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REVISTA AMAZÔNIA Science & Health

Creutzfeldt-Jakob Disease: First Cases Reported In The Brazilian Amazon

Doença De Creutzfeldt-Jakob: Primeiros Casos Notificados Na Amazônia Brasileira

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ABSTRACT

Objective: report three cases of Creutzfeldt-Jakob disease in the Amazon's interior, demonstrate the evolution of the clinical picture and diagnosis of the disease, study the relationship between COVID-19 and the triggering or acceleration of the prion disease and analyze the difficulties for diagnosis. **Methods:** a series of cases composed of three patients with a condition compatible with Creutzfeldt-Jakob disease, where two of them were infected by the coronavirus. It is an observational and descriptive study and the data were collected from the medical records. **Results:** all three patients had an expected clinical picture for the condition, characterized by myoclonus and neurological decline in several functions, especially cognitive, behavioral, and cerebellar. Two of them had COVID-19, but it is unsure whether there is a relation between it and the triggering or an accelerated progression of the prion disease. In this study, all patients died from sepsis secondary to pneumonia within an interval of 3 to 9 months. **Conclusion:** The dissemination of knowledge about Creutzfeldt-Jakob disease and professional capacity may be relevant for a more assertive diagnosis in remote places such as the Amazon and its relationship with COVID-19 needs to be better elucidated.

Keywords: Creutzfeldt-Jakob disease. Prion diseases. Prion proteins. SARS-Cov-2. Amazon region.

RESUMO

Objetivos: relatar três casos de doença de Creutzfeldt-Jakob no interior da Amazônia, demonstrar a evolução do quadro clínico e diagnóstico da doença, estudar a relação entre COVID-19 e desencadeamento ou aceleração da doença priônica e analisar as dificuldades para o diagnóstico. **Métodos**: trata-se de uma série de casos composta por três pacientes com quadro compatível com a doença de Creutzfeldt-Jakob, dentre os quais dois apresentaram infecção pelo coronavírus. É um estudo observacional, descritivo e os dados foram coletados a partir da análise dos prontuários. **Resultados**: os três pacientes apresentaram um quadro clínico esperado para a condição, caracterizado por mioclonias e declínio neurológico em diversas funções, especialmente cognitiva, comportamental e cerebelar. Dois dos pacientes apresentaram COVID-19, porém não se pode afirmar decerto se existe uma correlação direta entre ela e o desencadeamento ou uma progressão acelerada da doença priônica. Neste estudo, todos os pacientes evoluíram a óbito por sepse secundária a pneumonia em um intervalo que variou de 3 a 9 meses. **Conclusão**: A difusão do conhecimento sobre a doença de Creutzfeldt-Jakob e a capacitação profissional podem ser relevantes para um diagnóstico mais assertivo em lugares remotos como a Amazônia e a sua relação com a COVID-19 precisa ser melhor elucidada.

Palavras-chave: Doença de Creutzfeldt-Jakob. Doenças priônicas. Proteínas priônicas. SARS-Cov-2. Região Amazônica.

1. INTRODUCTION

The Creutzfeldt-Jakob disease (CJD) is a rapidly progressive dementia caused by the accumulation of prion proteins, which are pathogenic infectious proteins devoid of nucleic acid, which differs them from any known infectious agent.[1] It is a rapidly progressive neurodegenerative disorder that is clinically manifested through dementia, myoclonus, pyramidal and extrapyramidal signs, besides to cerebellar dysfunction, leading mostly to death in less than one year. CJD is classified as sporadic, genetic, iatrogenic and variant, being the sporadic form responsible for about 85% of cases and with a global incidence of 1 to 2 cases per 1 million inhabitants/year, with a discreet predominance on female.[2-3]

