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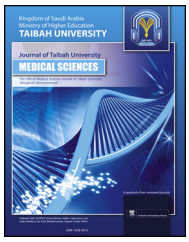

Letter to the Editor

Rapidly progressive encephalopathy with evidence of spongiform encephalopathy through biopsy

Mallyolo E. Pelayo-Salazar, MD [a], Octavio A. Salazar-Castillo, MD [a], Fernando E. de la Torre-Rendón, MD [b], Laura Mestre-Orozco, MD [d] and Julio C. López-Valdés, MD [c,e,*]

[a] *Neurological Surgery Department, Hospital Regional "Licenciado Adolfo López Mateos", I.S.S.S.T.E. Álvaro Obregón, Mexico City, Mexico*
[b] *Pathology Department, Hospital Regional "Licenciado Adolfo López Mateos", I.S.S.S.T.E. Álvaro Obregón, Mexico City, Mexico*
[c] *Research Department, Universidad Autónoma de Tamaulipas, Facultad de Medicina de Tampico "Dr. Alberto Romo Caballero", Tampico, Tamaulipas, Mexico*
[d] *Pathology Department, Hospital Central Sur de Alta Especialidad, Tlalpan, Mexico City, Mexico*
[e] *Neurological Surgery Department, Hospital Central Sur de Alta Especialidad, Tlalpan, Mexico City, Mexico*

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Dear Editor:

Transmissible spongiform encephalopathies (TSEs) represent a group of rare, rapidly progressive, lethal neurodegenerative diseases with a variable etiology (idiopathic, acquired, or genetic). Creutzfeldt-Jakob disease (CJD) is the most common type (85% of cases) followed by Gertsmann-Straüssler-Scheinken disease, lethal familial insomnia, and Kuru.[1–4]

Progressive neurodegeneration with short survival and symptoms such as dementia, ataxia, extrapyramidal symptoms, and psychiatric disorders are characteristic features of these diseases.[1,5,6] They are equally distributed between sexes and affect patients with an average age of 55–75 years. However, the classic variant of CJD is observed in patients with a median age of 68 years and a span of 4–5 months.[7]

Although there are no epidemiological data for each of the variants due to the scarcity of cases, statistics obtained through the "Creutzfeldt-Jakob Disease International Surveillance Network, formerly EuroCJD" report an incidence for CJD that varies between 0.32 (Estonia) and 1.73 (Switzerland) cases per million people, with an estimated 1–2 cases per million people worldwide.[5,8] Data from Mexico provided by Velásquez-Pérez et al.[4] have shown a mean age of presentation of 49 years, with an equal distribution for both sexes.

We discuss a case with clinical features and complementary studies compatible with CJD.

The patient was a 60-year-old Mexican male with hypothyroidism treated with levothyroxine. He had presented to the emergency room with hyperorexia and nausea accompanied by vomiting on multiple occasions. Hyperacusis and benign paroxysmal positional vertigo subsequently occurred, as well as hyperactive delirium with agitation, mood swings, and behavior, visual, and auditory hallucinations with spontaneous improvement. One month later, he was

