HEIDENHAIN VARIANT OF CREUTZFELDT-JAKOB DISEASE IN BRAZIL: A CASE REPORT

Variante Heidenhain da Doença de Creutzfeldt-Jakob no Brasil: um relato de caso

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ABSTRACT

Creutzfeldt-Jakob disease (CJD) is a rare spongiform encephalopathy characterized by a rapid neurodegenerative progress, caused by a misfolded variant of the cellular prion protein (PrP) known as PrPSc. The clinical presentation of sCJD includes a wide range of neurological signs of cortical, subcortical, or cerebellar origin, either isolated or in various combinations. Due to this protean clinical presentation form, sCJD must be distinguished from other dementias. In this case report, we discuss the Heidenhain variant of Creutzfeldt-Jakob disease (HvCJD), a rare variant characterized by early visual symptoms and typical findings in imaging scans. Our patient presented rapidly progressive dementia and a history of visual hallucinations. As for other prion diseases, only symptomatic treatment is available for HvCJD. Thirty years of clinical investigation of patients with prion disease have resulted in little progress in either defining or evaluating potential treatments.

KEYWORDS: dementia; geriatrics; prion diseases; prion proteins.

RESUMO

A doença de Creutzfeldt-Jakob (DCJ) é uma encefalopatia rara caracterizada por rápida progressão neurodegenerativa, causada pelo enovelamento incorreto da proteína priônica celular (PrP), conhecido como PrPSc. O quadro clínico da DCJ esporádica inclui um amplo espectro de sinais neurológicos de origens cortical, subcortical ou cerebelar, seja de forma isolada, seja combinada. Por causa da sua apresentação clínica variável, a DCJ esporádica deve ser distinguida de outras demências. Neste relato de caso, discutimos a variante Heidenhain da DCJ (vHDCJ), uma variante rara caracterizada por sintomas visuais precoces e características específicas no exame de imagem. Nossa paciente apresentou demência rapidamente progressiva e histórico de alucinações visuais. Assim como para as demais doenças priônicas, apenas o tratamento sintomático está disponível para a vHDCJ. Trinta anos de investigação clínica de pacientes com doença priônica têm resultado em pouco progresso, seja definindo os potenciais tratamentos, seja avaliando-os.

PALAVRAS-CHAVE: demência; geriatria; doenças priônicas; proteínas priônicas.

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BACKGROUND

Creutzfeldt-Jakob disease (CJD) is a rare spongiform encephalopathy characterized by a rapid neurodegenerative progress, caused by a misfolded variant of the cellular prion protein (PrP) known as PrP^{Sc}.[1] CJD occurs more commonly in its sporadic form (sCJD), although other forms of transmission exist.[2] The clinical presentation of sCJD includes a wide range of neurological signs of cortical, subcortical, or cerebellar origin, either isolated or in various combinations. According to Baiardi et al., different strains of prions, likely enciphered by alternative conformations of PrP^{Sc}, are the main cause of this phenotypic diversity.[1] Due to this protean clinical presentation form, sCJD must be distinguished from other dementias. Occasionally, Alzheimer disease, dementia with Lewy bodies, and corticobasal degeneration are associated with myoclonus and a more rapidly progressive course than is typical, and are therefore mistaken for CJD.[3]

In this case report, we will discuss the Heidenhain variant of Creutzfeldt-Jakob disease (HvCJD), a rare variant characterized by early visual symptoms.[4] Our patient presented with rapidly progressive dementia and a history of visual hallucinations. The fact that visual symptoms may persist in isolation for weeks without cognitive decline or motor signs, sometimes causing diagnostic difficulty, makes the Heidenhain variant of particular clinical interest. As for other prion diseases, only symptomatic treatment is available for HvCJD.[5] Thirty years of clinical investigation of patients with prion disease has resulted in little progress in either defining or evaluating potential treatments. All patients with these conditions should be followed and managed within a structured framework, preferably within randomized controlled trials.[6]

CASE PRESENTATION

A 54-year-old Brazilian woman was first evaluated at the Brasília University Hospital in March 2012, in response to a family complaint of forgetfulness of recent events since January 2011. According to her husband, as of December 2010, she was completely independent, but in May 2011 the family realized she was no longer bathing. By July, she required assistance for all activities of daily living, had developed a speaking disorder, and had sustained a fall followed by seizure-like tremors. The patient reported visual and auditory hallucinations, cried easily, was unable to speak more than 10 words, and could no longer ambulate. One month before her Hospital appointment, she became incontinent, requiring diapers.

