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Case Series

Sporadic Jakob-Creutzfeldt Disease: A Diagnostic Challenge in Low-Income Countries

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Abstract

Jakob-Creutzfeldt disease (JCD) is a fatal degenerative brain disorder caused by prion proteins. This condition belongs to the group of transmissible spongiform encephalopathies affecting people worldwide, with an incidence of 1 case per million per year. Due to the heterogeneity of symptoms and signs, prion diseases are considered a diagnostic and therapeutic challenge, due to the nonspecificity of the clinical presentation. We present three cases initially diagnosed with other conditions, subsequently establishing the definitive diagnosis of JCD. Next, a state-of-the-art review regarding this disorder will be carried out, and its implications in differential diagnosis and epidemiological surveillance.

Keywords: *Transmissible spongiform encephalopathies; Prion disease; Creutzfeldt–Jakob disease; Rapidly progressing dementia.*

Introduction

Prion diseases are a group of rare neurodegenerative disorders characterized by the presence of an abnormal form of an endogenous protein called prion-related protein (PrP) [1]. Historically, these diseases can be traced back to the 18th century, with scrapie being identified in sheep and goats [2]. In 1921, Alfons Maria Jakob described several cases of this terrible disease and one more in 1923, which he related to another case published by Hans Gerhard Creutzfeldt. In the incoming years, it was identified that only two cases published by Jakob correspond to the disease as we currently know it. Due to that, authorities in neurology are proposing the name change to Jakob-Creutzfeldt disease (JCD) in some articles and textbooks [3, 4]. Therefore, this term is considered more accurate and will be used in this article.

Due to the heterogeneity of symptoms and signs, prion diseases are considered a diagnostic and therapeutic challenge, especially due to the nonspecificity of the clinical picture, the epidemiological rarity, the difficulty in performing molecular tests (especially in low-income countries), and until now, the categorical absence of specific treatment and unconditional mortality.

Next, three cases initially diagnosed as other conditions will be presented, where the definitive diagnosis of JCD was stablished a *posteriori*. Subsequently, a state-of-the-art review regarding this disorder will be carried out, including its implications in differential diagnosis and epidemiological surveillance.

Case Reports

Case 1

A 63-year-old man, with no significant history, began his illness in October 2022 characterized by asthenia, adynamia, hyporexia, and dizziness, accompanied by visual hallucinations, and was treated on multiple occasions for apparent urinary tract infections. In November 2022 he began to have unstable gait and unspecified tremor of the upper extremities. He was hospitalized in another institution with the diagnosis of central nervous system (CNS) infection and probable Parkinson's disease. In January 2023, his voluntary discharge was decided, and he was transferred to Hospital General de México "Dr. Eduardo Liceaga" (HGMEL), where he was found in stupor, decreased oxygen saturation, rigidity-type hypertonia in the right upper extremity, and generalized myoclonus predominantly in the jaw, which was exacerbated by external stimuli.

The patient presented a torpid evolution, requiring advanced airway management, establishing the diagnosis of community-acquired pneumonia and probable viral encephalitis, and was transferred to the intensive care unit (ICU). The diagnostic protocol was initiated with a lumbar puncture (LP) with the next features in the cerebrospinal fluid (CSF): red, cloudy, leukocytes: 5 mm^3, erythrocytes 1650 mm^3, crenocytes: 0 mm^3, glucose 145 mg/dl, microproteins: 766.76 mg/dl, LDH: 560.40 IU/L, chloride 145.20 mmol/L. A CSF sample was sent for a polymerase chain reaction (PCR) meningitis and encephalitis panel which was negative, as well as serological studies, which were also negative. A non-contrast enhanced brain computed tomography (CT) was performed as an initial imaging study, which did not show significant abnormalities or those that were consistent with the patient's clinical picture.

In February 2023, he was admitted to the HGMEL neurology service, finding himself comatose, and showing myoclonus in the face and right upper extremity, which were compatible with focal epileptic seizures, which were treated with levetiracetam and valproate. A first electroencephalogram (EEG) was performed, which showed the presence of generalized polymorphic delta-theta brain activity, attributed to cortical-subcortical dysfunction, reflecting an encephalopathic pattern. Two weeks later, a second EEG was performed in which left centrotemporal focal epileptiform discharges were documented with a baseline activity characterized by generalized polymorphic delta waves. The patient did not experience myoclonic seizures again after adjustment of anti-seizure medications. A third follow-up EEG was abnormal showing periodic epileptiform discharges and generalized slowing (Fig. 1).

