

Cardiomyopathy associated with Creutzfeldt–Jakob disease: a diagnosis of exclusion: a case report

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Background

Creutzfeldt–Jakob disease (CJD), the most common prion disease in humans, is primarily known for its adverse neurological impact and inevitable mortality. Data regarding myocardial involvement in CJD are scarce.

Case summary

A 54-year-old female patient, presented with progressive effort dyspnoea, was diagnosed with unexplained non-ischaemic cardiomyopathy. An extensive cardiac work-up including cardiac magnetic resonance imaging (MRI) did not reveal any underlying aetiology. Simultaneously, the patient developed involuntary limb movements and progressive cognitive decline. Thalamic high-signal abnormalities on diffusion-weighted images were apparent on brain MRI. Based on these findings, she was subsequently referred to a neurology department, where she suddenly died the day after her admission. Brain autopsy demonstrated spongiform encephalopathy. A genetic analysis performed to her son revealed a mutation in the PRNP gene; all of these were consistent with CJD.

Discussion

This case describes the clinical association of CJD and cardiomyopathy and the diagnosis prion-induced cardiomyopathy by exclusion. It is not inconceivable that the coexistence of these two clinical entities may be related to genetic expression and contemporaneously deposition of infectious prions in myocardial muscle and brain tissue. Awareness of this possible association could be of important public-safety concern, and merits further collaborative cardiac-neurological work-up to elucidate this phenotype among patients with unexplained cardiomyopathy with neurological symptoms that resemble CJD.

Keywords

Case reports • Creutzfeldt–Jakob disease • Cardiomyopathy • Prions • Left ventricular dysfunction

Learning points

- This case raises the possibility of a prion-induced cardiomyopathy.
- The deposition of infectious prions in human heart tissue with possible human transmission could be an important public health issue.

Introduction

The most common prion disease in humans is Creutzfeldt–Jakob disease (CJD) with its two major clinical manifestations: progressive mental deterioration and myoclonus.¹ Creutzfeldt–Jakob disease results from the accumulation in the brain of an abnormal beta-helical isoform (PrP^{Sc}) of the cellular prion alpha-helical protein

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(PrP^c) that is resistant to proteases and, therefore, forms a hydrophobic neurotoxic prion rod.¹ A mutation at codon 200 in PRNP, termed E200K, resulting in the substitution of lysine (K) for glutamate (E), was identified among Jews of Libyan origin, many of whom have immigrated to Israel over the years.^{2,3} Thus, the incidence of CJD, which is one case per million people per year in the general population, is increased 30–100-fold in certain geographic regions including Israel.²

Timeline

Six months prior to admission	Progressive symptoms of exertional dyspnoea, fatigue, and abnormal limb movements
Admission no. 1: Cardiac intensive care unit	Evaluation during admission: <ul style="list-style-type: none"> • Electrocardiogram: T-wave inversions at precordial leads • Cardiac monitoring: normal sinus rhythm and no arrhythmias • Echocardiography: moderate left ventricular (LV) dysfunction • Coronary angiography: non-obstructive coronaries • Cardiac magnetic resonance imaging (MRI): no cardiac abnormalities other than LV dysfunction
Following discharge	Progressive involuntary limb movements, insomnia, and cognitive decline
Admission no. 2: Neurology department	<ul style="list-style-type: none"> • Brain MRI demonstrated restriction of the diffusion in the thalamus manifested as high signal in diffusion weighted imaging • The patient experienced sudden death
Autopsy	Brain autopsy compatible with Creutzfeldt–Jakob disease

Case presentation

A 54-year-old Israeli female patient of Hungarian descent who worked as a fitness trainer was hospitalized in our cardiology department due to exertion dyspnoea. She had no cardiovascular risk factors, though her sister and father died from what was reported as sudden cardiac death at age 53 and 70 years, respectively. Six months prior to this, the patient had complained of fatigue, which was first attributed to an unresolved upper respiratory tract infection. Moreover, while at work, she experienced new symptoms of exhaustion and worsening effort dyspnoea. During the 6 weeks prior to her admission, she also had reported of ‘anxiety attacks’ and new onset of involuntary limb movements during her sleep. An ‘incidental’ electrocardiogram tracking revealed symmetrical T-wave inversions in L1, avL limb leads, and V2–V6 chest leads ([Supplementary material online, Figure S1](#)). She was then admitted for cardiac evaluation. On admission, the patient denied any chest pain, palpitation, or syncopal symptoms. Her physical and cardiovascular examinations were