In Brazil, 603 suspected cases were reported between 2005 and 2014, where only 55 of them were confirmed, with a higher incidence on the South and Southeast, possibly due to the higher availability of diagnostic resources.[4-5] With the emergence of COVID-19, the hypothesis of a possible association of a more accelerated progression of CJD with SARS-CoV-2 infection has been reported, suggesting that this, by activating the systemic inflammatory cascade, might precipitate or accelerate neurodegenerative processes associated with prion diseases.[6-7]

The objective of this study was report three cases of Creutzfeldt-Jakob disease in the Amazon's interior, demonstrating the evolution of the disease's clinical picture and diagnosis, besides studying the relationship between COVID-19 and the triggering or acceleration of the prion disease and analyzing the difficulties in diagnosing the disease.

2. MATERIALS AND METHODS

It is the report of a series of cases composed by three patients with Creutzfeldt-Jakob disease and agrees with the recommendations of the Circular Letter No. 166/2018-CONESP/SECNS/MS on the processing of this type of study. It is an observational and descriptive study, since only observation and recording of the data collected was carried out, without the intervention of the researchers .[8] It is also characterized as transversal and retrospective, since it has aimed to record data from the past and its evolution over time.[9]

Sample Characterization

Composed of three adult patients, confirmed cases of Creutzfeldt-Jakob disease. Two of the patients had SARS-CoV-2 infection.

Techniques And Instruments

After evaluation and approval by the ethics council of the university through the opinion 5.106.784, in accordance with Resolution 466/12 of the National Health Council (NHC), data were collected between January and February 2022, based on the analysis of information from the medical records of the patients, including anamnesis, physical examination and complementary exams, such as magnetic resonance imaging (MRI), electroencephalogram (EEG) and cerebrospinal fluid (CSF) analysis, being recorded and described using the Microsoft Word 2010, objectively and in chronological order of events, to describe the general picture of the clinical presentation and evolution of the disease.

3. RESULTS

Three male patients were evaluated, two of whom presented SARS-CoV-2 infection. The medical history of each patient is described below.

Patient 1: male, 69 years old, farmer, resident of Santarém, Pará. Was admitted to hospital in February 2020 due to motorcycle trauma. In December of the same year, has evolved with tremor and involuntary movements in the right hand, with progression to the left side about a month later. Concomitantly, there was weight loss (about 30 kg), difficulty walking, memory loss and mood disorder. In the neurological examination, he was alert, disoriented, Mini Mental State Examination (MMSE) of 5, vertical conjugate gaze paresis, myoclonus in the upper limbs, tremor, grade 5 muscle strength (except in the hands), mild global spasticity, fasciculation in the pectoral and bicipital regions and bilateral Babinski sign. MRI revealed diffuse cortical atrophy and hypersignal with gyral distribution in posterior temporal lobes (Figure1). EEG detected a slowed background rhythm in the theta range, frequent multifocal epileptiform activity, and patches of generalized periodic complex discharges at 1-2 cycles/second. Lumbar puncture showed positive 14.3.3 protein, positive Tau protein and positive RT-QuIC. Over time, has evolved with tetraparesis, behavior

oscillation, agitation, infantile reactions (clapping) and sphincter dysfunction. It was confirmed that he had Covid-19. Died in about 9 months.

