ORIGINAL ARTICLE

Sporadic Creutzfeldt Jakob disease: Case series in Peru

Enfermedad de Creutzfeldt Jakob esporádica: Serie de casos en Perú

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Abstract

Description of the cases:

A series of 6 cases with a probable diagnosis of sporadic CJD, treated in a Peruvian national reference hospital, are presented.

Clinical findings:

The relevant clinical signs were rapidly progressive dementia and myoclonus, followed by akinetic mutism and pyramidal signs.

Treatment and results:

Of the cases presented, 80% were men, with an average age of presentation of 65 years and duration from diagnosis to death of 6.5 months. Laboratory tests, images (Brain Resonance) and protein dosage 14.3.3 were performed to support the clinical suspicion. There is no effective treatment at the moment for said pathology.

Clinical Relevance:

Creutzfeldt-Jakob disease (CJD) is a progressive, fatal, neurodegenerative disease of low prevalence and incidence. Great clinical suspicion and the exclusion of other etiologies are required. Currently there is no treatment for this entity and there is a high probability of death before one year.

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Ninguno

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Resumen

Descripcion de los casos:

Se presenta una serie de 6 casos con diagnóstico probable ECJ esporádica, atendidos en un hospital peruano de referencia nacional.

Hallazgos clínicos:

Los signos clinicos relevantes fueron la demencia rapidamente progresiva y las mioclonias , seguidas del mutismo acineticos y signos piramidales.

Tratamiento y resultados:

De los casos presentados , el 80% fueron varones , con edad de presentación promedio a los 65 años y tiempo de duración desde el diagnostico hasta el deceso de 6.5 meses . Se realizo examenes de laboratorio, imágenes (Resonancia Cerebral) y dosaje de proteina 14.3.3 para apoyo a la sospecha clinica .No se cuenta con un tratamiento efectivo al momento para dicha patología.

Relevancia Clinica:

La enfermedad de Creutzfeldt-Jakob (ECJ) es una enfermedad neurodegenerativa, progresiva, mortal, de baja prevalencia e incidencia . Se requiere de gran sospecha clínica y la exclusión de otras etiologías. Actualmente no hay un tratamiento para esta entidad y hay alta probabilidad de muerte antes del año

Remark

1) Why was this study conducted?

To present a series of cases from a National Reference Hospital using the current Diagnostic criteria for this disease, given that updated data on this pathology is poorly reported.

2) What were the most relevant results of the study?

- Of the cases presented, 80% were men; - The average age of presentation is 65 years;
- The duration of time from diagnosis to death was 6.5 months;
- The early clinical manifestations in our study were cognitive and behavioral;
- Our case series 100% of them presented a FIRDA pattern (intermittent frontal delta activity) followed by biphasic sharp waves 33%, triphasic sharp waves 50%.

3) What do these results contribute?

Expansion of knowledge regarding this pathology and its clinical presentation forms as well as findings in auxiliary tests.

