Case report

Possible Creutzfeldt-Jakob disease in a patient with a transplanted heart valve: case report, correlations and literature review

Possivel doença de Creutzfeldt-Jakob em paciente com válvula cardíaca biológica: relato de caso, correlações e revisão da literatura

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ABSTRACT

INTRODUCTION: Creutzfeldt-Jakob Disease (CJD) is a rare neurodegenerative disorder caused by the accumulation of abnormal prion proteins. It is characterized by rapidly progressive dementia, with an annual incidence of approximately 1 case per 1 million people. Most cases are sporadic, with an unclear pathophysiology. Around 5–15% are genetic, and less than 1% occur iatrogenically, including after procedures such as valve graft implantation. Diagnosis is complex and relies on clinical presentation supported by neuroimaging and electroencephalogram (EEG).

CASE REPORT: A 74-year-old woman with heart failure and a history of biological mitral valve replacement in January 2024 presented with a 3-month history of cognitive decline, behavioral changes, visual hallucinations, dysarthria, and ataxia, with worsening symptoms over the prior week. Brain MRI showed cortical diffusion restriction, and EEG revealed triphasic periodic complexes, both highly suggestive of CJD. Other potential diagnoses were excluded. Due to age, comorbidities, and rapid clinical decline, a brain biopsy was not performed. The patient was discharged with comprehensive palliative care and nutritional support via gastrostomy.

DISCUSSION: CJD presents with rapidly progressive dementia and can occurs iatrogenically after procedures. MRI and EEG findings are critical for diagnosis. While cerebrospinal fluid biomarkers such as RT-QuIC may aid in confirmation, definitive diagnosis requires histopathology. No curative treatment is currently available.

CONCLUSION: CJD should be considered in cases of rapidly progressive dementia. It can be occurred in iatrogenic way in patients who undergo procedures involving biological grafts. Early diagnostic evaluation and timely palliative care involvement are essential due to the disease's invariably fatal course.

Keywords: Creutzfeldt-Jakob disease, Heart Transplantation, Neurodegenerative disorders

RESUMO

INTRODUÇÃO: A Doença de Creutzfeldt-Jakob (DCJ) é uma doença neurodegenerativa rara, causada pelo acúmulo de proteínas príons anormais. Caracteriza-se por demência rapidamente progressiva, com incidência anual de aproximadamente 1 caso por 1 milhão de pessoas. A maioria dos casos é esporádica, com fisiopatologia incerta. Cerca de 5% a 15% são de origem genética e menos de 1% ocorrem iatrogenicamente, inclusive após procedimentos como implante de enxerto valvar. O diagnóstico é complexo e depende da apresentação clínica, apoiada por neuroimagem e eletroencefalograma (EEG).

RELATO DE CASO: Uma mulher de 74 anos com insuficiência cardíaca e histórico de substituição da valva mitral biológica em janeiro de 2024, apresentou declínio cognitivo, alterações comportamentais, alucinações visuais, disartria e ataxia há 3 meses, com piora dos sintomas na semana anterior. A ressonância magnética do encéfalo mostrou restrição à difusão cortical e o EEG revelou complexos periódicos trifásicos, ambos altamente sugestivos de DCJ. Outros diagnósticos potenciais foram excluídos. Devido à idade, comorbidades e rápido declínio clínico, uma biópsia cerebral não foi realizada. A paciente recebeu alta com cuidados paliativos abrangentes e suporte nutricional por gastrostomia.

DISCUSSÃO: A DCJ se apresenta com demência rapidamente progressiva e pode ocorrer iatrogenicamente após procedimentos. Os achados de ressonância magnética e EEG são críticos para o diagnóstico. Embora biomarcadores do líquido cefaloraquidiano, como RT-QuIC, possam auxiliar na confirmação, o diagnóstico definitivo requer histopatologia. Nenhum tratamento curativo está disponível atualmente.

CONCLUSÃO: A DCJ deve ser considerada em casos de demência rapidamente progressiva. Ela pode ocorrer de forma iatrogênica em pacientes submetidos a procedimentos que envolvem enxertos biológicos. Avaliação diagnóstica precoce e envolvimento oportuno de cuidados paliativos são essenciais, devido ao curso invariavelmente fatal da doença.

