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Creutzfeldt-Jakob disease:
literature review based on three case reports

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ABSTRACT. Creutzfeldt-Jakob disease (CJD) is one of the transmissible spongiform encephalopathies that lead to rapidly progressive dementia. CJD has a low prevalence, and the average survival is only 1 year after the onset of symptoms. As the patients with CJD develop rapidly progressive dementia, associated with myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism, the hypothesis of CJD must be raised. Classic magnetic resonance imaging (MRI) findings are hypersignals in the caudate nucleus, putamen, and cortical region. CJD must be considered a differential diagnosis of other types of dementia, and there is no effective treatment for this disease. In this article, we present a literature review based on the report of three cases of the sporadic form of this disease.

Keywords: Creutzfeldt-Jakob Syndrome; Prion Diseases; Myoclonus.

DOENÇA DE CREUTZFELDT-JAKOB: REVISÃO DA LITERATURA BASEADA NO RELATO DE TRÊS CASOS

RESUMO. A doença de Creutzfeldt-Jakob (DCJ) faz parte do grupo das encefalopatias espongiformes transmissíveis que levam a um quadro de demência rapidamente progressiva. A DCJ possui baixa prevalência, e a sobrevida média é de apenas um ano após o início dos sintomas. Diante de um paciente com demência rapidamente progressiva, associada a mioclonias, alterações visuais ou cerebelares, sinais piramidais ou extrapiramidais e mutismo acinético, a hipótese de DCJ deve ser levantada. Os achados clássicos na ressonância magnética são os hipersinais em núcleo caudado, putâmen e região cortical. A DCJ deve ser considerada como um diagnóstico diferencial de outros tipos de demência e não existe um tratamento eficaz para essa doença. Apresentamos neste artigo uma revisão da literatura baseada no relato de três casos da forma esporádica dessa doença.

Palavras-chave: Síndrome de Creutzfeldt-Jakob; Doenças Priônicas; Mioclonia.

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) was first described in 1920 by Hans Gerhard Creutzfeldt and Alfons Jakob[1]. It belongs to the group of transmissible spongiform encephalopathies (TSE), which are neurodegenerative diseases caused by prions. CJD is a rare disease, with an overall incidence of 1–2 cases per million individuals each year. In Brazil, only 55 cases were confirmed between the years of 2005 and 2014[2]. The other human prion diseases are Kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), and variably protease-sensitive prionopathy (VPSPr).

CJD is classified into sporadic, variant, iatrogenic, and familial or genetic forms. The sporadic form (sCJD) corresponds to most cases, which do not have an infectious source or evidence of familial disease. The acquired forms are the variant CJD (vCJD), known as "mad cow disease," and the iatrogenic (iCJD), which is mainly associated with dura mater graft and the use of human growth hormone[3,4]. vCJD was observed in 1980 in the UK population after ingesting contaminated beef[5]. The familial CJD (fCJD) is defined as definite or probable CJD plus definite or probable CJD in a first-degree relative or

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a disease-specific *PrP* gene mutation. About 10–15% of CJD cases are familial[6].

The sporadic form has a long incubation period, with an average age of onset of symptoms about 62 years and survival of only 1 year after the onset of the condition. vCJD affects younger age group, with an average age of onset of symptoms of 26 years, and has a longer duration of about 14 months[5,7].

As the patients with CJD develop rapidly progressive dementia, associated with myoclonus, visual or cerebellar problems, pyramidal or extrapyramidal features, and akinetic mutism, the hypothesis of CJD must be raised[7]. Suggestive findings on brain magnetic resonance imaging (MRI) and a positive result from a real-time quaking-induced conversion (RT-QuIC) support the diagnosis. However, only brain tissue biopsy provides a definitive diagnosis[7]. Other than clinical support, there is no treatment for this disease, which is uniformly fatal.

The purpose of this article is to review the literature based on the report of three cases of the sporadic form of CJD, which were diagnosed between 2018 and 2021, in the neurology service of the *Santa Casa de Misericórdia de Sobral* hospital in Sobral, Ceará, Brazil.

