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Case Report

CASE REPORT

A patient with sporadic Creutzfeldt–Jakob disease: challenges of rare diseases in the COVID-19 era

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Abstract

We describe a patient who presented to hospital during the coronavirus disease 2019 (COVID-19) pandemic with sporadic Creutzfeldt–Jakob disease (sCJD). The case demonstrates the typical clinical, radiological and laboratory features of this condition. It also highlights some of the challenges associated with diagnosis and care of patients with rare diseases such as sCJD, and how these have been intensified by COVID-19.

INTRODUCTION

Sporadic Creutzfeldt–Jakob disease (sCJD) is a rare but devastating cause of rapidly progressive neurological decline. Though the incidence is increasing [1], there are currently only about 100 cases per year in the UK, meaning most general physicians are unfamiliar with the disease. Making the diagnosis early is important for counselling the patient and their family, optimal management of symptoms and to avoid iatrogenic transmission. However, there is frequently delay in diagnosis [2, 3], due to a combination of its rarity as well as heterogeneity in the early stages of the disease [4]. We describe a patient with a typical neuropsychiatric presentation of sCJD, and some of the challenges in diagnosis and ongoing care exacerbated by the concurrent coronavirus disease 2019 (COVID-19) pandemic.

CASE REPORT

A previously independent 76-year-old lady was referred to hospital at the height of the COVID-19 pandemic, following a 6-week history of cognitive decline. Collateral history from her daughter described difficulty navigating around her own home and impairment in familiar tasks such as using cutlery. Over this period, her mood had been labile and she demonstrated psychotic features with intermittent lucid periods. These included delusions that her family was poisoning her and hallucinations of the room expanding and contracting.

She had a past medical history of rheumatic heart disease with paroxysmal atrial fibrillation, for which she took warfarin, as well as stable chronic kidney disease (Stage 3B). She also had a history of depression and had been commenced on sertraline 3 weeks previously following a telephone consultation in primary care.

On neurological examination, the patient was unsteady on her feet and had visual and tactile left-sided neglect. Her reflexes were brisk throughout and she exhibited startle myoclonus. During examination she had an inappropriate affect, giggling in response to questions, and her Abbreviated Mental Test Score was 5/10. Routine blood tests (Table 1) were normal, besides an elevated international normalized ratio (INR), which was attributed to a likely accidental overdose of her prescription warfarin in the context of confusion. Given the combination of high

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Table 1: Blood results at admission

Haemoglobin	152 g/L	[115–165 g/L]
White blood cell count	7.7 × 10^9/L	[4–11 × 10^9/L]
INR	9.9	[Target: 2–3]
Sodium	140 mM	[133–146 mM]
Potassium	4.2 mM	[3.5–5.3 mM]
eGFR	33 ml/min	[Baseline: 35 ml/min]
Alanine aminotransferase	20 U/L	[0–33 U/L]
Alkaline phosphatase	70 U/L	[30–130 U/L]
Calcium	2.53 mM	[2.2–2.6 mM]
Inorganic phosphate	1.00 mM	[0.8–1.5 mM]
TSH	1.76 mIU/L	[0.25–5 mIU/L]
Vitamin B12	>2000 ng/L	[197–771 ng/L]

Table 2: Differential diagnoses at initial presentation to hospital

Neurological	Subdural haematoma
	Alzheimer's or Lewy body dementia (combined with delirium, leading to rapid deterioration)
	Limbic encephalitis
	Cerebrovascular disease
	CNS neoplasm
	CNS infection (including COVID-19)
	Sporadic CJD
Systemic	Infection
	Electrolyte derangement
	Vitamin deficiency
	Inflammatory conditions: vasculitis, sarcoidosis, systemic lupus erythematosus
	Other systemic disease—hepatic, renal, thyroid
	Sertraline overdose leading to serotonin syndrome
Psychiatric	Depression
	First-episode psychosis
	Sertraline-induced mania
	Functional disorder

INR and progressive confusion, an urgent computed tomography head was carried out to exclude a subdural haematoma, and this was unremarkable. As she was apyrexial and without respiratory symptoms, she did not receive a polymerase chain reaction test for COVID-19. A broad range of differential diagnoses were considered at her initial presentation to hospital (Table 2).

Due to the neurological signs detected on examination, and no other cause being found for the patient's cognitive decline, a magnetic resonance imaging (MRI) head was performed (Fig. 1). This revealed a cortical ribboning pattern, which was hyperintense on diffusion-weighted imaging (DWI) and FLAIR sequences, along with increased signal in the right caudate nucleus. These changes, combined with her clinical presentation, were suspicious for CJD [5]. The predominance in the right cerebral hemisphere was consistent with her left-sided neglect. This patient was suspected to have sCJD, based on her clinical features and lack of family history or previous iatrogenic exposures.