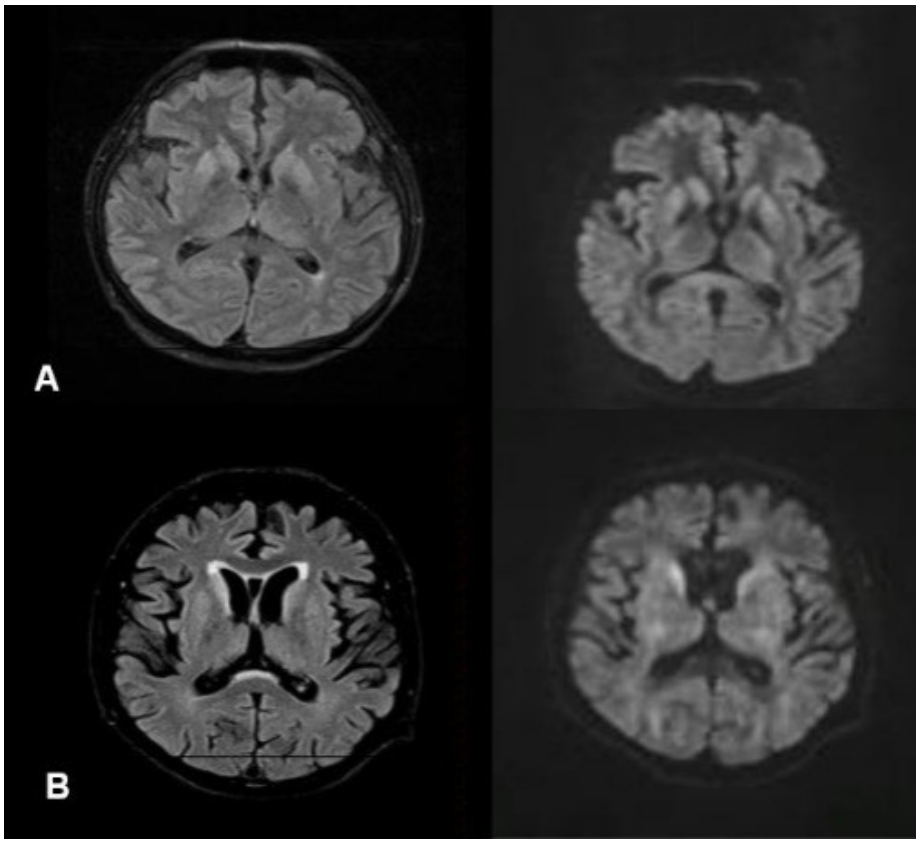

Figure 1. A) Brain MRI FLAIR and diffusion: Hypersignal and restriction, respectively, in caudate and putamen (Case 1). B) Brain MRI: Slight increase of intensity in FLAIR at the level of bilateral caudate nuclei, showing diffusion restriction. Moderate cerebral atrophy (Case 4).

Introduction

Creutzfeldt-Jakob disease (CJD) is a progressive and fatal neurodegenerative disease caused by the conversion of the normal brain prion protein (the cellular form of the prion-related protein PrPC) into a misfolded form, the scrapie protein (PrPSc) [1].

There are three main groups: sporadic CJD, genetic CJD and acquired CJD. Sporadic CJD (sCJD) is the most common and accounts for about 85% of cases. Genetic forms account for 10-15 %, including familial CJD, fatal familial insomnia and Gerstmann-Schäussler-Scheinker syndrome. Acquired forms account for 1-5 % including Kuru (related to historical ritual cannibalism in Papua New Guinea), iatrogenic CJD (iCJD) and variant CJD (vCJD) [2].

The overall incidence of CJD is estimated to be 1 to 2 cases per million per year and during the last 20 years this incidence may have increased, which could be explained by improved diagnostic methods. Most of them occur in late adulthood, between 50 and 70 years of age [3].

Variable clinical presentations can make it difficult to make a confident diagnosis. Necropsy remains the gold standard for definitive diagnosis. Diagnosis is based on a careful clinical history, physical examination to look for classic symptoms and signs, exclude other possible causes, and supportive diagnostic tests including brain magnetic resonance imaging (MRI), electroencephalogram (EEG), cerebrospinal fluid (CSF) 14-3-3 protein study and genetic testing [4].

There is no official registry in Peru that counts these patients, so each institution provides reports from time to time according to the frequency of this pathology. The main objective of the present study is to identify the main clinical manifestations and diagnostic methods of a series of cases of patients who met the criteria for probable sCJD, attended in a national reference hospital.

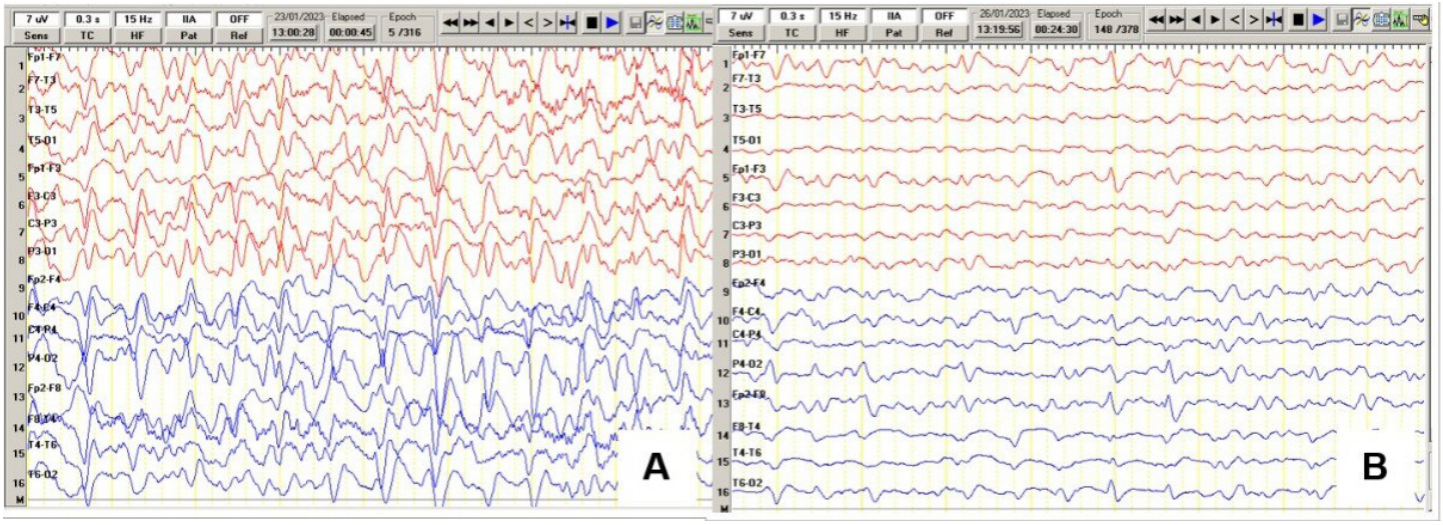

Figure 2. EEG of cases 2 (A) and 3 (B). On slowed (A and B) and attenuated (B) background, periodic generalized discharges to 0.5-1 Hz (A) y 0.8-1.2 Hz (B).