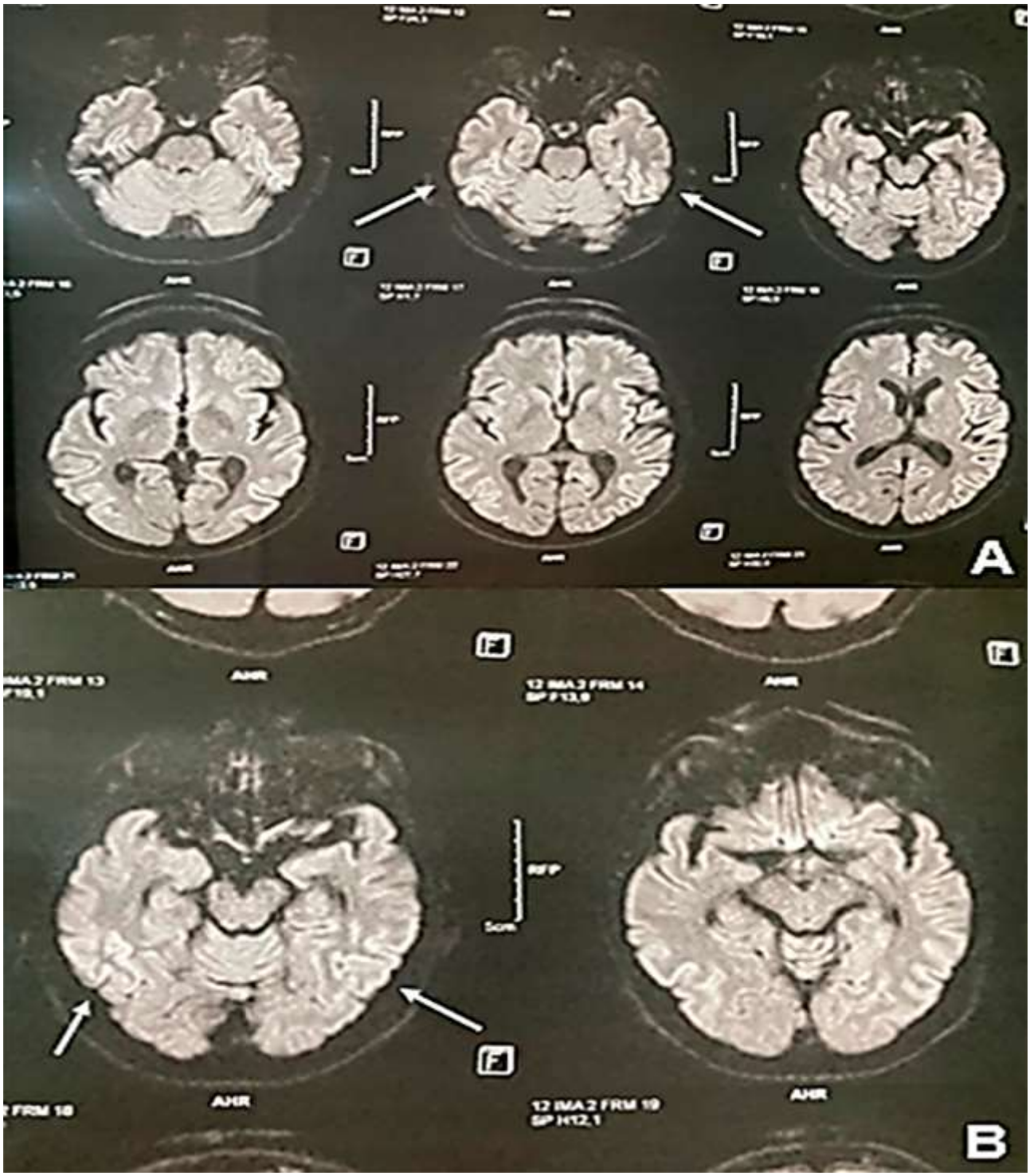
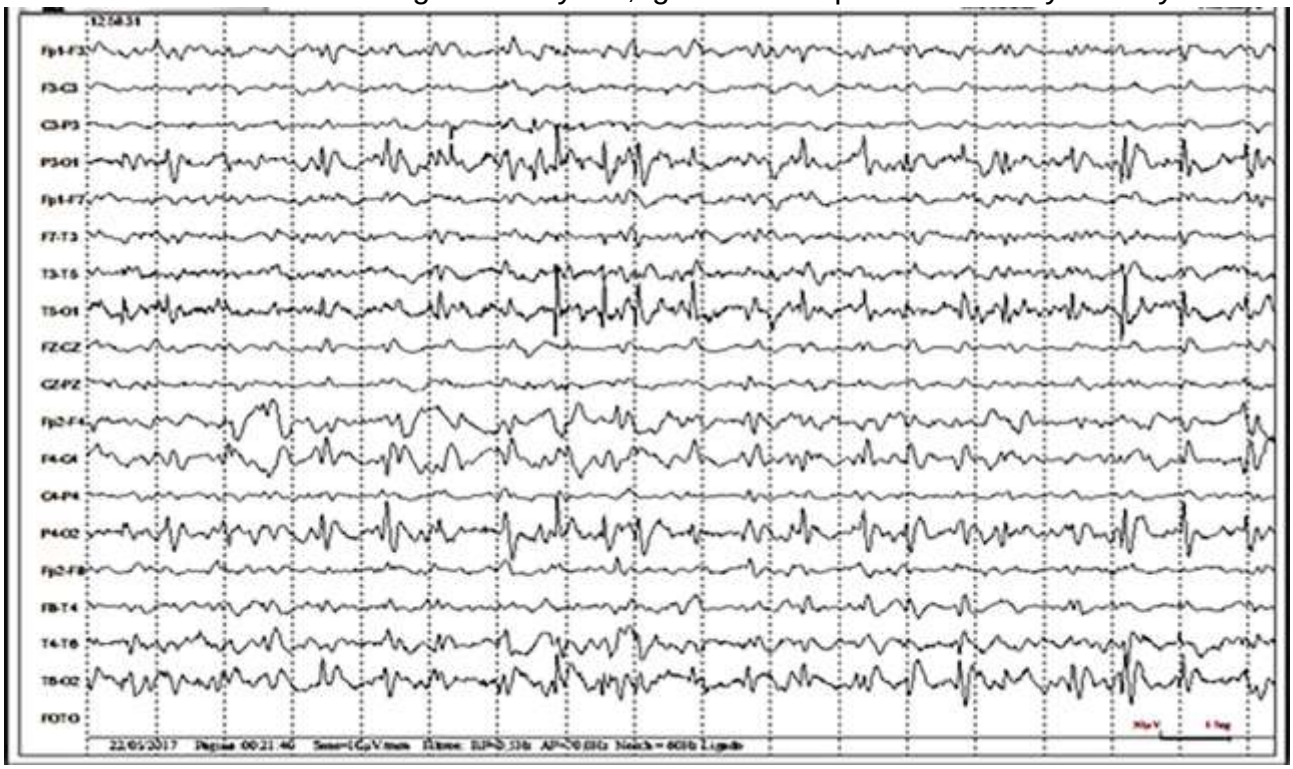