Once the diagnosis of sCJD was suspected, the patient was referred to the National Prion Clinic (NPC) and the National CJD Research & Surveillance Unit (NCJDRSU). Due to COVID-19 measures, much of this communication was conducted remotely via video link, with input from local neurology and microbiology services.

Cerebrospinal fluid (CSF) analysis showed elevated protein and several additional special tests were requested to investigate the suspected diagnosis of sCJD (Table 3). Real-time quaking-induced conversion (RT-QuIC) measures the aggregation of misfolded prion proteins *in vitro*. This assay yields 80% sensitivity and close to 100% specificity for CJD [6], with only a handful of false positives reported in the literature [7]. 14-3-3 and S-100b are both proteins released during CNS damage, which are elevated in the CSF of patients with sCJD.

The patient deteriorated throughout her admission, losing the ability to transfer independently and perform personal care. At times, she was distressed by the nature of her hallucinations, which were treated with regular donepezil and occasional midazolam as required. With the combination of these medications she appeared less distressed, particularly overnight. The patient was discharged to a hospice where she sadly passed away ∼1 month after her initial presentation to hospital.

DISCUSSION

Effective diagnosis and care of a patient with a rare, rapidly progressive disease can be challenging at the best of times, and this has been amplified by the constraints of practising medicine with social distancing in place. As is common in the early stages of sCJD [8], this patient had prominent psychotic features and mood fluctuations, which led clinicians to initially suspect a psychiatric illness. A dramatic shift towards telephone consultations in primary care throughout early 2020 [9] likely contributed to this misdiagnosis, by delaying face-to-face assessment and neurological examination. Subsequent detection of

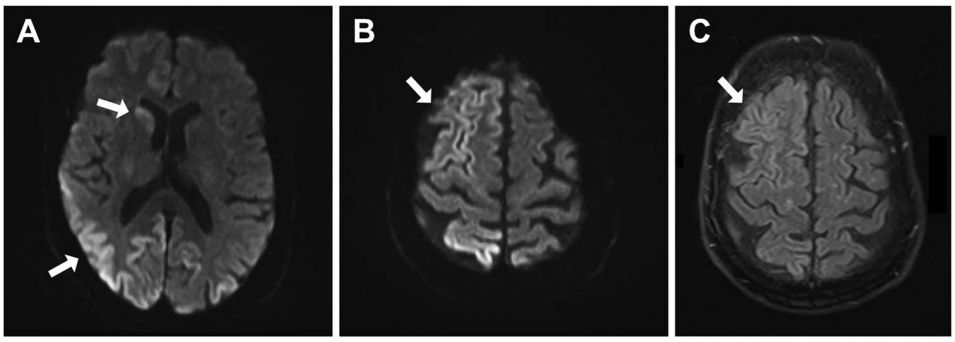

Figure 1: MRI head: DWI (A, B) showed high-intensity areas particularly affecting the right fronto-parietal cortex (cortical ribboning) and the right caudate nucleus. The areas in the right frontal cortex were also visible on FLAIR (C). The white arrows indicate the changes described.

Table 3: CSF analysis results

WBCs	1×10^6	[0–5 $\times$ 10^6 cells/L]
Protein	0.46	[0.15–0.40 g/L]
RT-QuIC	Positive	
14-3-3	Positive	
S-100b	0.49	[<0.41 ng/ml]

lateralizing sensory neglect and myoclonus on presentation to hospital prompted the crucial MRI scan.

Communication with relevant national centres was also hindered by COVID-19. While clinicians from NCJDRSU would ordinarily aim to assess the patient and counsel her family in person, this was not an option at the time. Instead, the neurological examinations were filmed for remote review, and relevant teams communicated with the family by video link. Similarly, it was decided that the additional diagnostic benefit of obtaining an electroencephalogram (EEG) was not sufficient to justify transferring the patient to a regional neurosciences centre. Perhaps most unfortunate in this case were the tight regulations on hospital visiting, which only allowed family members to see the patient once she was approaching end-of-life.