Presentation of cases

Case 1

63-year-old male, with a medical history of hypothyroidism, hepatitis B and intestinal amebiasis, with an illness duration of one month, characterized by progressive instability for walking and grasping objects, in addition to visual hallucinations and episodes of fluctuating confusion. On physical examination, the patient was awake, inattentive, oriented only in person, partially obeying orders, left hemiparesis, global hypokinesia, preserved osteotendinous reflexes, positive prehension reflex, postural and kinetic tremor predominantly in the left upper limb, no dysmetria, no meningeal signs. Three weeks later, myoclonus in upper limbs predominantly right, laryngeal stridor, gaze with tonic deviation to the left, rapidly progressive deterioration of the content of consciousness, spasticity and bilateral hyperreflexia, akinetic mutism. In view of the clinical picture, she completed studies with brain MRI which showed hyperintensity of the head of the caudate nucleus and putamen, with slight restriction in diffusion, in addition to atrophy of frontotemporal predominance (Figure 1), as well as EEG and positive result for protein 14.3.3 in cerebrospinal fluid. She died 5 months after respiratory complications.

Case 2

62-year-old woman, without pathologic history, with illness time of one month and a half, characterized by short-term alteration of the content of consciousness, attention deficit, dysphoria and emotional lability. In addition, progressive gait instability and negativistic childish behavior. On physical examination, the patient was awake, inattentive, decreased concentration, oriented only in person, hypofluent language, partially obeyed simple commands, mobilized the limbs, presented hypertonia, hyperreflexia and multisegmental myoclonias in four limbs, predominantly in the left hemibody. Two weeks later the patient evolved to total functional dependence, requiring a nasogastric tube for feeding. Subsequently, akinetic mutism was added, with accentuation of hypertonia and myoclonias. She had EEG (Figure 2A) and CSF 14.3.3 protein dosage. She died 3 months after respiratory complications.

Case 3

79-year-old male, with a history of arterial hypertension, with one month of illness characterized by progressive intermittent disorientation and alteration of recent memory, in addition to progressive gait instability and vertigo. On physical examination, the patient was

Table 1. Clinical and laboratory characteristics of patients.

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6
Age (years)	63	62	79	71	69	58
Sex	M	F	M	M	M	F
Time from illness to death (months)	5	3	6	6	12	9
Signs and symptoms	Ataxia, cognitive impairment, visual hallucinations, myoclonias	Ataxia, cognitive impairment akinetic mutism, myoclonias	Cognitive impairment, Confusion, ataxia, myoclonias	Ataxia, confusion, cognitive impairment, fasciculations	Cognitive impairment, myoclonias	Cognitive impairment, confusion, akinetic mutism
EEG	Generalized slowed baseline activity, without evidence of epileptiform discharges and periodic activity.	Slowed baseline activity in the theta range, medium to high voltage irregular, with interposition of diffuse and accentuated three-phase periodic activity in anterior right segments	Slowed baseline activity, bilateral periodic activity, with acute triphasic waves of medium to high voltage at 0.8 -1.2 Hz, right parasagittal predominance	Generalized slowed baseline activity, without evidence of epileptiform discharges and periodic activity.	Slowed base activity with three-phase waves at 0.5-1.5 Hz on severely slowing background.	Generalized and disorganized baseline slowed activity without epileptiform activity or periodic activity.
LCR (Protein 14 3.3)	Positive	Positive	Not performed	Positive	Not performed	Positive
Cytochemical, and unaltered cultures	Cytochemical, and unaltered cultures	Cytochemical, and unaltered cultures	Cytochemical, and unaltered cultures	Cytochemical, and unaltered cultures	Cytochemical, and unaltered cultures	Citoquimico , y cultivos sin alteracion

M: Male, F: Female, EEG: Electroencephalogram, RM: Magnetic Resonance, LCR: Cerebrospinal fluid

awake, inattentive, oriented, concentration decreased, language preserved, muscle strength preserved, with evidence of multisegmental myoclonus in 4 extremities, without pyramidal signs. Two weeks later hypofluent language, hyponymia, mild akinesia and rapidly progressive deterioration of the content of consciousness adding multisegmental myoclonias. Subsequently progresses to superficial coma, increased myoclonus in lower limbs, as well as fasciculations in 4 limbs. She had supporting examinations including EEG (Figure 2B) and died after 6 months of illness due to respiratory failure secondary to pneumonia.