Palavras-chave: Doença de Creutzfeldt-Jakob, Transplante cardíaco, Doenças neurodegenerativas

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INTRODUCTION

Creutzfeldt Jakob Disease (CJD) is a rare neurodegenerative disease characterized by rapidly progressive dementia that invariably results in the death of the affected individual. It has an annual incidence of approximately 1 case per 1 million people.[1] The disease was initially described in 1920 by Hans Gerhard Creutzfeldt and Alfons Jakob[2] and belongs to the group of transmissible spongiform encephalopathies. These are neurodegenerative diseases caused by prions, which are small particles containing an abnormal isoform of a protein naturally present in the human body.[3] From a pathophysiological point of view, prions can be deposited in various organs of the body, with special emphasis on the brain, retina and optic nerve. The deposition of prions in the brain parenchyma ends up leading to neuronal dysfunction due to synaptic loss and invariably neuronal death, manifesting from a histopathological point of view with the characteristic spongiform appearance, classically described in the literature[3,4,5].

The vast majority of CJD cases occur sporadically, accounting for 85% of cases, and the physiopathogenis is unknown in most of cases. Approximately 5-15% have a genetic basis for the disease, with a mutation identified in the PrP gene[3]. Less than 1% of cases may occur iatrogenically, which may occur in the context of surgical manipulation, especially organ transplantation including valve graft.[1] The transmissibility of the disease between humans was first reported in 1974, in a 55-year-old female patient who developed compatible symptoms 18 months after corneal transplantation from a donor with the disease who had already died. Subsequently, cases of CJD have been reported in the literature associated with other surgical procedures, such as dural graft transplantation, liver transplantation and through contaminated neurosurgical instruments.[1]

The transmissibility of the disease was demonstrated through studies in 1986, through the reproduction of the disease and characteristic histopathological findings in chimpanzees. During this period, it was observed that the disease has a prolonged incubation period, ranging from months to years, and presents a fatal course, usually in weeks to months.[3] In a case report published in 2016, the possibility of the disease developing after implantation of a biological heart valve in humans, originating from cattle, was raised. In this specific case, the patient underwent valve prosthesis 5 years before the onset of symptoms, subsequently developing a characteristic picture of the disease.[1]

CASE REPORT

A 74-year-old female patient with heart failure and a history of biological mitral valvuloplasty in January 2024 came to the emergency room due to mental confusion that had been developing for 3 months and had worsened for 1 week, associated with vertigo, dysarthria, ataxia, urinary incontinence, visual hallucinations, behavioral changes, and sleep disorders. She denied fever. The companion reported that the patient had had similar episodes that had been developing for three months, but none of the episodes had been of this intensity or duration, and that the loss of functionality had progressed over the last 20 days. The patient was admitted to a tertiary hospital for investigation of differential diagnoses of acute psychosis and delirium. During etiological screening, signs of infection were evidenced in a partial urine sample, and it was treated as a urinary tract infection in an elderly person, justified by the possible delirium. A cycle of antibiotic therapy and measures to control psychomotor agitation were performed.

During hospitalization, the patient developed worsening agitation and emotional lability, and the emergency care team was called to evaluate the patient and optimize the haloperidol dose. During the initial evaluation by the geriatrics team, the patient was confused, drowsy, and disoriented in time and space, and was suspected of having rapidly progressive dementia. The patient was advised to rule out causes of reversible dementia, such as hypothyroidism or other metabolic disorders, and to continue treatment for urinary tract infection, as the infection is an important contributor to delirium. Two CSF samples, collected due to behavioral changes to rule out encephalitis, were clear, with no cellularity, no protein and no other abnormalities. An EEG with a report of triphasic periodic complexes was requested for further diagnostic workup (figure 1).