unremarkable. Laboratory tests were all in normal range, including high-sensitive troponin levels in serial examinations. The chest X-ray was normal. Echocardiography ([Supplementary material online, Video](#)) demonstrated a non-dilated left ventricle with moderate global systolic dysfunction [LV ejection fraction (LVEF) 40%] with normal functioning valves. Coronary angiography performed the following day demonstrated non-obstructive coronary disease. Chest computed tomography did not reveal any signs for sarcoidosis or other chest pathology. Cardiac magnetic resonance imaging (MRI) was consistent with the echocardiographic findings showing moderate global LV dysfunction (LVEF 39%) with normal right ventricular function ([Figure 1](#)). Neither hypertrophy nor ventricular dilation was apparent. Other aetiologies of cardiomyopathy including non-compaction, Takotsubo, amyloid, hypertrophic cardiomyopathy, sarcoidosis, or myocarditis were ruled out ([Figure 2](#)). As our patient did not present with an acutely deteriorating heart failure suggesting giant-cell myocarditis or other myocardial disease that could be diagnosed only by myocardial tissue, an endomyocardial biopsy was not performed.⁴ The patient was discharged with heart failure-targeted treatment (bisoprolol 2.5 mg, ramipril 2.5 mg, and spironolactone 12.5 mg) and with a recommendation for future follow-up and avoidance of intensive physical activity.

A month later, she was readmitted elsewhere to a neurology department due to a progressive cognitive decline and involuntary limb movements. She also reported on new visual and auditory hallucinations. Characteristic ‘hockey stick’ shape of restricted diffusion in the thalamus was demonstrated on diffusion weighted imaging brain MRI ([Figure 3](#)). The next morning, she was found in cardiac arrest in her bed. Cardiac resuscitation attempt was unsuccessful. A post-mortem pathological examination of the brain was carried out.

Autopsy brain exam

The formalin-fixed brain weighed 1550 g and was unremarkable on macroscopic examination. On microscopic examination of representative samples, an extensive spongiform change involving all cortical regions examined, with areas of relatively large confluent vacuoles, while the hippocampus was relatively preserved. There was reactive gliosis, most prominent in superficial cortical layers of the neocortex, as well as entorhinal cortex, and CA3 and CA4 areas of the hippocampus. The most prominent spongiform change was found in the thalamus with relatively large confluent vacuoles, associated with substantial cellular gliosis. There was no significant inflammatory infiltrate in the samples examined. Immunohistochemical stain for PrP^{sc}, performed on samples from the thalamus and cerebral cortex, demonstrated a coarse staining pattern, mainly in areas of spongiform change, associated with occasional perivascular staining pattern. No brain tissue was immunostained for amyloid plaques. The neuropathology diagnosis was spongiform encephalopathy consistent with CJD.

Genetic evaluation

Unfortunately, the patient did not undergo a genetic evaluation. Her only son underwent a complete genetic exam a year after his mother death. The PRNP gene was molecularly evaluated. A heterozygotal change was noted at the PRNP gene, exon 2: c.598G>A(het); p.Glu200Lys rs28933385. This mutation is known as E200K mutation.