CASE 1

A 69-year-old female, from Sobral-Ceará, in April 2017 started to experience progressive visual loss, headaches, and vertigo. In October of the same year, she evolved with ataxic gait, upper limb tremors, depressed mood, and short-term episodic memory deficit. In January 2018, the patient was admitted to the hospital with muscle stiffness, spasticity, myoclonus, and akinetic mutism. There were no reports of similar illnesses in the family. Brain MRI showed hyperintensity in the caudate and lentiform nuclei bilaterally and in diffuse cortical gyri on T2-weighted and FLAIR (fluid-attenuated inversion recovery) sequences and restricted diffusion in the same regions in DWI/ADC (diffusion-weighted imaging/apparent diffusion coefficient). The electroencephalogram (EEG) showed diffuse triphasic wave discharges associated with periodic complexes with short periodicity. The immunoassay of the 14-3-3 protein in the cerebrospinal fluid (CSF) was negative. The patient remained in palliative care and died in March 2018.

CASE 2

A 66-year-old male, from Irauçuba-Ceará, in March 2019 presented bradykinesia, ataxic gait, delusions, and attempted suicide. In April of the same year, he developed torpor, right hemiparesis, spastic rigidity, and orofacial and bodily myoclonus, when he was admitted to the hospital. The patient had no previous comorbidities and no family history of similar diseases. The CSF examination did not show alterations, and the immunoassay of the 14-3-3 protein in the CSF was negative. EEG showed generalized periodic discharges with short periodicity, and the brain MRI showed hyperintensity in the head of the caudate nucleus, lentiform nucleus, and diffuse cortical gyri, in addition to a cortical ribbon signal, on the T2-weighted, FLAIR, and DWI sequences. After 7 days of hospitalization, the patient died.

CASE 3

A 47-year-old female, from Crateús-Ceará, in February 2021 started experiencing intense vertigo. In March of the same year, she presented ataxic gait, evolving a month later with loss of ambulation, sensitive aphasia, myoclonus in the upper limbs, oral feeding movements, dullness, confabulations, hyperreligiosity, and hallucinations, when she was admitted to the hospital. The patient presented hyperthyroidism as comorbidity, was treated with tapazol, and revealed a history of first-degree consanguinity between the parents. The analysis of the CSF showed no alterations, with the immunoassay of the 14-3-3 protein being negative. Brain MRI showed a diffusion restriction signal in the putamen and caudate nucleus bilaterally, associated with a cortical strand signal in the frontal region, in the DWI, and T2-weighted sequences. EEG showed periodic generalized bursts of biphasic and triphasic waves. During hospitalization, the patient evolved with severe infectious complications and atrial fibrillation. On the 39th day of hospitalization, the patient died.

DISCUSSION

CJD manifests itself in the presence of prions, which are small particles containing an abnormal isoform (PrPSc) of a protein (PrPc) naturally present in the human body. The deposition of prions in brain tissue is responsible for neuronal dysfunction due to synaptic loss and cellular death, resulting in a spongiform appearance in tissue microscopy[6,7]. Prions are deposited in various regions of the body, but reach higher levels in the brain, retina, and optic nerve, triggering the neurological and visual symptoms of the disease[5].

Demonstration of the transmissibility of CJD was made in 1968, through the reproduction of the disease and pathological findings in chimpanzees. It was observed that in prion diseases there is no detectable immunopathological response, the incubation period

is prolonged, ranging from months to years, and the course of the disease is fatal, from weeks to months[1,8].

The sporadic form of CJD has defined subtypes based on focal neurological findings, which reflect the predominant involvement of certain brain regions, e.g., predominantly visual (Heidenhain variant), cerebellar (Oppenheimer-Brownell variant), cognitive, and affective forms[9].