Her medical history was remarkable for acute myocardial infarction with angioplasty, hypertension, smoking (30 pack-years, stopped in 2009), and a family history of Alzheimer disease (her mother had been diagnosed at age 70). She had no history of diabetes, thyroid disease, or psychiatric disorders. Her medications included metoprolol succinate 50 mg/day, olmesartan medoxomil 20 mg/day, acetylsalicylic acid 100 mg/day, amlodipine 5 mg/day, simvastatin 10 mg/day, escitalopram 10 mg/day, memantine hydrochloride 10 mg/day, clonazepam 0.25 mg/day, and quetiapine 100 mg/day. On physical examination, rest and intention tremors were identified; muscle reflexes were symmetrical. The patient also had constipation, with bowel movements every 4 days.

Laboratory studies showed normal levels of vitamin B12, thyroid-stimulating hormone, and free T4. Serologies for the human immunodeficiency virus and syphilis were negative. Magnetic resonance imaging (MRI) of the brain, performed in January 2011, showed foci of white-matter and unspecific high T2 signal abnormalities, that may be related to microangiopathy. Electroencephalography showed 4 c/s slow-wave outbreaks in the temporal regions. The P300 evoked potential did not suggest a deficit in the conduction of cognitive pathways linked to mindfulness. A neuropsychological evaluation demonstrated temporo-spatial disorientation, impaired apraxia, and altered executive functions.

Cerebrospinal fluid analysis was negative for toxoplasmosis, cytomegalovirus, herpesvirus I and II, protein 14-3-3, neoplastic cells, and *Cryptococcus neoformans*. Laboratory tests for tuberculosis were negative. A second brain MRI was performed in March 2012 (Figure 1) noticed a remarkable volume loss, and diffusion weighted imaging (DWI) showed restriction in occipital cortex, suggesting neuron loss related to prion disease/spongiform encephalopathy.

In October 2012, the patient was hospitalized for a urinary tract infection and discharged after 24 days. Her inpatient course was complicated by decubitus ulcers on the ear, sacral region, and feet. By December 2012, the patient was bedridden with immobility syndrome and completely dependent. She died on February 23rd, 2013.