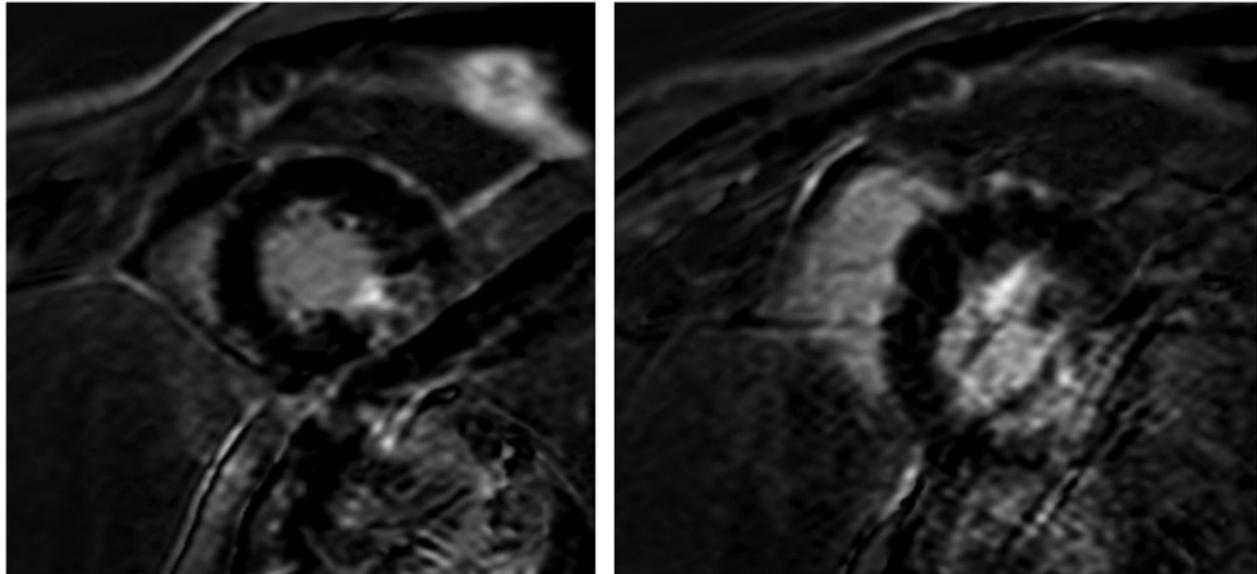


Figure 1 Cardiac magnetic resonance imaging revealing moderate systolic global left ventricular dysfunction. Measurements were based on the calculation of left ventricular ejection fraction (39%) according to the Simpson method (end diastolic volume 125 mL and end systolic volume 76 mL).

Diagnostic work-up algorithm

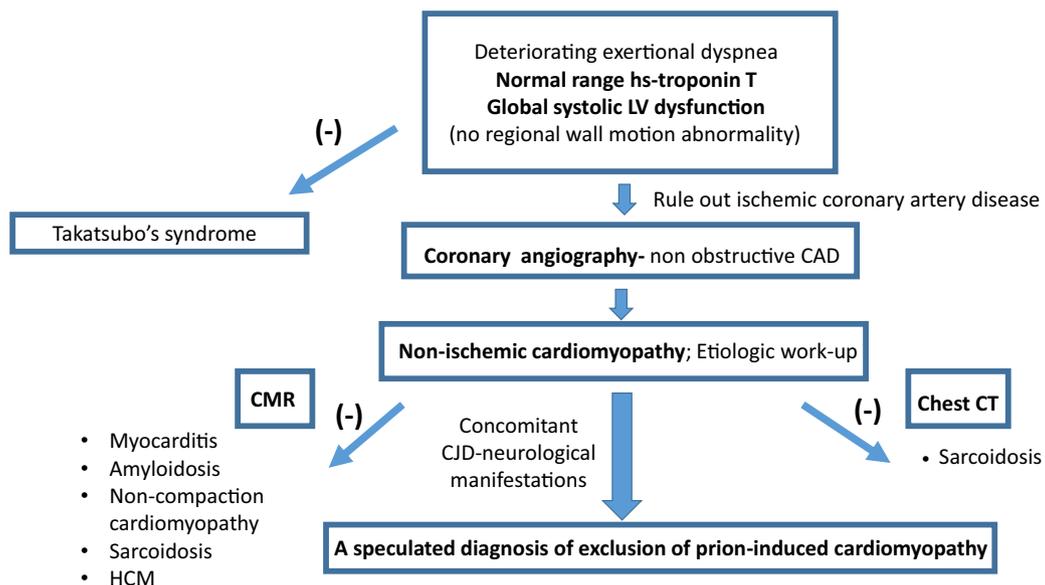


Figure 2 Diagnostic work-up algorithm describing prion-induced cardiomyopathy as a diagnosis of exclusion. CAD, coronary artery disease; CJD, Creutzfeldt–Jakob disease; CMR, cardiac magnetic resonance; CT, contrast tomography; HCM, hypertrophic cardiomyopathy; hs, high sensitive; LV, left ventricular.

Discussion

Tissue damage in prion diseases, including CJD, mainly involves the central nervous system. Nevertheless, the accumulation of PrP^{Sc} and

prion infectivity is not necessarily confined to neural tissues,⁵ and numerous studies have demonstrated the invasion of prions to the lymphoreticular system both in animal models⁶ and humans.^{6–8} Moreover, using highly sensitive methods of detection, Glatzel *et al.*⁵