Figure 1. Brain magnetic resonance imaging, axial slices, of patient 1, showing diffusion restriction in: A) affecting the cortex of the posterior regions of the temporal lobes (arrows); B) reaching the parietal lobe cortex bilaterally (arrows), 2020.

Patient 2: male, 59 years old, civil engineer, resident of Macapá, Amapá. In September 2020, was evaluated with memory loss, irritability, mood disorder, aphasia, tremor and worsening of coordination in the past two weeks. Showed a Covid-19 clinical picture in August 2020. On neurological examination he was inattentive, slowed, aphasic (expression), with apraxia, global deep hyperreflexia, bilateral Babinski sign, tremor, myoclonus in the upper limbs and MMSE of 16. EEG with slowed background rhythm in the theta range, frequent focal epileptiform activity in parieto-occipital regions and rare generalized paroxysms. Cranial MRI revealed hyperintense lesions in FLAIR sequences and diffusion reaching the basal nuclei bilaterally. He was hospitalized for pulse therapy with methylprednisolone for three days, given the possibility of autoimmune encephalitis. After one month, liquor analysis showed positive 14.3.3 protein, positive Tau protein and positive RT-QuIC. Evolved with agitation, needing sedatives. Then, with aspiration pneumonia and septic shock, worsening of aphasia, myoclonus, stiffness and global spasticity. Died in about 5 months.

