Sporadic Creutzfeldt-Jakob disease without dementia: a case report

Abstract

Creutzfeldt-Jakob disease is a rare condition caused by prions. Although the infectious form of the disease is the most well-known, the most common form is the so-called sporadic type, where the transformation of cytoplasmic proteins from glial cells into prions occurs. The disease is characterized by rapidly progressive dementia whose diagnosis can be made with great accuracy based on clinical signs, typical changes on magnetic resonance imaging and real-time quaking-induced conversion (Rt-QuIC) testing in cerebrospinal fluid. We report a case of the disease without cognitive disorders in the initial phase, but with other common clinical signs including behavioral abnormalities, ataxia, extrapyramidal features, and myoclonus; typical changes on magnetic resonance imaging of the skull (signal alterations affecting parietal and temporal lobes areas) and strongly positive Rt-QuIC test. This case report can serve to alert other health professionals on recognizing the disease and contribute to a more accurate diagnosis in similar cases.

Keywords: Creutzfeldt-Jakob Disease. Creutzfeldt-Jakob Syndrome. Prion Disease. Case report.

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INTRODUCTION

Prion disease is an untreatable, fatal, and rapidly progressive neurodegenerative disease. Making a confident diagnosis of prion disease can be challenging because it is rarely encountered and has many clinical mimickers. Among the different prion diseases, Creutzfeldt-Jakob Disease (CJD) is the most relevant.

First described in 1920 by Hans Gerhard Creutzfeldt and Alfons Jakob in Germany, CJD is a Human Transmissible Spongiform Encephalopathy (TSE) that causes a number of neuropathological changes whose cause is linked to the existence and abnormal dissemination of a pathogenic prion protein. Statistically, 80-95% of CJD cases are sporadic forms, 10-15% are genetic (often familial), and less than 1% are acquired. Although the latter are the least common, they are probably the most well-known.

The infectious agent causing prion disease, known as PrPSc, is unusual in that it lacks any specific nucleic acid and is a pathogenic misfolded aggregated form of the cellular prion protein, PrPC. Following transmission to a naïve host, prions seed the misfolding of host PrPC in an autocatalytic process, leading to an exponential increase in PrPSc within the brain and spinal cord that eventually leads to neuronal death.

In sporadic CJD, the conversion of PrPC to PrPSc is thought to occur spontaneously (or possibly through a somatic mutation of the prion protein gene, PRNP). In genetic prion diseases, it is thought that mutations in the PRNP make PrPC more susceptible to changing conformation (misfolding) into PrPSc. In acquired forms, PrPSc is accidentally transmitted to a person, causing their endogenous PrPC to misfold.

Patients with different etiologies of CJD have different clinical and pathological phenotypes. CJD is a rare disease, with an overall incidence of 1–2 cases per million individuals annually. In Brazil, only 359 cases were laboratory-confirmed between 2005 and 2021. The largest record of cases of the disease was made by Uttley et al., from 1993 to 2018, through studies published from 2005 and conducted in many countries around the world, especially in Europe. Switzerland was the country with the highest incidence or mortality per million people (1.73), followed by France (1.60), Austria (1.52), Denmark (1.47) and Slovenia (1.46), whereas Estonia (0.32), Taiwan (0.55) and Greece (0.62) had the lowest rates.

Cognitive and constitutional symptoms (such as dizziness/vertigo, fatigue/lethargy, sleep disturbance, headache, urinary incontinence, weight loss, gastrointestinal upset e palpitations) are described as the earliest symptoms, followed by cerebellar and behavioral symptoms.

In 1998, the World Health Organization (WHO) included a combination of specific symptoms, electroencephalography (EEG), and detection of 14–3–3 protein in cerebrospinal fluid (CSF) in the standard diagnostic criteria. Some years later, in 2009, the European MRI-CJD Consortium Criteria included brain imaging for diagnosis, suggesting that typical brain magnetic resonance imaging (MRI) findings (such as high signal abnormalities in caudate nucleus and putamen or at least two cortical regions - temporal-parietal-occipital - on DWI or FLAIR) and a positive result on a real-time quaking-induced conversion (RT-QuIC) test support a highly probable diagnosis.

Sporadic CJD is a rare disease, with an incidence of approximately 1–2 cases per 1 million people and is classically described as a rapidly progressive form of dementia. Currently, there is no effective specific treatment for the disease, as reported by Miranda et al. We describe a case of the disease with an unusual characteristic: the absence of cognitive impairment in the initial phase of the disease. The objective of the present study was to alert clinicians to the possibility of the absence of cognitive impairment as an initial manifestation of this serious and rare disease.
CASE REPORT

In March 2023, a 72-year-old male patient sought the emergency room in Marica (Brazil), complaining of right-sided paresthesia. He reported suffering from systemic arterial hypertension and diabetes mellitus and was using Nebivolol 5mg/day and Metformin 500mg twice daily. A computed tomography (CT) scan of the skull revealed no acute changes. The patient was discharged from the ER. However, as there was no improvement, he sought a specialized outpatient medical care service, which ordered a magnetic resonance imaging (MRI) scan of the brain. The scan revealed small hyperintense foci on T2 and FLAIR in the deep white matter adjacent to the margins of the lateral ventricles and subcortical gliosis in the frontotemporal regions, suggesting degenerative microangiopathy. Two weeks later, the patient’s neurological condition worsened, with muscle tremors, gait difficulty, dysarthria, myoclonus, and ballistic movements, with preserved sphincter control and cognition.

