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Case Series

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Creutzfeldt-Jakob Disease: A Focused Literature Review and Retrospective Case Series of Five Patients from a Community Hospital

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Abstract

Many patients present to a neurologist due to rapidly progressive dementia (RPD). One rare etiology is Creutzfeldt–Jakob disease (CJD), a neurological disorder that occurs in one to two people per one million population. CJD is caused by abnormal folding of brain prions, and approximately 85% of cases are sporadic. Other presenting symptoms can include ataxia, myoclonus, hallucinations, and seizures, but CJD can have an atypical presentation as well.

Although most clinicians may only see one case during their career, we had a unique opportunity to study five patients with CJD in our community hospital. This report presents a focused literature review with up-to-date information and raises awareness of disease presentation, diagnostic testing, and differential diagnoses for patients with rapidly progressive dementia. Important workup for patients with RPD includes brain MRI, EEG, and CSF studies for 14-3-3, tau protein, and RT-QuIC.

Keywords

Creutzfeldt–Jakob Disease, Prion, Rapidly progressive dementia, Real-time quaking-induced conversion

Abbreviations

CDC: Centers for Disease Control and Prevention; **CJD**: Creutzfeldt–Jakob Disease; **CSF**: Cerebrospinal Fluid; **EEG**: Electroencephalography; **FLAIR**: Fluid Attenuated Inversion Recovery; **MRI**: Magnetic Resonance Imaging; **NPDPSC**: National Prion Disease Pathology Surveillance Center; **PRPSC**: Protease-Resistant Prion Protein; **RPD**: Rapidly Progressive Dementia; **RT-QuIC**: Real-Time Quaking-Induced Conversion

Introduction

Creutzfeldt–Jakob disease (CJD) is a rare neurological disease, believed to occur when normal prion proteins in the brain spontaneously misfold into abnormal prions [1, 2]. The classic clinical triad is rapidly progressive dementia (RPD), ataxia, and myoclonus [3, 4], although the disease can present in a variety of ways, making it difficult to diagnose [5]. Patients who decline over weeks to months are considered to have RPD, in contrast to patients who decline over a few years due to slowly progressive dementias [6]. Approximately 85% of CJD cases are sporadic; there are also hereditary and variant forms [4]. Sporadic CJD occurs worldwide at an approximate rate of 1 to 2 cases per 1 million people per year [1, 7]. The average age of onset is 61 years of age, peak age of onset ranges from 55 to 75 years [4], and risk appears to increase with age [1]. Per

the Centers for Disease Control and Prevention (CDC), a definitive diagnosis requires brain biopsy positive for abnormal protease-resistant prion protein (PrPSc) [8]. However, a probable diagnosis can be made using clinical features in conjunction with laboratory tests, brain magnetic resonance imaging (MRI), and/or electroencephalography (EEG) [8]. In cases of sporadic CJD, changes are best seen on the diffusion-weighted imaging (DWI) sequence on MRI. These can include bilateral hyperintensities in the cerebral cortex, caudate, and putamen; cortical ribboning in the DWI has a sensitivity of 92% [7]. Results from a study published in 2020 using updated MRI criteria report sensitivity of 90 to 95% and specificity 90 to 100% [9]. Historically, researchers obtained cerebrospinal fluid (CSF) brain-derived proteins such as 14-3-3 and tau to aid in diagnosis. However, these tests have limited sensitivity and specificity as any acute neuronal damage can release these proteins [3, 10]. An assay using real-time quaking-induced conversion (RT-QuIC) was first applied to human brain specimens in 2011, and an improved second-generation assay was described in 2015 [10]. A meta-analysis in 2021 shows that RT-QuIC has high sensitivity (85.0 to 92.8%) and specificity (99 to 100%) with a false-positive rate of zero [10]. The high sensitivity of RT-QuIC allows for antemortem diagnosis of sporadic CJD. Since other potentially treatable diseases can present with RPD, it is imperative for clinicians to make an accurate diagnosis early in the clinical course [6]. We had a unique opportunity to observe five cases within five years and will describe a case series of these patients with RPD and clinical and diagnostic findings suggestive of CJD. The case series will further illustrate disease presentation, diagnostic testing, and differential diagnoses for patients with RPD.