Since the emergence of COVID-19, there have been numerous reports of neurological syndromes directly related to the SARS-CoV-2 virus. While cerebrovascular events appear to be the most common neurological sequalae of infection, a UK nationwide collaboration has identified that encephalopathy and neuropsychiatric features can also be prominent [10]. COVID-19 was briefly considered as a differential diagnosis for our patient, however she did not display any other features of the disease and this suggestion was rejected following the convincing MRI and CSF results for sCJD. Interestingly, another case report recently hypothesized that co-infection with COVID-19 may accelerate progression of sCJD [11].

Unfortunately, prion diseases in humans are invariably fatal at present. Preclinical studies have demonstrated some success by inhibiting prion protein conversion, stimulating cellular degradation pathways or the use of immunotherapies [12]. However, these are yet to translate into disease-modifying therapies for patients. Various drugs, while not specifically licenced, do have efficacy for symptomatic management. Following discussion with the NPC, we initiated donepezil, which has some evidence for treating similar distressing hallucinations in Lewy body disease [13].

Given its increasing incidence within our ageing population [1], sCJD is an important differential diagnosis to consider for elderly patients presenting with what initially appears to be a psychiatric illness with rapid cognitive decline. This case highlights the additional challenges that the COVID-19 pandemic has brought to the timely diagnosis and effective care of patients with rare, devastating conditions such as sCJD.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

None required.

CONSENT

Written consent from patient's family.

GUARANTOR

Dr Solomon Ugoya is the Guarantor of this article.

REFERENCES

1. Uttley L, Carroll C, Wong R, Hilton DA, Stevenson M. Creutzfeldt-Jakob disease: a systematic review of global incidence, prevalence, infectivity, and incubation. *Lancet Infect Dis*. 2020;**20**:e2–e10. doi: 10.1016/S1473-3099(19)30615-2.
2. Manix M, Kalakoti P, Henry M, Thakur J, Menger R, Guthikonda B *et al*. Creutzfeldt-Jakob disease: updated diagnostic criteria, treatment algorithm, and the utility of brain biopsy. *Neurosurg Focus*. 2015;**39**:1–11. doi: 10.3171/2015.8.FOCUS15328.

3. Carswell C, Thompson A, Lukic A, Stevens J, Rudge P, Mead S *et al*. MRI findings are often missed in the diagnosis of Creutzfeldt-Jakob disease. *BMC Neurol*. 2012;**12**. doi: 10.1186/1471-2377-12-153.
4. Mead S, Rudge P. CJD mimics and chameleons. *Pract Neurol*. 2017;**17**:113–21. doi: 10.1136/practneurol-2016-001571.
5. Vitali P, Maccagnano E, Caverzasi E, Henry RG, Haman A, Torres-Chae C *et al*. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology*. 2011;**76**:1711–9. doi: 10.1212/WNL.0b013e31821a4439.
6. Atarashi R, Satoh K, Sano K, Fuse T, Yamaguchi N, Ishibashi D *et al*. Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion. *Nat Med*. 2011;**17**:175–8. doi: 10.1038/nm.2294.
7. Green AJE. RT-QuIC: a new test for sporadic CJD. *Pract Neurol*. 2019;**19**:49–55. doi: 10.1136/practneurol-2018-001935.
8. Krasnianski A, Bohling GT, Harden M, Zerr I. Psychiatric symptoms in patients with sporadic Creutzfeldt-Jakob disease in Germany. *J Clin Psychiatry*. 2015;**76**:1209–15. doi: 10.4088/JCP.13m08915.
9. Primary Care Domain, NHS Digital. *Appointments in General Practice* https://digital.nhs.uk/data-and-information/publications/statistical/appointments-in-general-practice/april-2020 (20 July 2020, date last accessed).
10. Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL *et al*. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry*. 2020;**7**:875–82. doi: 10.1016/S2215-0366(20)30287-X.
11. [11]Young MJ, O'Hare M, Matiello M, Schmahmann JD. Creutzfeldt-Jakob disease in a man with COVID-19: SARS-CoV-2-accelerated neurodegeneration? *Brain Behav Immun*. 2020;**S0889-1591**:31522-1. DOI:10.1016/j.bbi.2020.07.007.
12. Aguzzi A, Lakkaraju AKK, Frontzek K. Toward therapy of human prion diseases. *Annu Rev Pharmacol Toxicol*. 2018;**58**:331–51. doi: 10.1146/annurev-pharmtox-010617-052745.
13. Stinton C, McKeith I, Taylor JP, Lafortune L, Mioshi E, Mak E *et al*. Pharmacological management of Lewy Body Dementia: a systematic review and meta-analysis. *Am J Psychiatry*. 2015;**172**:731–42. doi: 10.1176/appi.ajp.2015.14121582 Epub 2015 Jun 18.