In April 2023, an electroencephalogram with brain mapping was performed, which showed no abnormalities, and a new MRI of the skull was performed, showing signal alterations affecting the left parietal cortex in the topography of the postcentral gyrus, superior parietal lobe, and paracentral lobule, extending to the adjacent portion of the cingulate gyrus and insula (Figure 1). To evaluate the diagnosis of paraneoplastic neurological disease, the patient underwent a chest CT, which revealed scattered foci of centrilobular emphysema and band-like opacity in the left upper lobe. A lumbar puncture was performed (17mL of cerebrospinal fluid collected; initial pressure = 9cm water; final pressure = 5cm water; 1 leukocyte per cubic millimeter; 1 red blood cell per cubic millimeter; protein = 46mg/dL) with a panel search for encephalitis (Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Epstein-Barr Virus, Cytomegalovirus, Adenovirus, Herpes Simplex 1 and 2, Varicella-Zoster, Human Herpesvirus 6 and 7, Erythrovirus B19, Enterovirus, Parechovirus, and Mumps virus), anti-neuronal NMDA Receptor antibodies (NR1 and NR2), paraneoplastic panel of the cerebrospinal fluid (ANNA-1/2/3, AGNA-1, PCA-1, PCA-2, PCA-TR, Anti-Amphiphysin, CRMP-5 IgG), and anti-neuronal antibodies panel (Anti-Hu, Anti-Yo, Anti-Purkinje Cell, CV2, MA2, Anti-MGT 30, Anti-Recoverin), all of which were negative. From March to 19th May 2023, the patient presented no signs of cognitive impairment.


I. Clinical Signs:
   1. Dementia
   2. Cerebellar or visual
   3. Pyramidal or extrapyramidal
   4. Akinetic mutism

II. Tests:
   1. Periodic Sharp Wave Complexes (PSWCs) on EEG
   2. 14-3-3 detection in CSF (in patients with disease duration less than 2 years)
   3. High signal abnormalities in caudate nucleus and putamen or least two cortical regions (temporal-parietal-occipital) on DWI or FLAIR

III. Routine investigations should not suggest an alternative diagnosis

Probable CJD: Two out of I and at least one out of II
Possible CJD: Two out of I and duration less than 2 years
On 19th May 2023, the patient presented neurological deterioration and inability to walk, severe swallowing impairment, and motor incoordination of the upper limbs, and was admitted to the Federal Hospital of Andaraí. He developed fever and tachycardia, having a Glasgow Coma Scale score of 7 on admission, and progressed to gasping, requiring orotracheal intubation and admission to the intensive care unit (ICU) of the hospital.

On 14th June 2023, the patient was subsequently transferred to the ICU of Gaffrée and Guinle University Hospital, presenting with fever, increased volume of tracheal secretions, and pulmonary infiltrate, and was diagnosed with ventilator-associated pneumonia. During this hospitalization, the informed consent form was signed by the patient’s daughter. Treatment with polymyxin B + tigecycline was initiated, resulting in remission of fever and reduction of tracheal secretion volume after 48 hours. Another lumbar puncture was performed to investigate 14-3-3 protein and Rt-QuIC, suspecting prion disease. At the end of June 2023, the result of Rt-QuIC was strongly positive (Figure 2), confirming the hypothesis of sporadic CJD. On 8th July 2023, the results of the investigation for the presence of 14-3-3 protein in the CSF collected also proved positive. The patient died on 23rd July, due to severe sepsis of respiratory origin.

Figure 1. MRI showing signal alterations affecting left parietal cortex (yellow arrows). 2023, Rio de Janeiro, Brazil.

Source: MRI of patient’s skull performed in April 2023
DATA AVAILABILITY

The dataset is not publicly available because it contains information that may compromise the privacy of the study participants.

DISCUSSION

The patient described began to have motor symptoms in April 2023, undergoing imaging tests (computed tomography and magnetic resonance imaging of the skull) and cerebrospinal fluid studies. The neurological symptoms and signs progressed rapidly, with the patient requiring admission to intensive care approximately one month later. During hospitalization in our hospital, another CSF collection was performed, resulting in a strongly positive Rt-QuIC test.

Clinical diagnosis of Creutzfeldt-Jakob Disease is based on a combination of symptoms and ancillary tests, including brain MRI, EEG, and perhaps most importantly, CSF analyses. The classic clinical phenotype of sporadic CJD is rapidly progressive dementia with behavioral abnormalities, ataxia (usually gait), extrapyramidal features and, ultimately, myoclonus. Early symptoms may be constitutional and nonspecific, such as dizziness/vertigo, fatigue/lethargy, sleep disturbance, headache, urinary incontinence, weight loss, gastrointestinal upset and palpitations1–4.