Objectives

The purpose of this manuscript is to provide a focused review of CJD and to illustrate a case series from a hospital in the Chicago suburbs. Since CJD is a rare disease, clinicians may not be familiar with its presentation and workup. We will provide recent information about epidemiology, presentation, diagnostic testing/criteria, and differential diagnoses so healthcare providers can better evaluate patients with RPD and consider CJD versus other neurological conditions. Although currently there is no cure or treatment for CJD, a diagnosis can allow the patient and family more time for goals-of-care discussions and a plan for supportive and palliative care. Some other neurological conditions that present with RPD are potentially treatable, and thus it is imperative to make a diagnosis quickly.

Methods

This case series was reviewed by the Edward Hospital Institutional Review Board and approved as a retrospective study on February 11, 2022. We reviewed the electronic medical records of five patients who were referred to the Edward Hospital neurology service between August 2016 to May 2020 who had presented with RPD and/or acute mental status changes who also had clinical and diagnostic findings suggestive of CJD. We reviewed the patients' demographics, clinical presentation, clinical course, and diagnostic testing including brain MRI, EEG, and CSF markers such as RT-QuIC, 14-3-3 protein, and tau protein.

Results

We identified three patients with definite CJD, one with probable CJD, and one with possible CJD [8]. All patients had brain MRIs during their initial hospital admission. Patients 1 to 4 initially presented with RPD, a typical presentation for CJD, and also had CSF studies during their initial hospital admission. In addition to RPD, patients 2, 3, and 4 had vision changes including diplopia, flashing lights, and photophobia, and patient 1 had myoclonus. Patient 1 had a confounding factor of left parietal ischemic stroke two weeks before presentation; at home, family reported new symptoms of insomnia, aphasia, and incontinence, and brought him to the hospital where we obtained further workup. Patient 5 had an atypical presentation; his primary care provider obtained a brain MRI due to near-syncopal events. This revealed cortical ribboning, and patient was thus sent to a neurologist for further evaluation. However, initially this patient did not have any cognitive impairment or other typical clinical findings suggestive of CJD, and the abnormal MRI findings were at first attributed to possible postictal or toxic metabolic derangements. The neurologist recommended neuropsychological testing, but in the interim, the patient developed acute cognitive decline, hallucinations, and delusions. This prompted further testing including CSF studies.

Patients 2, 3, and 5 had autopsy results positive for abnormal protease resistant prion protein (PrPSc). This biopsy is a Western Blot analysis conducted on frozen autopsy samples and confirmed the diagnosis of sporadic CJD [8]. Patient 4 had probable CJD due to RPD in conjunction with positive RT-QuIC drawn from CSF. Patient 1 had possible CJD; his CSF tests were inconclusive due to blood in the sample, but the patient had RPD with myoclonus and aphasia. The patients all had typical CJD findings on brain MRIs, including cortical ribboning (Figure 1). Patients 1, 3, and 4 also had typical EEG findings of periodic sharp wave complexes (Figure 2).

The average age of presentation was 59.4 years with range 53 to 63 years. (Patient ages are presented in an age range to protect their privacy.) Four patients were white, one was of Middle Eastern descent; 60% were men and 40% were women. All five patients are now deceased. Patient 5 died 15 months after his initial presentation, in contrast to the other patients, who died within 1 to 2 months after their initial presentations.