In March 2023, a magnetic resonance imaging (MRI) of the brain was performed showing a decrease in frontal cortical volume and showing hyperintensities on diffusion-weighted images (DWI) in the left frontal cortex, right temporal cortex, insulae, and left basal nuclei (Fig. 2). A second LP was performed where pleocytosis with 22 cells at the expense of neutrophils and mild hyperproteinorrachia was documented. CSF was sent for study to pathology, only reporting inflammatory alterations. Given the suspected diagnosis of JCD, it was decided to send a sample for determination of 14-3-3 protein, presenting a positive result with >80,000 U/ml.

The clinical characteristics, in conjunction with the imaging findings, neurophysiological and biochemical studies, were compatible with the diagnosis of JCD. It was decided to discharge the patient at the conclusion of the diagnostic approach, taking into consideration the prognostic implications.

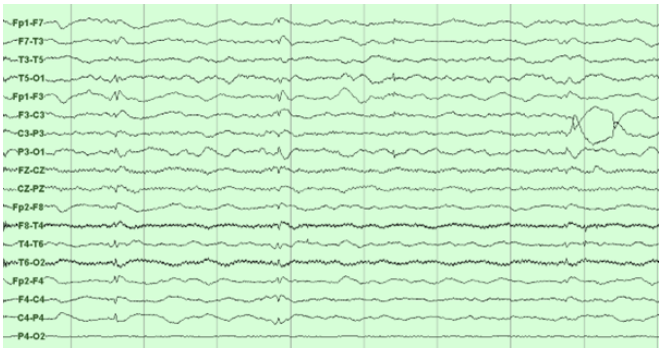

Figure 1. *EEG with periodic epileptiform discharges and generalized slowing.*

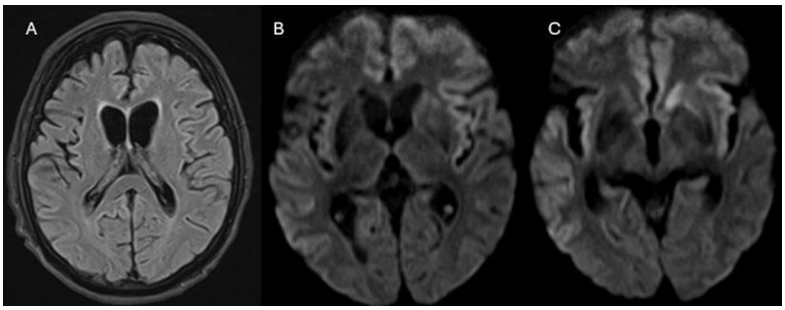

Figure 2. *MRI of patient presented in case 1.* ***A)*** *T2-FLAIR brain image showing decrease in frontal cortical volume.* ***B)*** *DWI image showing hyperintensities in bilateral frontal mesial cortex, as well as in both insulae. An image suggestive of hockey sticks sign in both pulvinars.* ***C)*** *DWI showing the alterations described in image B, as well as hyperintensities in both caudate nuclei, with predominance of the left one.*

Case 2

In January 2024, a 64-year-old woman with no significant history began with uncontrollable crying, disorientation in time and space, and decreased speech production associated with prolonged periods of inattention alternating with staring. Two weeks later she started experiencing anorexia, loss of sphincter control, and unstable gait. She was initially evaluated by a general practitioner who made the diagnosis of urinary tract infection, for which she received antimicrobial treatment, without improvement. In February 2024, the family members observed involuntary movements in the right side of the face, so it was evaluated by neurosurgery in a private setting, identifying the movement as myoclonus. She was hospitalized for suspected encephalitis and empirical antiviral therapy with acyclovir was started. Due to lack of financial resources, his voluntary discharge was requested. The patient developed stiffness in her extremities and difficulty walking, which made her mobilization impossible. She persisted with limitation in the production of words, and only made incomprehensible sounds. She was admitted at the emergency room where she was evaluated by the neurology service, finding herself in stupor and with spasticity of all four extremities with a decortication position.