Patient 3: male, 84 years old, farmer, resident of Óbidos, Pará. In March 2017, was evaluated with memory loss, confusion, spatial disorientation, insomnia, and MMSE of 18. Over weeks, he evolved with gait loss, myoclonus, loss of sphincter control and disorientation in time and space. Cranial MRI showed moderate diffuse cortical atrophy. EEG revealed slowed background rhythm, generalized periodic activity 1-2 cycles/sec



practically continuous, suggestive of prion disease (Figure 2). Lumbar puncture detected positive 14.3.3 protein. Died within three months.

Figure 2. Fragment of electroencephalogram of patient 3 showing generalized periodic complexes of high voltage with a frequency of 1-2Hz in wakefulness, with higher voltage in the posterior areas, 2017.

Table 1 shows the main clinical data and complementary exams related to each patient for comparison.

Table 1. Sociodemographic and clinical data, and complementary exams of patients, 2023.

VARIABLES	PATIENT 1	PATIENT 2	PATIENT 3
AGE	69 years old	59 years old	84 years old
OCCUPATION	Farmer	Civil Engineer	Farmer
GENDER	Male	Male	Male
PREVIOUS CONDITIONS	Arrhythmia	SAH	AMI
START OF DISEASE	February/2020	September/2020	March/2017
LANGUAGE DYSFUNCTION	Yes	Yes	No
AGRAPHIA	No	Yes	No
MEMORY LOSS	Yes	Yes	Yes
MINI MENTAL STATE EXAMINATION	5	16	18
GAIT CHANGE	Yes	Yes	Yes
AGITATION/AGGRESSIVENESS	Yes	Yes	No
DISORIENTATION IN TIME/SPACE	No	No	Yes
TREMOR	Yes	Yes	No
MYOCLONUS	Yes	Yes	Yes
ATAXIA	Yes	Yes	Yes
APRAXIA	No	Yes	No
MOOD DISORDERS	Yes	Yes	No
INSOMNIA	No	No	Yes
FEVER	No	Yes	No
HYPERREFLEXIA	No	Yes	No
STRENGTH/SENSITIVITY DEFICIT	Yes	No	No
BABINSKI SIGN	Yes	Yes	No
SPASTICITY	Yes	Yes	No
SPHINCTER DEFICIT	Yes	No	Yes
CEREBROSPINAL FLUID	Positive 14-3-3 protein, positive Tau protein and positive RT-QuIC	Positive 14-3-3 protein, positive Tau protein and positive RT-QuIC	Positive 14-3-3 protein
MAGNETIC RESONANCE IMAGING	Global atrophy and changes in the diffusion of sulci and gyri in posterior temporal lobes	Lesions in the basal nuclei	Moderate diffuse cortical atrophy
ELECTROENCEPHALOGRAM	Slowed background rhythm, frequent multifocal epileptiform activity, and generalized periodic complex discharges at 1-2 cycles/second	Slowed background rhythm, frequent focal epileptiform activity in parieto-occipital regions and rare generalized paroxysms	Slowed background rhythm, generalized periodic activity 1-2 cycles/sec practically continuous
COVID-19 INFECTION	Yes	Yes	No

CAUSE OF DEATH	Aspiration pneumonia, sepsis	Aspiration pneumonia, sepsis	Aspiration pneumonia, sepsis
DURATION OF DISEASE	9 months	5 months	3 months

Source: produced by the authors, 2023.