Discussion

We believe this cluster of five cases within five years at a community hospital warrants a review and discussion. It provided a unique opportunity for us to diagnose and observe a relatively large number of CJD cases in a short span. Cognitive decline and dementia are common symptoms in the elderly population, and although CJD is rare, it should be considered as a diagnosis in patients with RPD. Clinical presentation can

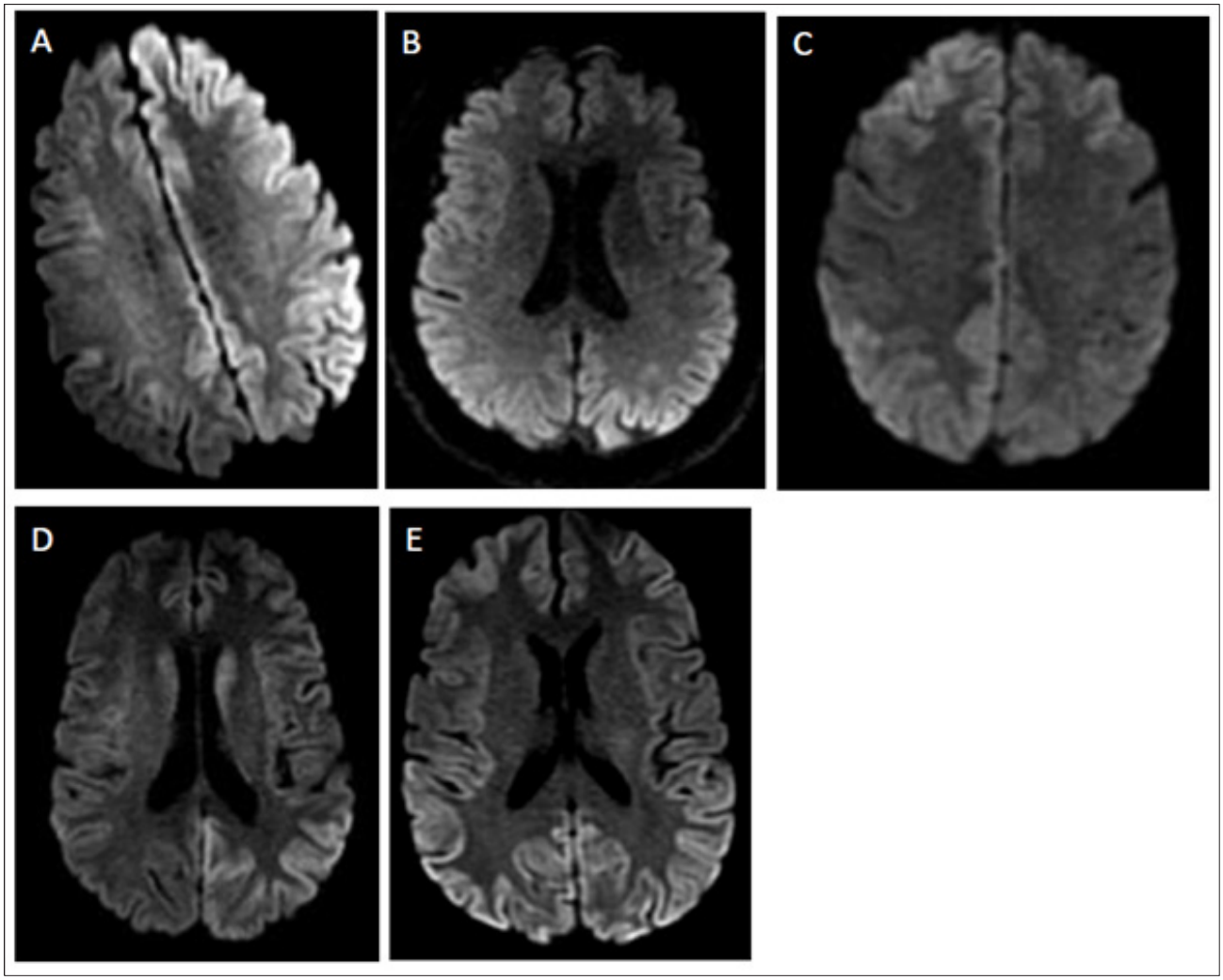

Figure 1: Examples of cortical ribboning in diffusion-weighted MRI brain.

A. Patient 1: cortical ribboning, more prominent in the left hemisphere, MRI from initial hospital admission August 2016.