The diagnosis of infectious encephalitis was suspected, so empirical antimicrobial treatment was started in accordance with international guidelines. An LP was performed, which showed no abnormalities. The patient completed a cycle of treatment without showing improvement, so the diagnosis was reconsidered as autoimmune encephalitis. The diagnostic protocol was initiated and treatment with pulses of methylprednisolone was initiated. A second LP was performed which also showed no abnormalities. A brain MRI was performed where hyperintensities were observed on T2-weighted images, DWI and on fluid attenuated inversion recovery (FLAIR) images, in the superior frontal gyrus, superior parietal lobe, cingulate gyrus and insula, head of the caudate nucleus and putamen (Fig. 3). The EEG performed showed focal epileptiform activity in the right temporal frontal region and quasiperiodic secondary bilateral synchronization phenomenon. Treatment with levetiracetam was started. After treatment with systemic steroid, the patient continued without improvement. CSF sample for biochemical diagnosis was sent, identifying 14-3-3 protein levels of >80,000 U/ml. Given the clinical context, as well as the paraclinical findings, the diagnosis of JCD was established. The last EEG showed generalized triphasic waves and generalized slowing (Fig. 4). The patient was subjected to nutritional support measures and management of secretions, and was discharged home in March 2024 for achieving maximum therapeutic benefit.

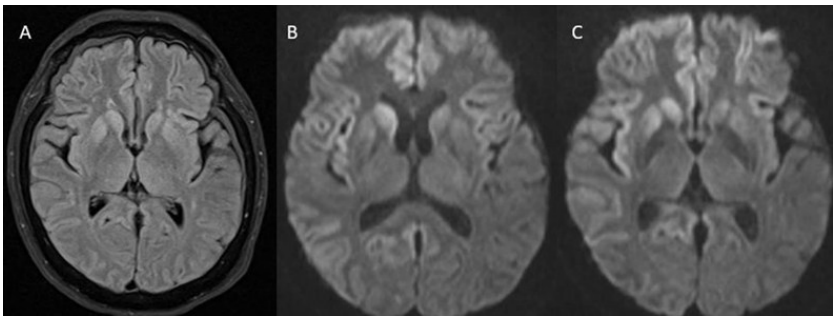

Figure 3. *MRI of patient presented in case 2.* ***A)*** *T2-FLAIR brain image showing discrete hyperintensities in the cortex as well as in the basal ganglia.* ***B)*** *DWI image showing hyperintensities in bilateral frontal cortex with predominance of the mesial region and both insulae and basal ganglia being more prominent in the right head of the caudate nucleus.* ***C)*** *DWI showing the alterations described in image B in a more dorsal view*

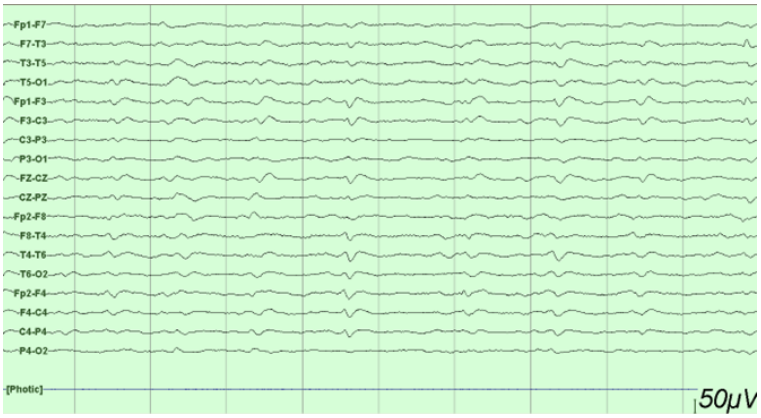

Figure 4. *EEG with generalized triphasic waves (0.7 Hz /250 ms) and generalized slowing.*

Case 3

A 56-year-old man with type 2 diabetes mellitus and arterial hypertension, started with vertigo in March 2022. Later in August 2023 he manifested a staggering gait, as well as bilateral pelvic limb weakness that started proximally, progressing to distal in a month and a half with dragging feet, that progress to prostration in 3 months. It was accompanied with muscle spasms of the four extremities and nocturnal myoclonus. A year later he presented speech disorders characterized by bradylalia, hypophonia and dysarthria, in addition to alterations in semantic memory, as well as apraxia for writing, irritability, aggressiveness and abnormal hyperkinetic movements with postural and action tremor of great amplitude, which prevented him from holding objects. Also, he presented agitation and nightmares, accompanied by loss of control of sphincters.