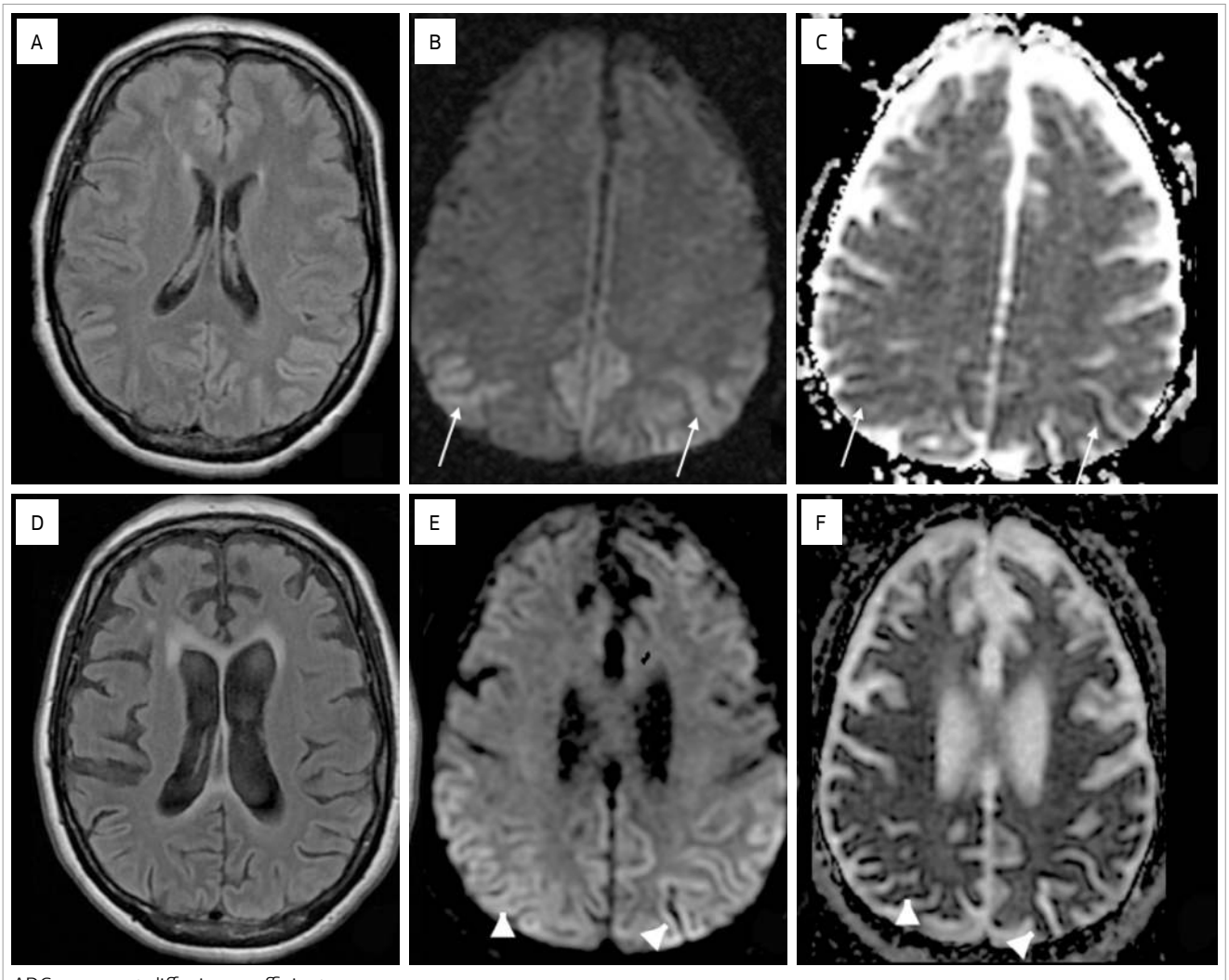
DISCUSSION

Creutzfeldt-Jakob disease (CJD) is one of the human transmissible spongiform encephalopathies or prion diseases, a group of neurodegenerative disorders characterized by tissue deposition of the misfolded (PrP^{Sc}) form of the cellular prion protein PrP.[1] It is a rare, rapidly progressive neurodegenerative disease, with no gender predilection, preferentially affecting patients between the fifth and eighth decades of life. CJD can be classified as sporadic, which is the most common form, accounting for 85% of cases; inherited, which is

caused by various heritable mutations in the prion protein (*PRNP*) gene; iatrogenic, caused by inoculation of prions through contaminated materials; or a variant form (vCJD), which usually results from the transmission of bovine spongiform encephalopathy to humans, most commonly through the consumption of contaminated meat.[7]

A limited number of conditions, all of which are relatively uncommon, produce a syndrome of rapidly progressive dementia that can be mistaken for CJD. Some are treatable; therefore, the evaluation should be thorough. Early in the disease course, a primary psychiatric disorder may be suspected, as behavior and personality changes may be prominent enough to obscure accompanying cognitive deficits. CJD must be distinguished from other dementias. Alzheimer disease, dementia with Lewy bodies, and corticobasal degeneration may sometimes occur with myoclonus and a rapidly progressive course, and may thus be misdiagnosed as CJD.[3] The wide-ranging clinical presentation of sCJD may be explained by different strains of causative prions, probably encoded by alternative PrP^{Sc} conformations.[1]

At present, subtypes of sCJD are more usually classified according to the genotype of *PRNP* codon 129 and the molecular properties of PrP^{Sc}. The *PRNP* genotype may be homozygous or heterozygous for methionine (M) or valine (V) at codon 129. The PrPSc type is determined by Western blot analysis and classified in the Parchi and Gambetti



ADC: apparent diffusion coefficient.

Figure 1 (A, B, C) First row shows prior magnetic resonance imaging (MRI) and (D, E, F) second row the last one. They are 78 days apart. (A, D) Fluid attenuated Inversion Recovery (FLAIR) images show a brain atrophy with ventricular enlargement. Diffusion weighted imaging (DWI) (B and E: B=1000; C, F: ADC maps) demonstrates diffusion restriction at occipitoparital cortex (arrows in first exam and arrowheads in the last one). Cortical diffusion restriction may correlate with pathological findings on neurons loss.

nomenclature as type 1, type 2, or type 1 + 2, depending on the size and electrophoretic mobility of the protease-resistant core fragment (PrPres).[1,8] The current sCJD classification recognizes six major variants, with distinctive clinicopathological features. The MM1/MV1 classic CJD phenotype accounts for approximately 70% of cases; it is characterized by advanced age at onset, a rapidly progressive dementia with early and prominent myoclonus, and a short duration of illness (mean 3.9 months). The VV2 ataxic variant accounts for approximately 10% of sCJD cases, and presents with ataxia at onset, often as an isolated feature; late dementia; and a slightly longer duration of illness (mean 7 to 9 months). The MV2 kuru plaque variant accounts for another 10% of sCJD cases, and presents with ataxia, progressive dementia with prominent psychiatric features, and longer duration of illness (mean 17.1 months). MM2T (thalamic MM2 or sporadic form of fatal insomnia, sFI) accounts for 2% of cases and is characterized by prominent atrophy of thalamic and inferior olivary nuclei, insomnia, psychomotor hyperactivity, ataxia, and cognitive impairment; the mean disease duration is 15.6 months. MM2C (cortical MM2) accounts for another 2% of cases, with a mean disease duration of 15.7 months; dementia is the predominant manifestation, while cerebellar and visual signs are rarely described at presentation. Finally, VV1 accounts for only 1% of cases and is notable for progressive dementia, younger age at onset, and longer duration (mean 15.3 months).[1,8,9]

Mixed types, comprising clinicopathological features of two pure types (especially MM1 and MM2C), have also been recognized. The Heidenhain variant of CJD is linked to the MM-MV1, MM2C, and MM2C+1 types of sCJD (1). The clinical course (slower progression) and laboratory findings (CSF negative for 14-3-3 protein, EEG with slow-wave complexes) of our patient are most consistent with the MM2C + 1 type. However, diagnostic confirmation will not be possible, since the patient's family refused brain necropsy.