The main prodromes of CJD are anxiety, dizziness, blurred vision, asthenia, and unusual behavior[8]. Such symptoms were present in the three cases reported. The clinical picture of CJD is quite heterogeneous. A very characteristic sign of the disease is myoclonus, often caused by varied sensory stimuli, which is present in 90% of cases[8].

Neuropsychiatric symptoms include dementia, behavioral and mood changes, such as apathy and depression, in addition to deficits in higher cortical functions, such as apraxia, aphasia, and visuospatial difficulties (e.g., spatial neglect, Balint's syndrome)[10]. Some patients may have psychotic symptoms, especially visual hallucinations[11], such as the patient mentioned in case 3. Cerebellar manifestations, such as nystagmus and ataxia, occur in approximately two-thirds of patients, and signs of involvement of the corticospinal tract, including hyperreflexia, Babinski's sign, and spasticity, appear in 40–80% of cases. Some patients may have extrapyramidal signs such as hypokinesia, bradykinesia, dystonia, and rigidity. The final stage of the disease is characterized by akinetic mutism[12]. All these symptoms are compatible with the clinical picture presented by patients in the three reported cases (Table 1). Evaluation of suspected cases includes brain MRI, EEG, and analysis of CSF[7]. The cranial computed tomography is usually normal, being useful, mainly, to exclude other conditions. The current diagnostic criteria for CJD used in Europe are listed in Table 2[13]. MRI is an important mean of investigation in the sporadic

Table 2. Diagnostic criteria for surveillance of sporadic Creutzfeldt-Jakob disease from January 1, 2017.

1.1 DEFINITE: Progressive neurological syndrome AND Neuropathologically or immunohistochemically or biochemically confirmed
1.2 PROBABLE: 1.2.1: I + two of II and typical electroencephalogram* OR 1.2.2: I + two of II and typical magnetic resonance imaging brain scan+ OR 1.2.3: I + two of II and positive CSF 14-3-3 OR 1.2.4: Progressive neurological syndrome and positive real-time quaking-induced conversion in CSF or other tissues
1.3 POSSIBLE: I + two of II + duration <2 years
I - Rapidly progressive cognitive impairment
II - A Myoclonus B Visual or cerebellar problems C Pyramidal or extrapyramidal features D Akinetic mutism

*Generalized periodic complexes; +high signal in caudate/putamen on magnetic resonance imaging brain scan or at least two cortical regions (temporal, parietal, occipital) on either diffusion-weighted imaging or fluid-attenuated inversion recovery; CSF: cerebrospinal fluid.

Table 1. Review of reported cases.

	Case 1	Case 2	Case 3
Age	69 years	66 years	47 years
Time from symptom onset to death	12 months	3 months	5 months
Main signs and symptoms	Vertigo, rigidity, ataxic gait, myoclonus, and akinetic mutism	Hypokinesia, ataxic gait, psychosis, sensory aphasia, rigidity, and myoclonus	Vertigo, ataxic gait, sensory aphasia, myoclonus, and hallucinations
MRI findings	High signal in caudate nucleus, lentiform, and diffuse cortical gyri on DWI, T2-weighted, and FLAIR	High signal in the head of the caudate nucleus, lentiform nucleus, and diffuse cortical gyri, in addition to "cortical ribboning" signal on T2-weighted, FLAIR, and DWI	Diffusion restriction signal in putamen and caudate nucleus, associated with cortical ribbon signal in frontal region on DWI and T2-weighted
EEG findings	Diffuse repetitive triphasic wave discharges with short periodicity	Diffuse repetitive wave discharges with short periodicity	Diffuse repetitive wave discharges with short periodicity
CSF findings	Normal CSF Negative 14-3-3 protein	Normal CSF Negative 14-3-3 protein	Normal CSF Negative 14-3-3 protein

MRI: magnetic resonance imaging; DWI: diffusion-weighted; FLAIR; fluid-attenuated inversion recovery; EEG: electroencephalogram; CSF: cerebrospinal fluid.