On May 2024 he was admitted to HGMEL, having fluctuation in attention status, disorientation and altered semantic memory. A Montreal Cognitive Assessment (MoCA) was performed with a score of 10/30 points with visuospatial/ executive, abstraction, deferred memory, attention, language and orientation impairment. The physical examination showed paratonia and hypotrophy of the four limbs, dysmetria and bilateral dysdiadochokinesia. The patient had action, postural and intention tremor. The examination of the gait reveled difficulty in standing, and inability to initiate ambulation.

During the diagnostic approach, the LP performed showed a colorless CSF with the following characteristics leukocytes 0 mm^3, erythrocytes 165 mm^3, glucose 70.41 mg/dl, microproteins 57.41 mg/dl, LDH 29 IU/L, chloride 122 mmol/L. Another CSF sample was sent for a PCR meningitis and encephalitis panel which was negative. A non-contrast brain MRI was performed, showing hyperintensities in the cortex, hippocampus, basal ganglia and thalami in T2 and T2 FLAIR (Fig. 5). The EEG during sleep was normal, showing involuntary movements in the left limbs without electroencephalographic correlation (Fig. 6). Given the findings, another CSF sample was sent for 14-3-3 protein determination, resulting in 67,815 U/mL, confirming the diagnosis of JCD.

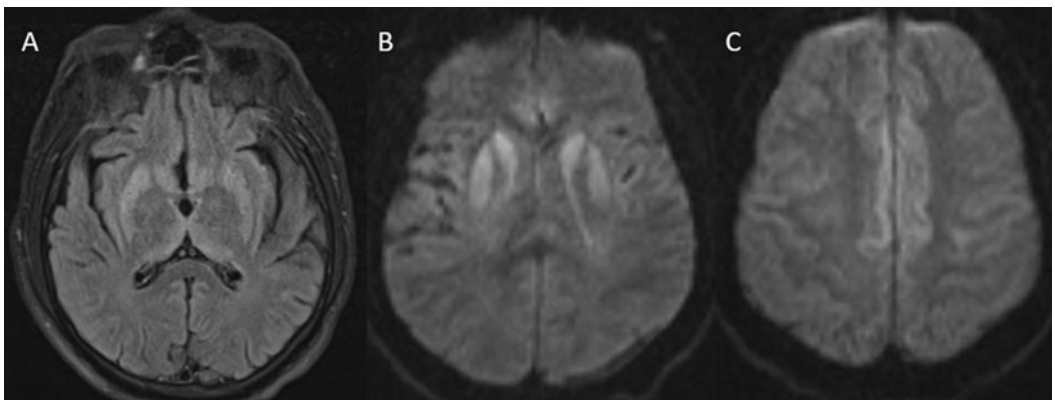

Figure 5. *MRI of patient presented in case 3.* ***A)*** *T2-FLAIR brain image showing hyperintensities in the basal ganglia. The hockey stick sign can be observed as well.* ***B)*** *DWI image showing hyperintensities in the basal ganglia and in both insulae.* ***C)*** *DWI showing hyperintensities in the mesial region of the dorsal frontal and parietal cortex.*

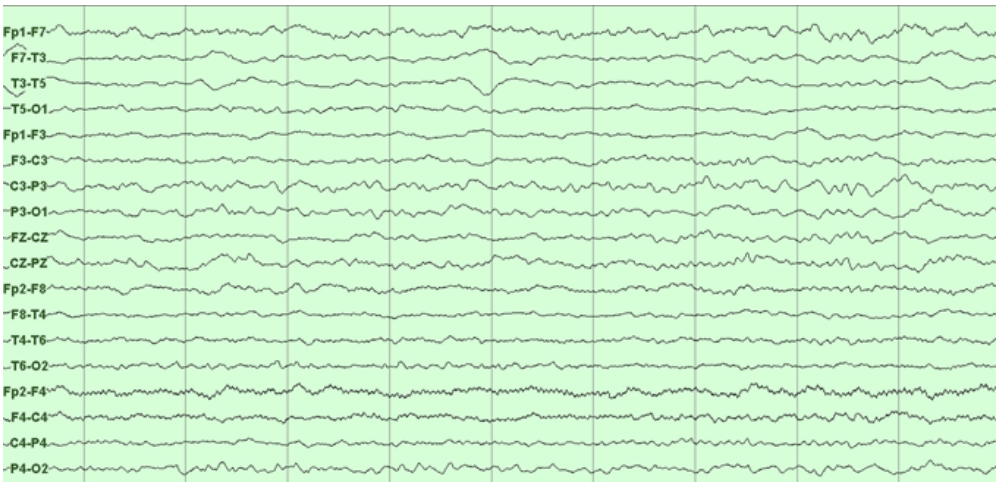

Figure 6. *Normal EEG during sleep. The patient showed involuntary movements in the left limbs without any electroencephalographic changes.*

