the detection of vCJD prion infection that was shown to have a 70% sensitivity and 100% specificity for identifying vCJD [7, 8]. None of the blood samples collected from 27 sCJD patients as part of the control arm of the study by Edgeworth et al. tested positive, suggestive that the test may be specific for the variant form of CJD [8]. Prion protein genotyping detected MV heterozygosity at codon 129.

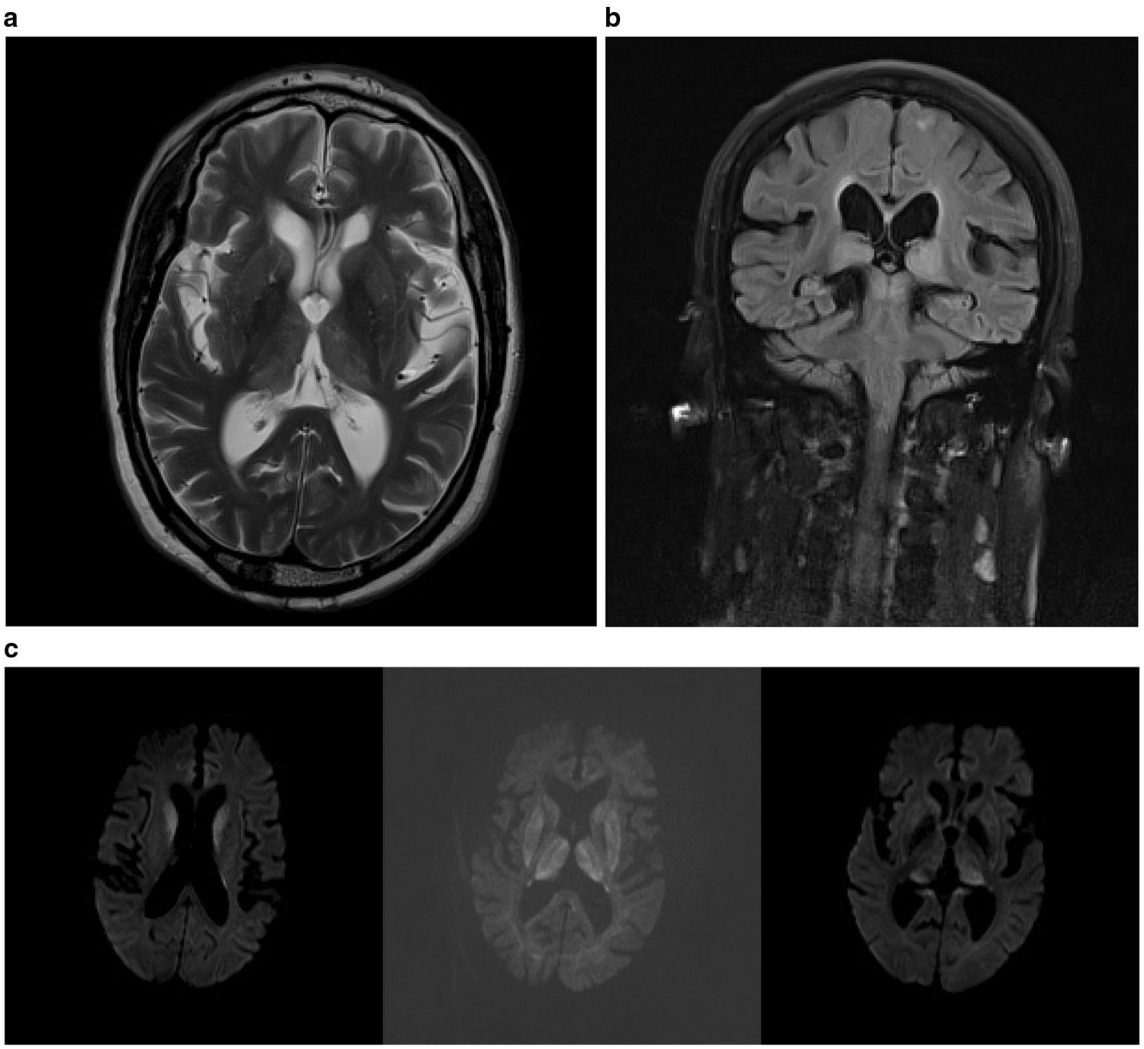

Fig. 1 MRI revealed high signal on FLAIR, diffusion-weighted and T2-weighted imaging in the posterior and medial thalamus. There is abnormal signal in the caudate and posterior brain stem consistent with the pulvinar sign in CJD. **a** MRI head with gadolinium: axial T2 showing abnormal signal in the 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

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. In the cortex, there were minimal and patchy spongiform changes most visible in the deeper cortical layers and mild widespread gliosis. In the white matter, there was diffuse widespread fibrillary gliosis. Immunohistochemical staining for abnormal prion protein showed that in the frontal and temporal cortices there were widespread strong diffuse labelling of neurons and very mild synaptic labelling in the deep cortical layers. In the parietal and occipital cortices, there were widespread perineuronal network labelling in the deeper cortical layers and multiple small prion protein plaques. The white matter was spared. In the cerebellum, there were mild spongiform changes, minimal gliosis and widespread strong deposition of prion protein in a synaptic pattern in the granular layer, as well as multiple plaques. The pituitary gland showed widespread immunolabelling for the abnormal prion protein. There was no immunohistochemical detection of the abnormal prion protein in the spleen, appendix, liver, small intestine or kidney.

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 [9, 10].

A recent case was reported of a patient with chronic stable HIV developing sCJD [11]. With only two 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 two reported cases do not raise concern about a causal link [12]. With HIV becoming more controlled on ARVs, non-HIV-related neurological presentations become more common.

Compliance with ethical standards

Conflicts of interest The authors report no disclosures relevant to this work.

Ethical approval No requirement for ethics committee review. The patient's wife has given approval for this case report to be submitted.

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