B. Patient 2: cortical ribboning in bilateral hemispheres, MRI from initial hospital admission October 2016.

C. Patient 3: cortical ribboning in bilateral hemispheres, MRI from initial hospital admission November 2016.

D. Patient 4: cortical ribboning, more prominent in left hemisphere, MRI from initial hospital admission April 2017.

E. Patient 5: cortical ribboning in bilateral hemispheres, MRI from second hospital admission March 2021

vary widely, but can include RPD with myoclonus, gait ataxia, cerebellar or extrapyramidal symptoms, anxiety, depression, vision changes, hallucinations, seizures, or behavioral changes [2-4]. However, many patients have an atypical presentation such as Patient 5, who presented with syncope.

Clinicians should order a thorough workup of serum laboratory tests including blood count, comprehensive metabolic panel, Vitamin B12, Vitamin B1, thyroid-stimulating hormone, paraneoplastic panel, heavy metals, syphilis, and autoimmune markers. In addition, clinicians should obtain CSF studies, brain MRI, and EEG [2, 3, 6, 7]. These tests assess for diseases including metabolic encephalopathy, stroke, CNS infections, vasculitis, autoimmune or paraneoplastic disease, hypothyroidism, and Vitamin B12 or B1 deficiencies [2, 3]. Some of these conditions are potentially treatable or reversible, while others can be stabilized, so clinicians should consider a broad differential. Underlying neurocognitive disorders such as Alzheimer disease, vascular dementia, Lewy Body dementia, frontotemporal dementia, and Parkinson disease, can also initially present with RPD [2, 6, 7]. In a retrospective study spanning 13 years at the RPD program at University of California-San Francisco, 25% of patients referred did not have CJD or another prion disease [6]. For patients with suspicious findings on brain MRIs such as cortical ribboning on the diffusion-weighted imaging sequence or high signal in the fluid attenuated inversion recovery (FLAIR) in the striatum or thalamus [3, 5, 7, 8], clinicians should check for the CJD markers 14-3-3, tau protein, and RT-QuIC from CSF.

Having five cases within five years in our community of approximately 150,000 people is a higher prevalence than the current reported 1-2 cases per million [1, 7]. However, the CDC reports the average annual rate (from 1979 to 2020 in the United States) was 3.6 cases per million for persons 50 years or older [1]. Patients may not present with typical