Literature Review

Epidemiology

Globally, the incidence is 1 to 2 cases per million people, this with geographical variations, with a greater number of cases in developed countries [5], generating disparities. In Mexico, JCD has been underdiagnosed. The only series of cases come from a national center, being to date the reference regarding the epidemiology of these disorders [6, 7]. Due to its low incidence identified worldwide, to date there are no epidemiological studies in Mexico that evaluate this indicator, estimating around 110 cases per year [8]. Between 1995 and 2011, 26 cases were identified [9], and between 2014 and 2019 another 24 patients were identified [7]. It had previously been mentioned that in Mexico there is a low overall incidence compared with other countries [9]. This could be explained by the low availability of diagnostic methods, as well as the low rate of diagnostic suspicion. The above is consistent with what was described by Watson et al., considering that epidemiological surveillance of JCD is extremely difficult [10], especially in countries with limited resources.

Etiology and pathogenesis

In 1985, prions were identified as the cause of JCD [11]. As previously mentioned, there is an endogenous protein, PrPC (C refers to its normal cellular form), which is encoded by the PRNP gene. It has its locus on chromosome 20, whose function is not fully understood until now [12], and which is probably related to copper metabolism in the CNS, cell adhesion, calcium modulation and interactions with receptors of N-methyl-D-aspartate (NMDAr), and antiapoptotic actions with subsequent neuroprotection. The pathogenic form of the protein, PrPSc (Sc refers to scrapie, a prion disease in sheep), has a different structure, being composed of 12 beta sheets, although with a similar amino acid sequence [4]. A fascinating feature about prions is their ability to polymerize and replicate, as if it were an infectious agent [13]. In the sporadic variants of the disease, it is not clear how the endogenous protein makes the conformational change that converts it into a prion [14]. However, once this transformation occurs, PrPSc induces the abnormal folding of PrPC, acting as a model or template that generates the conversion of the normal protein to the abnormal one in an exponential manner and a tendency to form proteinaceous aggregates that cause injury and neuronal death [15]. It is important to note that other proteins that cause neurodegeneration such as α-synuclein can have a pathogenic behavior similar to prions [16]. Mutation of PrPC towards its misfolded form leads to direct neurotoxicity, as well as loss of physiological functions leading to the manifestation of the disease [17]. The term spongiform encephalopathies was used synonymously with this group of neurodegenerative disorders, however, neuropathological studies of the sporadic variant of JCD (sJCD) may show absence of these changes, or mild to severe abnormalities [4].

Phenotype of prion diseases

Sporadic Jakob-Creutzfeldt disease

sJCD is the most common form of the disease, covering 85% of cases [5, 12]. The incubation period is extremely long, from one to 42 years [5]. Rapidly progressive dementia (RPD), defined as a neurocognitive impairment which progresses in less than two years [18], is one of the most frequent manifestations of sJCD, this also being identified in Mexico [7]. In fact, JCD is considered the second cause of RPD, after Alzheimer's disease [19]. In addition to RPD include neuropsychiatric disorders, cerebellar abnormalities such as ataxia, movement disorders such as myoclonus [12], as well as visual disorders [20], which, when they appear as an initial manifestation of the disease, is known as the Heidenhain variant [4, 21]. In 1998, Parchi and collaborators established a classification of six subtypes of sJCD [22], which are useful in the histopathological and clinical context, based on the molecular characteristics of the PRNP gene, receiving nomenclature according to homozygosity or heterozygosity to methionine and valine.