* Corresponding address: Neurological Surgery Department, Hospital Central Sur de Alta Especialidad, Tlalpan, Mexico City, Mexico.
E-mail: jc.lopz@live.com (J.C. López-Valdés)
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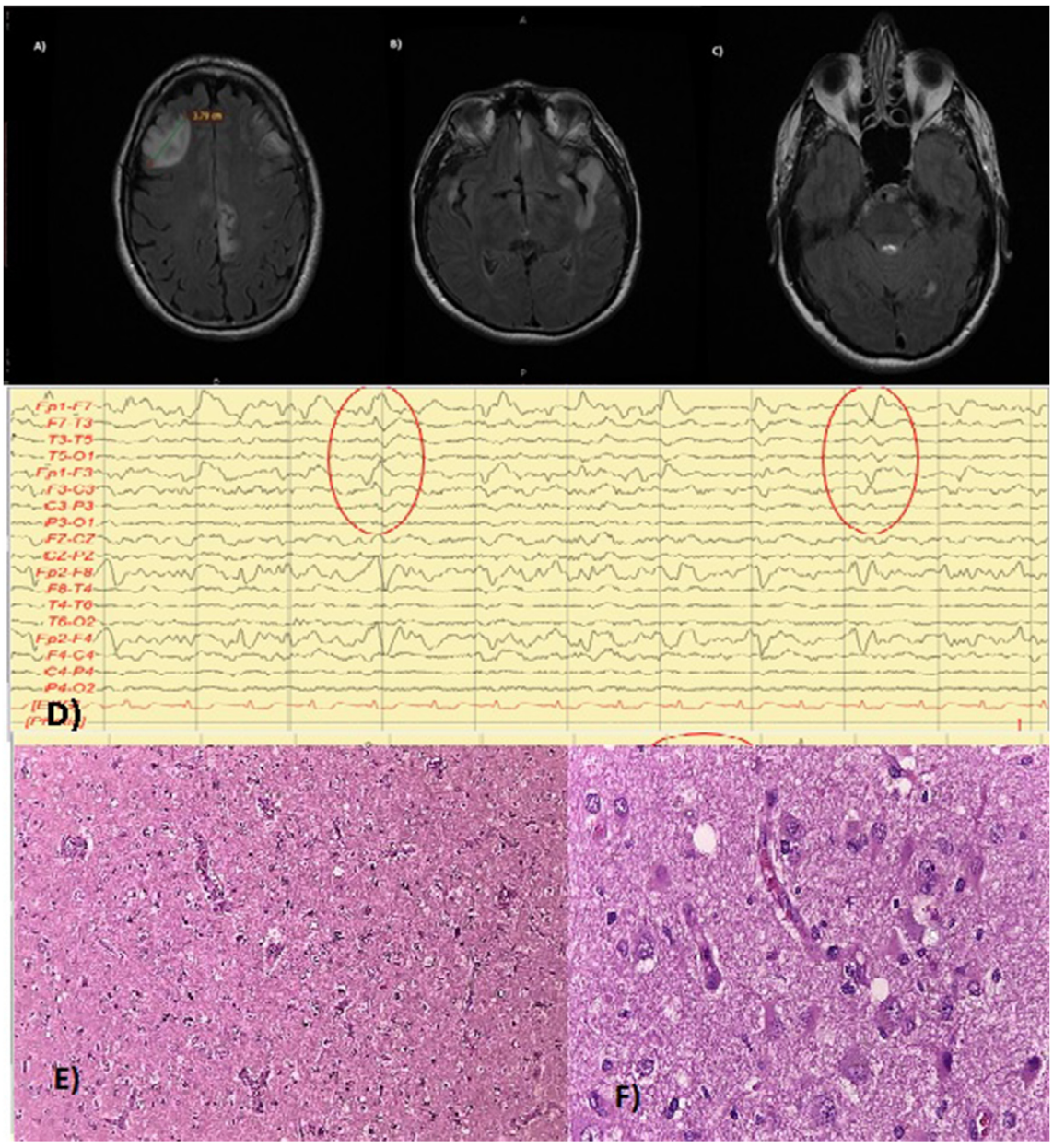

Figure 1: A, B and C) Heterogeneous hyperintense T2 images with poorly defined borders in the left occipital, temporal, parietal, and bilateral frontal lobes; the largest lesion was in the right frontal region; 37.91 × 25.62 × 22.56 mm in the anteroposterior, lateral–lateral, and face–caudal axes, respectively, with a calculated volume of 11.01 cm^3. Displacement of midline structures of 2.54 mm from left to right by mass effect. (D) Electroencephalogram showed mild to moderate diffuse corticosubcortical dysfunction (theta–alpha activity), and some outbreaks of low-voltage acute waves with a predominance of left frontocentrotemporal regions. (E) Severe dysfunction and diffuse hypofunction (low-voltage delta activity) followed by episodes of attenuation of the activity of 2–3 seconds; acute waves were mixed with triphasic morphology with greater left expression.

hospitalized for clonic movements of the right lower limb and emotional lability without response to medication. Upon admission, he presented with 2-min tonic–clonic seizures with *ad integrum* recovery. Physical examination revealed a Glasgow Coma Scale score of 10 (OCULAR4, VERBAL1, MOTOR5), 2 mm normoreflective pupils, facial symmetry, gag reflex, right thoracic limb strength of 3/5, rest of 0/5, reactivity to painful stimuli, and indifferent plantar responses, without meningeal or cerebellar data. Electroencephalography revealed generalized slowing, predominantly in the bilateral frontal regions, angulated waves in the left frontotemporal region, generalized moderate dysfunction, and increased left frontal excitability (Figure 1). The viral panel was negative for human immunodeficiency virus, hepatitis B virus, and hepatitis C virus.