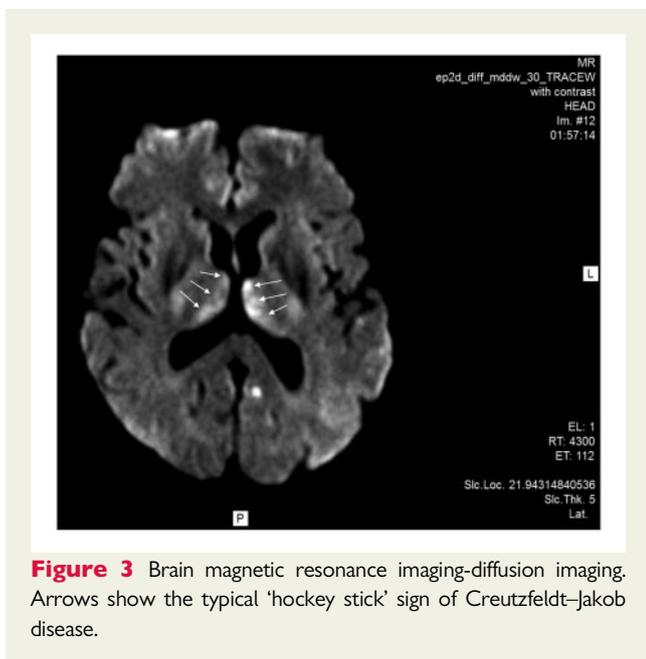


Figure 3 Brain magnetic resonance imaging-diffusion imaging. Arrows show the typical 'hockey stick' sign of Creutzfeldt-Jakob disease.

were able to identify extra-neural deposition of PrP^{Sc} in skeletal muscle samples of CJD patients. Scrapie-infected transgenic mice expressing prion protein lacking the glycol-phosphatidylinositol membrane anchor develop infectious cardiac amyloidosis with high levels of PrP^{Sc} along with myocardial stiffness.⁹ Moreover, PrP^{Sc} was detected in the heart tissue of bovine spongiform encephalopathy (BSE)-infected non-human primates,¹⁰ and in a BSE-infected macaque with a prion-amyloid cardiomyopathy, where PrP^{Sc} was deposited as amyloid across large stretches of heart tissue, reaching 1/100 of the amount seen in brain tissues.¹¹ In view of the legitimate obstacles in obtaining heart autopsy in post-mortem CJD patients, a substantial lack of pathological data regarding cardiac involvement in prion diseases is expected. However, PrP^{Sc} has been reported in the heart of one CJD patient.¹² Ashwath *et al.* reported on a female patient with sporadic CJD who had dilated cardiomyopathy with simultaneous rapid cardiac and neurologic decline. Following the implementation of special tissue preparation, an accumulation of abnormally folded prion protein in the heart muscle was detected. Pathophysiologically, PrP^C, expressed in cardiac muscle tissues has a protective role against programmed cell and oxidative stress,¹³ thus its conversion to its PrP^{Sc} isoform could possibly promote the development of cardiomyopathy. Nevertheless, results published by others failed to detect PrP^{Sc} in either CJD heart tissues^{14,15} or human amyloid hearts.^{14,16}

Our report describes an enigmatic case of a female patient with a newly diagnosed non-ischaeamic cardiomyopathy who was almost simultaneously diagnosed with CJD. The diagnosis of CJD was made by post-mortem brain biopsy, the gold-standard diagnostic tool for prion diseases.¹ A genetic testing was not performed. Nevertheless, both the patient's son and the patient's unborn grandchild (based on pre-implantation genetic diagnosis following *in vitro* fertilization) were later diagnosed as carriers for the same E200K CJD mutation. Unfortunately, due to healthcare providers' legitimate concerns, an autopsy of the patient's heart was not performed, leaving the diagnosis of prion-induced cardiomyopathy solely speculative.

Nevertheless, as no other aetiology for the patient's cardiomyopathy was found on a comprehensive cardiac evaluation (including cardiac MRI), and due to the patient's simultaneous cardiac and neurologic presentations, it is plausible to suspect a prion-induced cardiomyopathy. Furthermore, although CJD is an incurable disease, the deposition of infectious prions in human heart tissue with possible human transmission is an important public health issue, which deserves clinical awareness.

In conclusion, we present an interesting case of a patient with newly diagnosed CJD and cardiomyopathy given the diagnosis of exclusion of prion-induced cardiomyopathy. We further call for a multi-centre registry of such cases and for collaborative cardio-neuro research in order to shed light into the pathogenesis and disease progression of possible prion infiltration of the human heart.

Lead author biography



Osna Itzhaki Ben Zadok has specialized in internal medicine and is a cardiology fellow in the Rabin Medical Center in Israel.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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