form of CJD, as it is highly sensitive and specific, in addition to being widely available. The classic findings of the disease are T2-FLAIR hyperintensity and restricted diffusion in the caudate, putamen and cortex, which are present in 80% of cases[14]. The sensitivity and specificity of these findings are 83–92% and 87–95%, respectively[15]. 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, these findings may be present in other conditions, such as end-stage Alzheimer's disease, Lewy body dementia, and metabolic encephalopathies[14]. The three patients reported in this study presented these typical findings on brain MRI and EEG (Figure 1), associated with a compatible clinical picture, thus reinforcing the diagnosis of CJD. CSF analysis is usually normal, although protein levels may be elevated in 40% of patients[8]. Four proteins have been detected by immunoassay or Western blot in CSF, with high sensitivity for the detection of patients

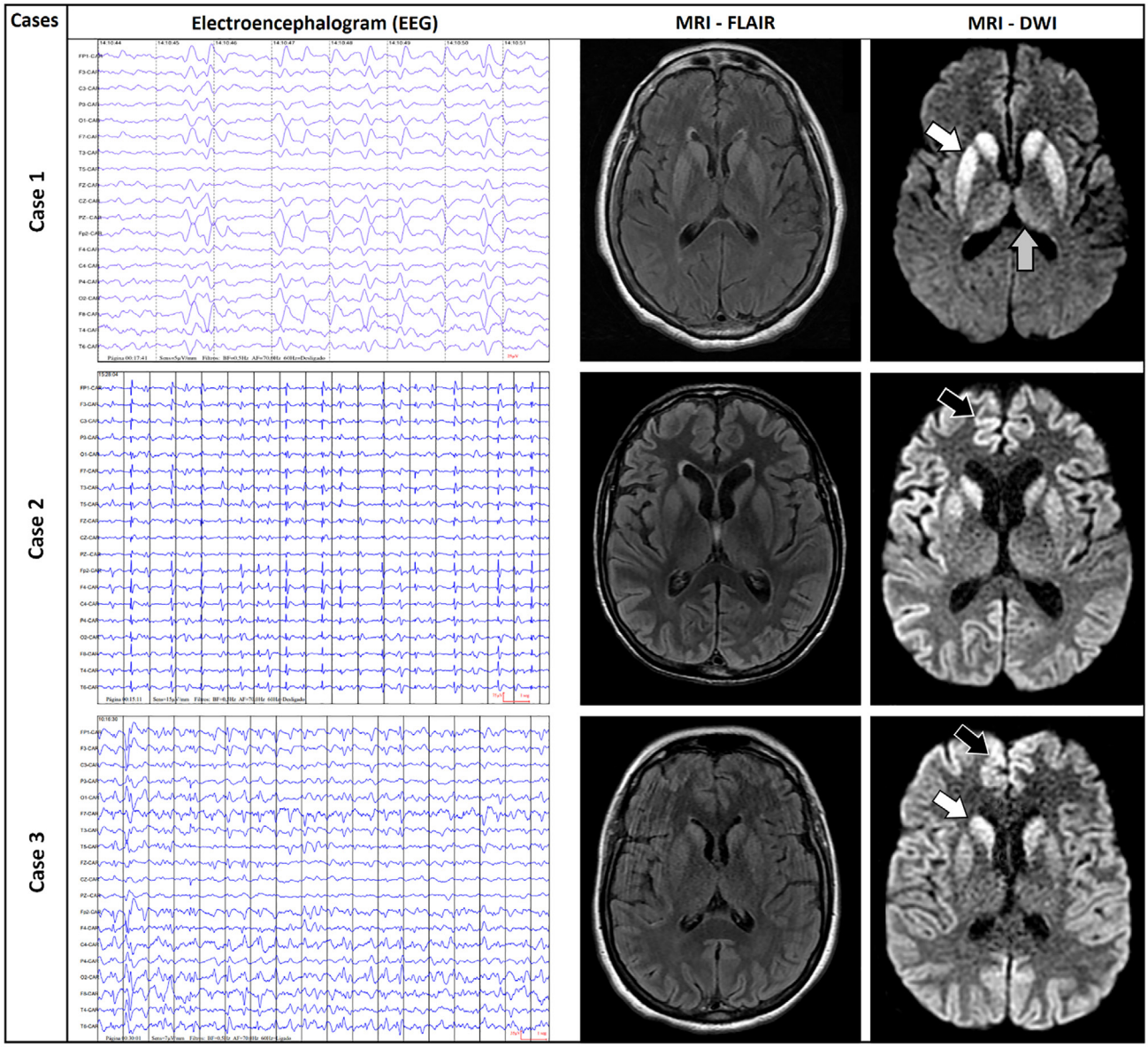

Figure 1. Axial diffusion-weighted and fluid-attenuated inversion recovery images showing bilateral involvement of the basal ganglia (Cases 1 and 3 – white arrows) and thalami (Case 1 – gray arrow). Axial diffusion-weighted shows more widespread signal hyperintensity in the cortical ribbon (Cases 2 and 3 – black arrows). Those findings are reported as usual Creutzfeldt-Jakob disease magnetic resonance imaging signs. Regarding the electroencephalograms, it is possible to note a diffuse repetitive triphasic wave discharges pattern with short periodicity in Case 1 and diffuse repetitive wave discharges pattern with short periodicity in Cases 2 and 3.

with CJD: protein 14-3-3, tau, neuron-specific enolase, and S-100[16,17]. A high level of non-phosphorylated tau protein has greater specificity for the diagnosis of CJD when compared to 14-3-3 protein dosage. 14-3-3 protein dosage is considered an adjunct rather than a diagnostic test, since its 80% of specificity applied to a disease with a prevalence as low as CJD means that most positive tests are actually false positives[18]. A negative test for this protein, as in the three cases reported, does not exclude the diagnosis, as the sensitivity may be lower in the early and late stages of the disease[19,20]. However, the RT-QuIC test has made the diagnosis of CJD easier, because it can detect minimal levels of prion protein in the CSF, increasing the chances of diagnosis while still alive. The sensitivity and specificity of this test are 91 and 98%, respectively[21].