The estimated prevalence of HvCJD ranges from 3.7% to 4.9% of all cases of sCJD,[1] which, in turn, has an annual incidence of approximately 1 care per million population.[10] Although several case reports of HvCJD have been published in the literature, there are no prevalence data for the Heidenhain variant in Brazil.

The classic clinical manifestation of HvCJD is cortical blindness, due to involvement of the parieto-occipital cortex.[7] Isolated visual symptoms including poor vision, disturbed perception of colors or structures, visual defects, hemianopsia, visual agnosia, abnormal color/spatial perception and optical distortions, as well as optical hallucinations without any ocular disease, may also occur.[1,11] At disease onset, patients apparently not fully demented typically give up reading or watching television due to visual impairment, with visual field restriction, blurred vision, vision loss, or even total blindness. Metamorphosia, optical hallucinations, or visual neglect are additional manifestations. The clinical picture can be classified as typical of Heidenhain variant if visual disorders occur as the leading symptom and if these disorders remain predominant over the course of the disease.[2]

Our patient presented with early visual hallucinations and a rapidly progressive dementia. Other findings, such as myoclonus, resting tremors, intention tremors, and MRI evidence of prion disease without indication of any other possible etiology on routine investigation, suggests a probable diagnosis of HvCJD. The fact that visual symptoms may persist in isolation for weeks, without cognitive decline or motor signs, makes the Heidenhain variant of particular diagnostic interest. Indeed, affected patients sometimes present to ophthalmologists and are subjected to needless ocular interventions with risk of onward transmission.[1]

Histopathological analysis remains the gold-standard diagnostic method, showing marked neuronal loss, spongiform changes, intense astrogliosis, and immunoreactivity to PrP^{Sc}.[12] Some tests can be helpful in providing clinical support for the diagnosis: on brain MRI FLAIR images show high signal in the cortex, usually most pronounced in the parietal and occipital lobes. Diffusion restriction at DWI may occur in the same regions. MRI with DWI has 91% sensitivity and 95% specificity, and 94% accuracy with DWI for CJD diagnosis, although it is not part of any formal criteria for the diagnosis of sCJD.[13] The Heidenhain variant usually show MRI abnormalities (80%), usually occipitoparietal restriction on DWI or hypersignal on FLAIR.[14] In HvCJD, the electroencephalogram typically shows acute, periodic triphasic waves, predominantly in the posterior areas.[15] Analysis of the cerebrospinal fluid can reveal elevated 14-3-3 protein levels (above 35 ng/mL). DNA analysis may show homozygosity for methionine at codon 129 of *PRNP*.[2]

There is no cure yet for any prion disease, nor any treatment that slows the progression of the disease; only symptomatic interventions are available. The prognosis is dismal, with death usually occurring within a year of diagnosis.[5,16] A number of potential therapies have been investigated in sCJD, such as flupirtine, pentosan polysulfate (PPS), quinacrine, and doxycycline. While hampered by methodological limitations, including heterogenous patient populations and small trial sizes, these studies have not demonstrated any treatment effect, whether symptom improvement or longer survival.[9] Some experimental strategies targeting the prevention of prion diseases are under development, such as one study

of an innocuous misfolded protein that seems to compete with pathogenic prions[17] and another of a compound that showed therapeutic effect on bovine spongiform encephalopathy-infected macaques.[18] Unfortunately, these strategies remain in the early stages of development, and there are no specific treatments that can prolong the lifetime of patients with the Heidenhain variant of Creutzfeldt-Jakob disease.

CONCLUSION

Although sporadic Creutzfeldt-Jakob disease is rare, its protean clinical presentation makes it an important component of the differential diagnosis in any investigation of dementia. The Heidenhain variant is associated with more than one subtype of sCJD, including mixed subtypes, and is thus a particularly challenging diagnosis due to its variable symptoms and test results — our patient is an example of HvCJD with negative 14-3-3 protein in CSF. Sadly, the prognosis for prion diseases remains dismal, with irreversible neurologic degeneration, psychiatric manifestations, and death within a year of diagnosis. Despite many years of research, there is no cure yet for any prion disease, and current treatment strategies are restricted to symptom management. The hope remains that future research may discover therapies capable of overcoming the wide range of clinical presentations of sCJD and demonstrating significant treatment effects.

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