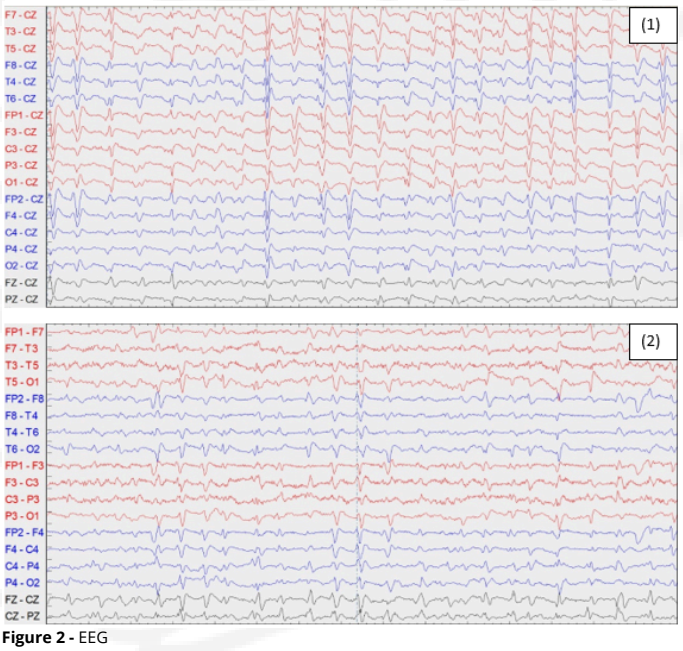

Figure 2 - EEG

(1)Reference assembly of earpieces (A1 A2) - Sensitivity 7 µV/mm, High Filter = 40 Hz, Low Filter = 0.5 Hz, Notch 60Hz on
(2)Anteroposterior lag, often seen in triphasic waves (a subtype of Generalized Periodic Discharges), finding wich suggests CJD

An MRI showed restricted water diffusion in cortical areas, characteristic of CJD (figure 2).

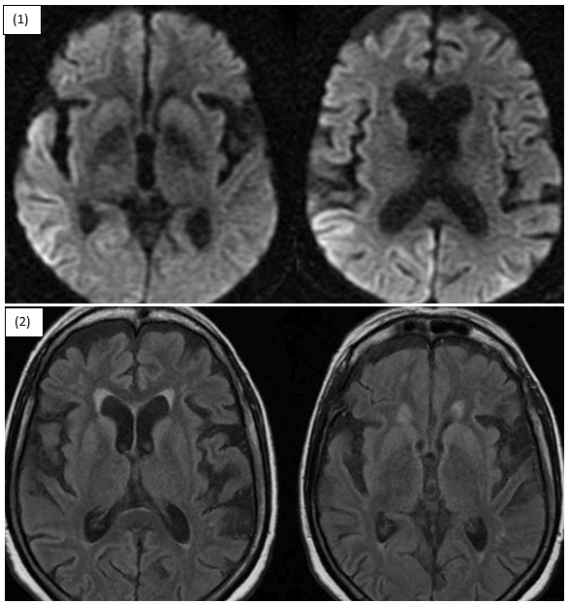

Figure 1 - Brain's MRI:

(1) DWI sequences cortical hyperintensity predominantly in right cerebral hemisphere . Furthermore, the caudate nucleus show hyperintense signal in this same sequence.
(2) FLAIR sequence the same signals shown in the DWI.

The neurological physical examination showed altered levels of consciousness, ideomotor apraxia, hypertonia with global rigidity, and bilateral Babinski sign.

Given the classic clinical signs, mainly marked by myoclonus, and complementary MRI and EEG exams, the main hypothesis raised was CJD. However, diagnostic confirmation is only performed with histopathological analysis through brain biopsy. Since this was an elderly patient with relevant cardiovascular comorbidity and significant loss of functionality and performance, it was not possible to perform this procedure. Assessment of tau protein levels and RT-QuIC in cerebrospinal fluid was considered as part of the diagnostic workup, however, testing was not performed due to the lack of institutional authorization, primarily related to the high associated cost. After ruling out other rapidly progressive causes of dementia and undergoing psychiatric evaluation, the patient was discharged with comprehensive home care, contact with the Palliative Care team, and nutritional support via gastrostomy.