- Subtype 1 (MM1 and MV1) - It is the most common form (40%) and is characterized by a survival of 3 to 4 months, with RPD, ataxia, myoclonus, and visual disorders within the Heidenhain variant.
- Subtype 2 (VV2) - The ataxic-cerebellar variant, where ataxia is the initial manifestation, accompanied by upper motor neuron signs and myoclonus, as well as RPD.
- Subtype 3 (MV2) - Initially described as the ataxic variant of Brownell-Oppenheimer [23], which is accompanied by cognitive and psychiatric abnormalities, which are more common than subtype 2.
- Subtype 4 (MM2-cortical) - Patients present with cognitive impairment (main sign) and aphasia with myoclonic jerks, upper motor neuron signs, and epileptic seizures in late stages.
- Subtype 5 (VV1) - This is the rarest form of JCD, with onset around age 39 (early-onset sJCD), and characterized by psychiatric symptoms and dementia.
- Subtype 6 (MM2-thalamic) - Patients present with insomnia and psychomotor hyperactivity, with ataxia and cognitive impairment. It is also a rare form and is considered to be indistinguishable from familial fatal insomnia (FFI), which is why it is also known as sporadic fatal insomnia (sFI). Patients may also present dysautonomia [24].

The histopathological description of each of the variants exceeds the objectives of this article. It is noteworthy that cognitive abnormalities are found in all variants, and according to the original study, they were found in more than 67% of each subtype [22]. The first patient presented in this article could belong to subtype 1 of the classification of Parchi, while the second patient is consistent with subtype 4, this according only to her clinical characteristics.

In Mexico, a mean survival of 5.8 months has been reported according to the latest published case series [7], which is consistent with what is reported globally [5, 25].

Other types of Jakob-Creutzfeldt disease

There are even rarer types of JCD. Genetic or familial forms with autosomal dominant inheritance, or with de novo mutations, have been described, including Gerstmann-Sträussler-Scheinker disease (GSS), FFI, and familial JCD (fJCD) [12]. They are considered clinical variants with a well-described natural history, including slowly progressive ataxia and late-onset dementia in GSS, refractory insomnia with hallucinations and dysautonomia in FFI (the hereditary component is added for its differentiation with MM2-thalamic sJCD); and RPD with myoclonus and pseudoperiodic electroencephalographic discharges for fJCD [26]. Iatrogenic acquisition of JCD has also been documented since 1974, especially by neurosurgical procedures including dura mater grafts, corneal transplantation, and use of growth hormone, all of which coming from infected patients, and whose incubation period is variable [27]. The variant of JCD (vJCD), identified in the United Kingdom in 1996 after the outbreak of bovine spongiform encephalopathy (BSE) between 1980 and 1990, receives special attention. It was associated with the consumption of food contaminated with prions from cattle that suffered from this disease [28].

Diagnosis

The number of diseases and disorders that can mimic JCD is overwhelming, many of them potentially treatable, and which must be ruled out before establishing the diagnosis of a universally fatal disease. Within them is the entire spectrum of RPDs; infectious diseases such as viral encephalitis, progressive multifocal leukoencephalopathy and dementia associated with human immunodeficiency virus (HIV), Lyme disease, and neurosyphilis; metabolic disorders such as hepatic encephalopathy and Wernicke's encephalopathy, thyroid abnormalities, and metal or drug toxicity; immune-mediated diseases such as CNS vasculitis and autoimmune encephalitis; and even other neurological disorders such as stroke, non-convulsive status epilepticus (NCSE), and some psychiatric disorders [29].

To rule out or evidence these differential diagnoses, it has been proposed to perform screening laboratory tests, which include the determination of vitamin B12 and folates, thyroid-stimulating hormone, serum levels of calcium, magnesium, and glucose, ammonia, and blood cytometry, kidney and liver function tests, and serologies for syphilis, *Borrelia burgdorferi*, and HIV [30]. Likewise, rheumatological screening tests are recommended that include antibodies associated with autoimmune encephalitis (including NMDAr), and tumor markers [29].

Electroencephalography

Prior to the era of molecular and imaging diagnosis, EEG was an essential part of the diagnosis of JCD. It is currently considered to be less useful than these diagnostic methods [29], although it is still recommended in the most recent guidelines for the diagnosis of RPD [30] due to its non-invasive nature.

In early stages of the disease, nonspecific abnormalities have been described in the EEG, such as bilateral alpha activity, with irregular delta and theta waves [31], which can be focal or diffuse, consistent with an encephalopathic pattern, as well as frontal intermittent rhythmic delta activity (FIRDA) [32].