Male 71 years old, without pathological history, with 2 months of illness, characterized by progressive gait instability and weight loss of 10 kg, plus dysarthria, dressing apraxia and recent memory disorder. On examination, the patient was awake, inattentive, not concentrated, with null abstraction and frontal release reflexes present, hypofluent language, preserved muscle strength, with dysmetria in extremities, bilateral extensor plantar reflex and clonus. In addition, there was evidence of fasciculations in the lower limbs, predominantly in the thighs. Studies were completed with MRI of the brain showing cortical atrophy predominantly mesial temporal and bilateral frontal, periventricular hyperintensity in frontal poles, lacunar hyperintensities of the radiate coronas of micro ischemic aspect with diffusion restriction (Figure 1), EEG and CSF, protein 14.3.3. Clinical picture progresses, dying 1 year after the beginning of the clinical picture due to respiratory complications and prostration state.

Case 5

69-year-old male, with no medical history, with one month of illness, characterized by short-term memory impairment, headaches, apathy and tendency to drowsiness. Subsequently, disorientation, balance disturbance, hypofluent language and gait instability were added, as well as rapidly progressive deterioration of the content of consciousness. On clinical examination, the patient was awake, inattentive, with akinetic mutism, with reactivity to deep nociceptive stimulus (pain gestures and withdrawal to the stimulus), preserved muscle strength, persistent cephalic and left brachial myoclonus, presence of bilateral extensor plantar reflex, no meningeal signs. Patient during hospital stay presents with respiratory complications, died 1 year after the onset of clinical picture.

Case 6

A 58-year-old woman with a medical history of arterial hypertension and diabetes mellitus, with a 7-month illness characterized by short-term memory impairment, irritability, emotional lability and insomnia. Subsequently, she had episodes of unmotivated laughter and difficulty swallowing. On physical examination she is awake, hypoattentive, does not obey simple commands, episodes of unmotivated laughter, anosognosia, preserved muscle strength, hyperreflexia, extensor plantar cutaneous reflex, cautious gait. After 3 weeks the picture progresses to akinetic mutism. She died 2 months later.

Discussion

CJD is a progressive and fatal neurodegenerative disease that is considered rare due to its incidence [5,6]. We present six patients (Table 1), predominantly male, with a mean age of 70 years. The main clinical manifestation was progressive cognitive impairment, within the approach to a rapidly progressive dementia it is necessary to rule out other pathologies, in our institution metabolic, infectious, tumor, autoimmune and drug diseases were ruled out. During the course of their studies, other symptomatologies were added, such as myoclonias, motor and cerebellar symptoms, and almost all of them ended up with mutism [7,8]. Initially, the electroencephalogram study showed slow waves, like an encephalopathy. In our case series, 3 of the cases presented evidence of periodic generalized discharges. The remaining 3 presented only slowed baseline rhythm [9,10]. The time to obtain an MRI in our institution is 2 - 4 weeks. Which is sensitive and specific to detect typical findings. Only 2 patients had such examination, showing hyperintensities in the basal ganglia areas, one in bilateral caudate and putamen and the other in both caudates. The other patients presented prolonged appointments [11,12] while some pathologies were ruled out. Some of them presented the suspicion of autoimmune cause and were managed as such. In the absence of improvement and progression of symptoms, they began to meet the criteria of probable prion disease [12]. The relatives of the patients who had the necessary resources were asked for the 14.3.3 protein, which is sensitive and specific, and which is only performed in a particular way in our environment. In the cases presented in our series, 4 of the patients had positive results. The rest of the patients did not undergo the study due to the high cost in an extra-institutional manner [13-15]. Our patients were discharged with symptomatic treatment only. They did not agree at any time to perform a necropsy to confirm the diagnosis. For this reason, all our patients were left with a probable diagnosis of prion disease [14]. The time from diagnosis to death ranged from 3-12 months [9-11]. Most of our patients died of respiratory causes. Multiple therapeutic interventions have been investigated for CJD, however, no treatment has been shown to be effective. Due to the low incidence of CJD, there is a difficulty in the clinical management of patients, both because of the lack of knowledge of the management of the disease and the difficulty of having well-defined flow diagrams, so that the objective is focused on minimizing the symptoms and maintaining the quality of life of the patients [16,17].

Conclusion

In our environment, sCJD has a varied clinical presentation, manifesting most frequently with rapidly progressive dementia, followed by myoclonias with subsequent evolution to akinetic mutism. This type of patient is a diagnostic challenge, which implies clinical suspicion and exclusion of other etiologies. EEG, 14-3-3 protein in CSF and brain MRI contribute to the diagnosis. Currently there is no treatment for this entity and there is a high probability of death before one year.

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