DISCUSSION

While the majority of CJD cases are sporadic, iatrogenic transmission, though uncommon, remains a possibility, particularly in patients who undergo procedures involving biological materials. Our patient had a history of biological mitral valve replacement, a procedure that carries a potential risk of transmitting prion diseases, including CJD. Although such instances are rare, there have been reports of CJD following the implantation of biological valves derived from bovine tissue. A 2016 case report illustrated the development of CJD in a patient who presented with symptoms five years after receiving a biological heart valve. While the precise mechanism of prion transmission through tissue grafts remains unclear, the occurrence of CJD following such procedures, though infrequent, raises concerns about a possible link. In this case, the patient's clinical presentation, characterized by rapidly progressive dementia, myoclonus, dysarthria, ataxia, and visual hallucinations, combined with the characteristic MRI findings of cortical diffusion restriction (figure 1) and EEG showing triphasic periodic complexes, strongly pointed to CJD (figure 2). Although the definitive diagnosis of CJD requires histopathological confirmation through brain biopsy, the clinical presentation and diagnostic findings were sufficiently compelling to suggest the possibility of prion transmission via the biological valve. It is noteworthy that the onset of symptoms occurred months after the surgery, which is consistent with the prolonged incubation period often observed in prion diseases.

There is no evidence in literature confirming that patients with biological valve graft can develop Creutzfeldt Jakob disease. Nevertheless, this paper underscores a relevant causal history in symptom development, which may prompt clinicians to investigate this association and include prior biological valve grafts in the patient's medical history during anamnesis. Clinically, patients with CJD present with rapidly progressive dementia associated with cerebellar and visual disturbances, as well as myoclonus, pyramidal dysfunction, and akinetic mutism. Complementary examinations are of fundamental importance for differential diagnosis, especially brain MRI, which, with characteristic findings, can provide support for diagnostic criteria.[3] The sporadic form of CJD also presents some variants according to the predominantly affected region of the brain. Among them, the Heidenhain variant, characterized by significant visual dysfunction from the onset of the condition, the Oppenheimer-Brownell variant with cerebellar disturbance, and the cognitive variant, among others.[3] According to Hashoul et al, an 82-year-old woman was diagnosed with the Heidenhain variant of Creutzfeldt–Jakob disease, with visual disturbances rather than cognitive decline, after a bovine bioprosthetic aortic valve implantation five years earlier. Her initial symptom was unexplained visual loss, followed by rapidly progressive dementia and neurological deterioration. Diagnostic findings included homonymous hemianopsia, nonspecific brain MRI changes, characteristic EEG patterns, and elevated tau protein levels in the cerebrospinal fluid. The patient died 2.5 months after symptom onset. No autopsy was performed. This was the first known report linking Heidenhain variant of CJD to a bovine pericardium-derived bioprosthetic valve, raising the possibility of prion transmission through such implants. Though definitive

proof is lacking, the time interval and clinical findings suggest a potential connection.[1]

In our case, it was also an older woman with rapidly dementia symptoms but after 3 months of the valve graft. The cognitive and motor symptoms were predominated. Patients with CJD typically present prodromes of anxiety disorder, blurred vision, dizziness, asthenia, and behavioral changes. A highly characteristic and classically described sign of the disease is myoclonus, often induced by sensory stimuli. Myoclonus is present in up to 90% of cases.[3] Neuropsychiatric symptoms are common in affected patients, including complex dementia with cortical function disorders such as apraxia, aphasia, and visuospatial difficulties. Some patients may have psychotic manifestations, with visual hallucinations.[3] Cerebellar dysfunction, characterized by nystagmus and ataxia, may occur in up to two-thirds of patients, associated with pyramidal involvement with signs of hyperreflexia, Babinski sign, and spasticity in approximately 40 to 80% of cases. Some patients may also present extrapyramidal dysfunction, with bradykinesia, dystonia, and global muscle rigidity. Late stages of the disease are characterized by akinetic mutism.[3] Other correlations cases were described, according to Kouyoumdjian et al, a 76-year-old man was diagnosed with Creutzfeldt-Jakob Disease after a chemical trauma to the right eye from plant sap 12 to 18 months prior, and the authors note a speculative link between plant viroids and prion disease. The report also discusses the potential role of príons as the infectious agent. Concerns are raised about iatrogenic transmission, particularly through human growth hormone therapy from cadaveric pituitary glands, citing cases reported in the 1980s.[2]