Periodic sharp wave complexes (PSWC) are characteristic of JCD [31]; however, a sensitivity of 64% and a specificity of 91% have been demonstrated, being found to be a false positive for Alzheimer's disease [33]. Usually, PSWC occur in late stages of the disease, and are not observed in all subtypes within the Parchi classification, being less frequent in subtype 2 (VV2), subtype 3 (MV2), and subtype 4 (MM2-cortical) [34].

When performing EEG as part of the diagnostic approach, it should be considered that it is very difficult to differentiate JCD from NCSE, since both can respond to benzodiazepines, and that the latter is a differential diagnosis [29, 35, 36], and at the same time, part of the clinical manifestations of JCD [34].

Magnetic resonance imaging

CT scan does not offer significant data, sometimes showing nonspecific atrophy [37], especially in late stages [38], although in countries with limited resources it is usually the first imaging study performed.

Brain MRI is the study of choice [30]. As part of the imaging protocol, T2-weighted images, FLAIR, DWI and apparent diffusion coefficient (ADC) images are required, the abnormalities are best observed in DWI and ADC [39], with hyperintensities in basal ganglia, thalamus and cerebral cortex being typical, having some classic patterns such as “cortical ribbon sign”, and “the hockey stick sign”. The hockey stick sign is observed in axial sections and consist of hyperintensities in the medial portion of the thalamus and in the pulvinar, this being observed more frequently in vJCD [40]. Brain MRI findings, especially in DWI, have been shown to have a good diagnostic performance with a sensitivity of 91% and a specificity of 97% [41].

It is important to add that in late stages of the disease, hyperintensities decrease, so it is possible to only find atrophy [27].

Cerebrospinal fluid and biomarkers

LP with CSF collection is mandatory, usually showing normal results, or a slight elevation of proteins which usually do not exceed 100 mg/dl, and in occasions oligoclonal bands have been found. Since its identification in 1986, the 14-3-3 protein has been used as a biomarker for the diagnosis of JCD, including it within the diagnostic criteria of the World Health Organization (WHO) [38]. Despite the above, this biomarker has limited specificity, since other pathological processes can present it, being considered by experts as only a marker of neuronal damage [4]. Positivity has been reported in hypoxic and metabolic encephalopathies, ischemic and hemorrhagic stroke, paraneoplastic syndromes and brain metastases, Alzheimer's disease, corticobasal degeneration, and other neurodegenerative disorders [14, 38, 42]. However, in the appropriate clinical context, and in accordance with the guidelines of the American Academy of Neurology [43], and the Federation of European Neuroscience Societies [30], it is recommended the determination of the 14-3-3 protein in order to reduce diagnostic uncertainty and as part of the diagnostic approach to RPD. The sensitivity and specificity of the test vary between authors. In 2012, Hamlin and collaborators identified a range of sensitivity from 43% to 100%, and specificity between 47% to 97% [44]. Greater specificity is expected in clinical syndromes that are compatible with JCD, however, this decreases significantly when the test is performed indiscriminately [40]. The use of other biomarkers such as neuronal-specific enolase, total tau, or S100β has been reported, but they are not sufficiently sensitive or specific [1].

In 2010, Real-Time Quacking-Induced Conversion (RT-QuIC) was described, which, in general terms, is capable of detect the ability of PrPSc to induce the conversion of PrPC towards its misfolded form [45]. A sensitivity of up to 91.6% and a specificity of 100% have been demonstrated, based on a case-control study published in 2022 [46]. This high specificity had been already reported in 2018 by Hermann et al. [47]. False positives are rare, with diagnoses such as cerebral venous thrombosis, and paraneoplastic disorders including autoimmune encephalitis [48]. Despite its excellent diagnostic performance, the acquisition of the test is difficult due to economic disparities in countries with limited resources.

Histopathological diagnosis

The definitive diagnosis requires a mandatory brain tissue biopsy or autopsy. Performing brain biopsies for diagnosis of the disease does not alter the treatment strategy in patients with high suspicion, which is why it is rarely performed, mainly due to the potential risk of transmission to the personnel in charge of performing the procedure. [14]. According to the most recent guidelines, obtaining brain tissue should be performed only in selected cases of RPD where a treatable cause cannot be excluded after having exhausted all non-invasive diagnostic tests [26] and in highly specialized centers [30].