It is important to note that MRI and EEG are easily accessible tests, but the identification of the 14-3-3 protein and the RT-QuIC assay in CSF are still a challenge, because they are not available in some hospitals in Brazil.

Considering the average age of onset of symptoms, it is possible that some cases of CJD are confused with other neurological conditions that commonly affect the elderly, such as Lewy body dementia, autoimmune encephalitis, Alzheimer's disease, and primary psychiatric disorder[5].

Over the past few years, some treatment possibilities for the sporadic form of CJD have been investigated, but none of them have improved symptoms or increased survival. Flupirtine, a centrally acting non-opioid analgesic, showed cytoprotective activity in vitro in neurons inoculated with prion protein, but no significant effects were evidenced in clinical trials. Pentosan polysulfate (PPS) is a high-molecular-weight polymer similar to heparin that appears to interfere with the conversion of PrPC to PrPSC when administered intraventricularly. Studies have shown longer survival with the use of PPS, but there was a frequent association with subdural hemorrhages, not being a viable treatment option. The association of quinacrine use with slower cognitive decline in patients with sCJD remains controversial in the clinical trials performed. Doxycycline was effective in in vitro models and in animals with prion disease, possibly by preventing the abnormal folding of the prion protein, but its clinical benefit remains uncertain[22].

Therefore, there is no effective treatment for CJD, which is uniformly fatal. Supportive measures include symptomatic treatment of neuropsychiatric disorders and myoclonus, which may respond satisfactorily to benzodiazepines, such as clonazepam, and to certain anticonvulsants, such as levetiracetam and valproate[23].

CJD is a rare diagnosis that should be suspected in cases of rapidly progressive dementia mainly associated with myoclonus. Typical findings on brain MRI and EEG support the diagnosis. However, new discoveries about CJD are needed, including earlier diagnostic techniques and a treatment capable of modifying or delaying the fatal evolution of the disease.

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