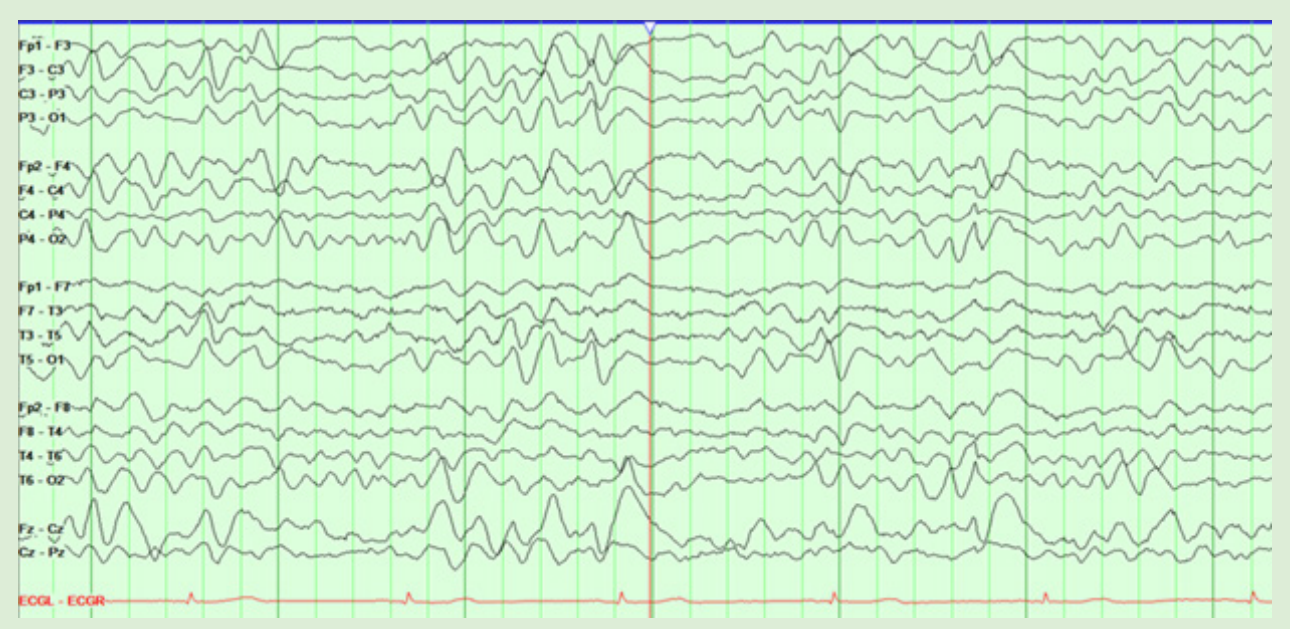

Figure 2: EEG with PSWC, typical findings of CJD.

Patient 4, study from initial hospitalization, April 2017.

Abbreviation: PSWC, periodic sharp wave complexes

Table 1: Summary of patients' demographics, CSF studies, MRI, EEG, and brain autopsy.

	Gender	Age Range, y	Presenting Date	Date of death	14-3-3	Tau protein	RT-QuIC	MRI DWI	EEG results	Brain Autopsy[1]	CJD Diagnosis
Patient 1	Man	60-70	Aug 2016	Sep 2016	inc[2]	8406	inc[2]	cortical ribboning	PSWC	unknown[4]	possible
Patient 2	Man	60-70	Oct 2016	Nov 2016	positive	4435	positive	cortical ribboning	delta-theta slowing	positive	definite
Patient 3	Woman	60-70	Nov 2016	unknown[3]	positive	8695	positive	cortical ribboning	PSWC	positive	definite
Patient 4	Woman	50-60	Apr 2017	May 2017	positive	3457	positive	cortical ribboning	PSWC	unknown[4]	probable
Patient 5	Man	50-60	May 2020	Aug 2021	positive	2518	positive	cortical ribboning	intermittent slowing	positive	definite

Results

1. Brain autopsy positive for abnormal protease resistant prion protein (PrPSc)
2. 14-3-3 and RT-QuIC were inconclusive for patient 1 due to blood in CSF sample.
3. Exact date of death is unknown for patient 3, but brain autopsy is dated January 2017.
4. It is unknown if brain autopsy was performed.

Abbreviation: y, years. inc, inconclusive.

symptoms, and thus not be tested for CJD. With heightened awareness of the varied disease presentation, knowledge of typical MRI findings, and the highly sensitive and specific RT-QuIC test, clinicians can better diagnose CJD and avoid under- or misdiagnosis [5]. Early diagnosis allows patients and their families more time to understand the disease and its outcome, create a care plan, find supportive resources, and consider if they would like to participate in clinical trials [4, 11] and/or obtain a post-mortem brain biopsy. A recent trial tested prion protein monoclonal antibody therapy, a validated therapeutic target, in six patients who were diagnosed with CJD [11]. Although the patients had progressive neurological decline and death, they tolerated the treatment without clinically significant adverse reactions and three patients appeared to have a stabilized Prion Disease Rating Scale [11]. In the United States, the National Prion Disease Pathology Surveillance Center (NPDPSC) offers the following resources: coordinating autopsies, neuropathological brain tissue analysis, CSF testing, Brain MRI consultation program, genetic testing, and clinician education [12]. The NPDPSC also monitors for changes in prion disease incidence. While CJD is currently untreatable and fatal, there are resources for patients, families,

researchers, and clinicians in hopes of promoting awareness and funding for future trials and treatments.

Conclusions

Clinicians should keep CJD in their differential when presented with a patient with RPD. The RT-QuIC CSF study in conjunction with brain MRI, EEG, and clinical presentation, allows for antemortem diagnosis of CJD. Future research on early diagnostic, prognostic, and potentially pre-symptomatic biomarkers is dependent on early clinical surveillance and diagnosis.

Conflicts of Interest

The authors have no financial disclosures nor other conflict of interest to report.

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