In the evaluation of suspected cases of the disease, complementary exams should be performed, such as brain MRI, EEG and analysis of CSF.[3] Brain MRI presents findings highly characteristic of sporadic forms, with high sensitivity and specificity. Typical findings are hyperintensities in the T2-FLAIR sequence with diffusion restriction in the caudate, putamen and cerebral cortex (figure 1), present in up to 80% of cases.[3] Diffusion-weighted sequence (DWI) is of great value for suspected cases of the disease, demonstrating excellent diagnostic accuracy. In DWI, lesions are most frequently found in the neocortex and striatum simultaneously (60% of cases), followed by neocortex in isolation (30%) and striatum in isolation (7%). Lesions in the thalamus and cerebellum may also be evidenced.[7] EEG can reveal patterns highly suggestive of CJD when combined with other compatible clinical findings. It can be found diffuse slowing and frontal rhythmic delta activity or lateralized discharges in early stages, periodic sharp wave complexes in intermediate and late stages and even areactive coma or alpha waves. The electroencephalographic pattern classically described in the disease is triphasic waves (a subtype of Generalized Periodic Discharges – figure 2), but biphasic waves can be seen to. Within the compatible clinical picture, the electroencephalographic tracing can present specificity of up to 90% for CJD. It is important to emphasize that such findings can be found in other diseases that are differentially diagnosed with CJD, such as advanced Alzheimer's disease, dementia with Lewy bodies and metabolic encephalopathies.[6] CSF examination is usually within normal limits; however, some patients may manifest increased protein in up to 40% of cases. Four different proteins can be detected in the CSF of patients to aid in diagnostic reasoning, among them: 14-3-3 protein, tau protein, neuronal specific enolase and S-100. A high level of nonphosphorylated tau protein in the CSF has greater specificity than the 14-3-3 protein for the condition. The 14-3-3 protein is considered an adjuvant test for diagnosis, but is not necessarily mandatory, and a negative result does not exclude the disease.[3] Also noteworthy is the use of real-time tremor-induced conversion (RT-QuIC), assessed through CSF, with a sensitivity of 91% and specificity of 98%. It should be noted that specific CSF tests are not widely available in many countries, making other complementary tests such as cranial MRI and EEG essential.

[3]In recent years, some therapeutic possibilities for CJD have been sought, but none of them have demonstrated significant improvement in symptoms or increased survival, therefore, it is a disease with no effective treatment and an invariably fatal course. Supportive measures for symptomatic treatment include the management of neuropsychiatric disorders and myoclonus, which may respond to benzodiazepines and some anticonvulsants such as levetiracetam or valproate. Considering the average age of diagnosis, cases of CJD can be confused with other neurological conditions that commonly affect the elderly population, such as dementia with Lewy bodies, autoimmune encephalitis, Alzheimer's disease and other psychiatric disorders.[8] Therefore, CJD is a rare diagnosis that should be especially remembered in patients with rapidly progressive dementia and associated myoclonus. EEG and cranial MRI patterns are characteristic and support the diagnosis.[3] According to the World Health Organization (WHO), definitive diagnosis of the disease is made through histopathological analysis of the affected brain parenchyma.[1]

CONCLUSION

CJD is a rare neurodegenerative disease characterized by rapidly progressive dementia. It can be occur in iatrogenic way in patients who undergo procedures involving biological grafts. It is difficult to definitively diagnose due to the complexity of performing a brain biopsy for histopathological analysis. Currently, there is no treatment that alters symptoms or mortality. Complementary exams such as MRI, EEG and CSF are essential to confirm the diagnostic suspicion, presenting characteristic findings of the disease.

Differential diagnoses are extremely important and other types of dementia, other neurological and psychiatric diseases should be investigated. Since there is no proven treatment for the disease, management consists of symptom relief and comfort measures, including linking the patient and family with the Palliative Care team.

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