Unfortunately, the histopathological diagnosis of the three cases presented could not be made due to epidemiological and infectious safety issues, which is common globally. It has been reported that in the United Kingdom only 50% of deceased patients with suspected JCD have an autopsy performed [5]. It should be considered that the visibility of the disease in the United Kingdom increased after the appearance of cases of JCD, BSE, and the vJCD. In countries where such cases did not exist or where the prevalence of the sporadic form is even lower, the performance of autopsies is almost non-existent.

Diagnostic criteria

The WHO has issued diagnostic criteria which have been modified on multiple occasions to improve their performance, with the addition of abnormalities in neuroimaging [49], and the performance of RT-QuIC [34]. These criteria were validated in 2022 [46]. To date, there are no predictive or diagnostic models that can help identify the disease when paraclinical resources are limited. The creation of these hypothetical criteria be complicated due to the wide range of clinical manifestations and differential diagnoses, considering that JCD is a diagnosis of exclusion in these circumstances.

Normally, before making the diagnosis, patients and relatives have exhausted economic and human resources by performing other tests for the diagnosis of other potentially treatable differentials, before determining the 14-3-3 protein or RT-QuIC, which generates not only an economic burden, but also emotional implications due to the uncertainty of the presence of this fatal disease.

Treatment

At the time of publication of this article, there are no treatments that have been shown to stop or modify the course of the disease. Interdisciplinary management is important in order to improve the quality of life of the patient and their families, considering consultations with palliative care, psychology, and thanatology. This management should include symptomatic treatment of agitation, movement disorders such as myoclonus, as well as the use of anti-seizure medications in case of epileptic activity [50]. The use of benzodiazepines, valproate salts, and levetiracetam can be useful for the treatment of epileptic seizures and myoclonus [38]. The main causes of distress in caregivers have been identified, which include the rarity of the disease, the difficulty in making the diagnosis and its clinical implications, including the speed of the deterioration and loss of functionality, as well as guaranteed fatality [51]. Nutritional support must be ensured with appropriate measures, which also works for the delivery of medications. The placement of a gastrostomy tube has been recommended; however, the use of nasogastric tubes is usually chosen due to concerns regarding the transmission of the disease in invasive procedures, which has also been seen in developed countries [52]. It should be remembered that the WHO considers tissues without detectable infectivity blood, saliva, feces, and intestines, only identifying high infectivity in the CNS and eyes, and low infectivity in the CSF and other organs such as kidneys, liver, lungs, spleen and lymph nodes. Likewise, it has established guidelines in the case of performing surgical procedures [38].

In the authors' experience, the burden and consequences of the disease generate a great burden for primary caregivers, as well as health service providers, more than for the patient, who, finding himself in a state of disconnection from the world, seems unfazed of the neurological and systemic abnormalities that he or she presents. In our Institution and in general, there have been discrepancies regarding the potential transmission of the disease to family members, health personnel and other patients, being explained by the almost zero perception of this terrible disorder, which has generated problems for adequate palliation of the disease, including nutritional support. This should lead to visibility strategies, especially in tertiary or reference centers, both nationally and internationally.

Prognosis

Overall, the prognosis is ominous. In sJCD, the onset of the disease at an early age, female gender, as well as the presence of the 14-3-3 protein in cerebrospinal fluid [25] were identified as predictors of longer survival. However, inevitably 100% of patients will die, usually from complications due to immobility, or aspiration pneumonia, in addition, taking into account the limited therapeutic options.

Conclusions

JCD is a rare but underdiagnosed disease. It should be considered as part of the differential diagnosis of RPD. Its clinical manifestations are heterogeneous within the subtypes, which complicates the approach. Diagnosis requires laboratory and cabinet studies that also present heterogeneous results according to the stage of the disease. Performing such test is difficult and challenging, especially in countries with limited resources, due to the high cost of the tests based on biomarkers, as well as its limited availability. There is no treatment against the disease, being limited to the control of symptoms and palliation. It is vital to carry out diagnostic criteria that can be applied in these areas, in order to involve the necessary amount of paraclinicals with a balance in cost-effectiveness, and with adequate performance, which would be considered a challenge in the coming years. The awareness and visibility strategies of the disease will serve both to generate an adequate care model for patients, and to implement adequate epidemiological surveillance measures based on evidence, which not only reduce health costs, but also improve the quality of life of patients and caregivers.

Conflict of Interest

The authors declare that they have no conflict of interest.

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