About a third of patients with sporadic CJD have constitutional early symptoms, sometimes considered prodromal features, many of which are difficult to classify neuroanatomically1–4. In the clinical case described, a predominance of cerebellar symptoms and myoclonic movements were initially observed, later progressing to behavioral symptoms, including hallucinations.

Unusually, no cognitive impairment was evident in the initial phase of the disease, although this finding has been previously reported by other authors8–11. Saraceno et al.9 reported a similar case, attributing the absence of cognitive disorder to the particular areas affected by the disease. In their case, there was involvement of the basal ganglia without affecting the cerebral cortex, as evidenced by MRI, with hyperintensity in the right caudate and lenticular nuclei with mild cortical involvement and no atrophy. Marciani et al.10 stated the absence of mental decline in the case they reported was difficult to interpret, but the histological results suggested changes in gray

Figure 2. CSF Rt-QuIC result. 2023, Rio de Janeiro, Brazil.
Source: Patient’s CSF examination, carried out in June 2023.
matter, without neuronal loss. Pauri et al. reported a case in which cognitive changes appeared only in the final weeks of disease course, where post-mortem examinations showed spongiform changes and gliosis of astrocytes in the frontal cortex and other areas, which could explain the late manifestation of these impairments. MRI performed earlier in the case initially showed involvement of the periventricular white matter and basal ganglia, with involvement of the frontal cortex only evident in a third imaging scan at a later phase of the disease.

Historically, EEG was the first in vivo test to be used to support the clinical diagnosis of CJD. The typical EEG pattern shows bilateral synchronous periodic epileptiform discharges, such as biphasic or triphasic waves, with 90% specificity for CJD, in a compatible clinical setting. However, typical periodic EEG activity may be lacking in some patients with CJD during its early stages and also less common at terminal stages of the disease. In the present case, EEG disclosed no changes, perhaps because it was performed in the first few weeks after the onset of symptoms.

The classic findings of the disease on MRI are T2-FLAIR hyperintensity and restricted diffusion in the caudate, putamen and cortex, featuring in 80% of cases. The European MRI-CJD Consortium Criteria cites that findings in at least two cortical regions (temporal-parietal-occipital) on DWI or FLAIR also confirm diagnosis. The patient reported presented signal alterations affecting parietal and temporal lobes areas.

Aside from brain biopsy, Rt-QuIC is the only disease-specific antemortem biomarker for diagnosing prion disease that directly detects prions. In the study of Geschwind, akin to other investigations, Rt-QuIC showed high sensitivity (90.3%) and specificity (98.5%) for detecting prion disease. The present patient had a strongly positive result on Rt-QuIC testing, confirming the diagnosis.

The patient began to present changes in sensitivity in March 2023, undergoing imaging tests (computed tomography and magnetic resonance imaging of the skull) and cerebrospinal fluid studies. Multiple diseases were investigated that were part of the differential diagnosis of abnormalities presented by the patient, such as infectious encephalitis (Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Epstein-Barr virus, cytomegalovirus, adenovirus, herpes simplex 1 and 2, varicella-zoster, human herpesviruses 6 and 7, erythrovirus B19, enterovirus, parechovirus and mumps virus), paraneoplastic encephalitis (ANNA-1/2/3, AGNA-1, PCA-1, PCA-2, PCA -TR, Anti-Amphiphysin, CRMP-5 IgG), autoimmune encephalitis (anti-neuronal NMDA receptor antibodies - NR1 and NR2) and other diseases that produce anti-neuronal antibodies (Anti-Hu, Anti-Yo, Anti-Purkinje Cell, CV2, MA2, Anti-MGT 30, Anti-Recoverin), and none of the tests yielded a positive result.

During hospitalization, another CSF collection was performed, resulting in a strongly positive Rt-QuIC test, enabling confirmation of the etiological diagnosis. As observed by Miranda et al. in a systematic review on therapeutic options, CJD is an incurable disease with no specific treatment able to increase survival of these patients. Medications investigated for this purpose have included quinacrine, doxycycline, flupirtine and pentosan polysulfate, in case series studies, randomized and non-randomized clinical trials and even double-blind randomized clinical trials. In the case reported, only 5 months elapsed between symptoms onset and patient death, demonstrating the rapid progression of the disease, previously described in other publications.

CJD is an incurable disease with no effective treatment to date. Early diagnosis allows patients and their families to prepare for the expected course of the disease and receive palliative care. It is important to establish an early assertive diagnosis because some infectious diseases with similar symptoms and signs are treatable. The present case indicates that cognitive impairment may not always be present in the early stages of the disease and this must be taken into consideration, so as not to delay diagnosis.

This study was approved by the Ethics Committee of the Institution under permit number 5.735.062 (Hospital Universitário Gaffree e Guinle/HUGG/UNIRIO).
CONCLUSION

CJD is an incurable disease with no generally accepted treatment at this time. Early diagnosis allows patients and their families to prepare for the expected disease course and arrange palliative care. It is important to establish an early accurate diagnosis because some infectious diseases are treatable. The present case illustrates that cognitive impairment may not necessarily be present in the early stages of the disease.

REFERENCES