4. DISCUSSION

Prion diseases are neurodegenerative diseases that are part of rapidly progressive dementia syndromes. They are also called transmissible spongiform encephalopathies (TSEs) due to the histopathological characterization of vacuoles formation in the gray matter of the central nervous system (CNS), which gives it a spongy appearance and can be transmitted between animals of the same or different species.[10]

It is a pathology that causes several neuropsychiatric symptoms resulting from the accumulation of infectious agents composed exclusively of proteins, which are called prions. Consequently, there is apoptosis and cell death of the nervous tissue. The main prion diseases found in humans are Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI) and Kuru, with CJD being the most common one.[11-12]

It is a disease of variable etiology, with sporadic, genetic and iatrogenic forms being described. Genetic causes are classically associated with three forms with similar clinicopathological characteristics: FFI, familial CJD and GSS, in addition to the form associated with mutation in the prion related protein gene (PRNP).[13] The iatrogenic form is characterized by transmitting the infectious agent through the use of contaminated surgical instruments, growth hormone extracted from contaminated corpses, human dura mater grafts, corneal transplantation, use of contaminated electrodes in surgical procedures and blood transfusions.[14]

The sporadic form of CJD is the most common and has its peak incidence between 55 and 75 years of age, with a duration of about 1 year until death.[13] Patients in this study had the onset of the disease at a mean age of 70.6 years. Patients 1 and 2 were in the age group in agreement with the available literature. Patient 3 had a later-onset form, but clinical and complementary exams findings are similar in individuals under or over 80 years old, except for myoclonus and cerebellar symptoms that tend to be less common in individuals over 80 years old.[15]

Besides specific genetic alterations, such as the PRNP mutation, there are no known risk factors for CJD.[16] All the patients in the study had a cardiovascular history, but this relationship is not described in the literature and their coexistence can be explained by the high prevalence of cardiovascular diseases in this age group.

The initial clinical picture can be variable, being cognitive manifestation the most common in the beginning, followed by cerebellar syndrome and behavioral symptoms. Some patients may also present nonspecific prodromal manifestations that are difficult to establish a precise topography, such as fatigue and asthenia, headache, vertigo, sleep disturbances and unexplained weight loss. Ocular motor manifestations, aphasia, apraxia, acalculia, among others, may also be evidenced. Due to this wide range of manifestations, the diagnosis of the disease is difficult at the beginning of the condition and can be confused with several other neurological or psychiatric diseases.[13]

In our study, patients 2 and 3 started with memory deficits consistent with the classic presentation of the disease.[13] Patient 2 initially presented irritability and mood disorder as well. There are other cases in the literature where neuropsychiatric manifestations have opened the disease and therefore CJD shall be remembered when such abnormalities are associated with cognitive decline, myoclonus or ataxia.[17]

Insomnia was reported in patient 3. It is known that in addition to it, hypersomnia and restless legs syndrome have already been described in the disease.[18] Patient 1 had the onset of his clinical picture with tremor and involuntary movements in the right upper limb after trauma in a motorcycle accident. There are not enough data on trauma and CJD to establish a causal link between these two variables.

Confirmatory diagnosis of the disease is only possible through post-mortem analysis of prions in the brain tissue. However, it can be assumed through the association of different propaedeutic methods, such as typical changes in electroencephalogram (EEG), cranial magnetic resonance imaging (MRI), and biomarkers present in the cerebrospinal fluid (CSF), as well as the clinical manifestations of the patient.[3]

Typical MRI finding is hyperintensity on T2 and FLAIR sequences, involving the cortical area and basal nuclei, mainly head of the caudate and putamen, associated with brain atrophy. Eventually, hyperintensity may be subtle or absent, especially early in the disease. Changes in the globus pallidus, thalamus, white matter, and cerebellar cortex may also be seen.[19]

Patients in this study showed expected changes on MRI. Patient 1 presented global atrophy and changes in diffusion affecting the sulci and gyri in the posterior temporal lobes, characteristic of the disease, while patient 2 had predominant lesions in the basal nuclei bilaterally. Patient 3 presented only moderate diffuse cortical atrophy, probably because the examination was done early in the disease.

Regarding the EEG, all patients in this study had a slowed background rhythm in the theta range. In addition, patients 1 and 3 had generalized discharges of periodic complexes of 1 to 2 cycles per second. Historically, the EEG is one of the first exams to be done in case of clinical suspicion of CJD, the characteristic finding being the generalized sharp biphasic or three-phase discharges of 1 to 2 Hz, present in patients 1 and 3 of this study. However, these findings may be late. Typically, slowing in the theta range as background rhythm is initially observed, which may or may not be associated with typical discharges.[13,20]

The CSF analysis is useful in ruling out infections or other encephalitis. [12]Also, the search for 14-3-3 protein with variable sensitivity and specificity for CJD can be done.[13] In this study, all patients showed positive 14-3-3 protein. Another available biomarker is the total tau (t-tau) protein, which has greater diagnostic accuracy than other biomarkers alone.[21] There is also the detection of the prion in the liquor through a technique called real-time-quaking-induced conversion (RT-QuIC), which consists of the amplification of the prion in amyloid fibrils. It has a specificity of 99 to 100%, but reduced sensitivity, and can be used along with the more sensitive tests mentioned above, increasing the diagnostic capacity.[22]

Patients 1 and 2 in this study were positive for t-tau protein and RT-QuIC, corroborating the data available in the literature. In this study, the time taken for the diagnosis of the disease through the detection of specific biomarkers in the CSF ranged from 3 to 4 months, above what other studies show, with an average of 2 to 3 months from the onset of symptoms to diagnosis.[23]

In about 90% of cases, patients with CJD evolve to death within 12 months, usually due to infectious complications.[24] In this study, all patients died from sepsis secondary to pneumonia, in agreement with the data in the literature. There is a hypothesis about the association of the disease with SARS-CoV-2 infection. Young et al.[6] reported a case of a previously healthy patient who simultaneously developed, within just two weeks, both COVID-19 and CJD, suggesting that the infection, by activating the systemic inflammatory

cascade, can precipitate or accelerate neurodegenerative processes associated with prion diseases.[6]

On the other hand, Ciolac et al.[25] described the case of a patient with a previous diagnosis of CJD who, after an acute infection with the new coronavirus, presented an important neurological decline resulting in death within three weeks.[25] In our study, patients 1 and 2 had COVID-19. Patient 2 sought care for the first time in December 2020, with the onset of the neurological clinical picture approximately 2 to 3 months earlier. He had COVID-19 in August of the same year. Evolved to death about 6 months after the onset of symptoms due to sepsis secondary to aspiration pneumonia. A case with similar clinical evolution and 4-month survival was reported.[26]

However, in disagreement with previous cases reports about this association, Watson et al.[23] analyzed 148 individuals diagnosed with CJD during the pandemic by the new coronavirus, and these patients showed higher mortality from COVID-19 than the general population, since they previously had functional deficits or hospitalizations, but observed no association between SARS-CoV-2 infection and decline in neurological status.[23] However, an impact that the pandemic brought to these patients was the logistics itself in the clinical field and diagnosis of the disease, which was also observed in other diseases, as attested by other authors.[27]

This fact may be even more significant in remote regions, such as the Amazon, due to the difficulty of accessing diagnostic methods, then limiting the reception, diagnosis and, consequently, the ideal care for patients with CJD and other uncommon diseases in our environment.

5. CONCLUSION

The Creutzfeldt-Jakob disease is a valuable diagnosis because, although very rare, its early recognition from the most common symptoms may avoid unnecessary treatments and exams, as well as assist in future studies on new treatment possibilities. Its confirmation and management are still a challenge in remote locations and where there are few medical resources, such as the Amazon. The pandemic has raised the possibility that COVID-19 is a catalyst for triggering or accelerating CJD, but this is still unclear and requires further study.

The importance of further research directed to this disease is emphasized, both in relation to the treatment, which remains of a supportive-palliative nature, as well as in relation to methods that enable professionals to more accurately diagnose this condition,

since, as it is a very rare pathology, cases of this type might be underreported, especially in regions without access to cutting-edge technology, such as the Amazon.

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