Twelve days later, motor aphasia occurred, with no additional helpful data in complementary studies (Table 1). However, brain magnetic resonance imaging (MRI) with

Table 1: Complementary studies and results.

1 Nov 2019	EEG	Abnormal
6 Nov 2019	Viral panel VIH, VHC, VHB	Negative
6 Nov 2019	PCR for meningitis (Biofire®) in CSF	Negative
8 Nov 2019	Double-contrast thoracoabdominal CT	No evidence of metastasis or primary tumor
14 Nov 2019	PCR for arbovirus	Negative
14 Nov 2019	PCR for HIV	Negative

CSF, cerebrospinal fluid; CT, computed tomography, EEG, electroencephalogram; HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

Table 2: Recommended diagnostic criteria for sporadic creutzfeldt-jakob disease.

		WHO (2003)	CDC (2018)	Pelayo-Salázar et al.
1	Progressive dementia	√	√	+
2	Myoclonus	√	√	+
3	Cerebellar or visual alterations	√	√	+
4	Pyramidal/extrapyramidal alterations	√	√	−
5	Akinetic mutism	√	√	+
6	Characteristic EEG	√	√	+
7	14-3-3 protein in CSF	√	√	ND
8	RT-QuIC for prionic protein	−	Pr	ND
9	Less than 2 years of clinical evolution	√	√	+
10	Compatible MRI	−	√	+
11	Negative studies for any other alternative diagnosis		√	+
12	Neuropathological confirmation	D	D	+
13	PrP protein by inmunohistochemistry	D	D	ND
14	PPrP protein by western blotting	D	D	ND

CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; ND, not done; PrP, protein by western blotting; RT-QuIC, real-time quaking-induced conversion; WHO, World Health Organization.

gadolinium revealed heterogeneous hyperintense T2 images with poorly defined borders in the left occipital, temporal, parietal, and bilateral frontal lobes (Figure 1). The patient underwent a frontal craniotomy where a grossly normal cerebral cortex was observed. Cortex and white matter biopsies were performed. The pathology report showed multifocal neuronal necrosis in the cerebral cortex as well as isolated vacuolar changes and satellitosis. Spongiform changes of neuropils with intense reactive gliosis by astrocytes and microglia were reported. A focal perivascular lymphocyte reaction and occasional sclerosis of small capillary and arteriolar vessels were observed. There were no alterations in the arachnoid mater and no amyloid plaques, viral inclusion bodies, infarct zones, or neoplastic changes.

This case represents the diagnostic challenge that a TSE poses and its consequential fatal outcome. It is worth mentioning that the diagnosis of probable prion encephalopathy was suggested both by the MRI and histopathological study.

It must be emphasized that, although in this case it was not possible to gain access to the specific protein molecular study, according to most criteria proposed by both the World Health Organization[1] and the Centers for Disease Control and Prevention,[9] the clinical evolution of the patient was indicative of sporadic CJD (Table 2). The histopathological study showed changes characteristic of CJD. Although brain biopsy is currently the last resort for diagnosis, Bai et al.[10] reported a diagnostic success rate of up to 85%, in addition to its high utility in immunocompromised patients with focal or multifocal brain lesions and patients with neoplastic lesions. Meanwhile, Manix et al.[11] and Kwon et al.[12] cited brain biopsy as the method of choice for assisting in determining a diagnosis. All of the authors suggested performing brain biopsy after evaluating the risk benefit.[10–12]

Prionopathies were named based on the presence of cellular proteins called prions that can form amyloid aggregates, which are deposited as plaques in the brain, causing lesions and gray matter with neuronal death, gliosis, and spongiform changes. It is perhaps for this reason that the spectrum of symptoms is usually so wide.[1,11,12] It should be noted that alterations in higher mental functions and progressive deterioration that led to eventual death of the patient took months. The time of incubation and/or form of transmission are unknown.

Source of funding

This research has not received specific aid from public sector agencies, the commercial sector, or non-profit entities. The study was conducted in accordance with the Declaration of Helsinki, as well as the hospital's ethics protocols.

Conflict of interest

The authors have no conflicts of interest (based or fee-based worker; consultancy, advice, research studies, participation in the development of medicines or company shares) to declare. If at any time the authors establish a commitment with pharmaceutical industries or related organizations that influence or generate a conflict of interest in decision-making, they will inform in a timely manner and prior to its realization.

Ethical approval

Informed consent was obtained from the family of the patient involved in the study. There is no personal information in the text to identify the patient. Patient data were handled in accordance with the International Codes of Ethics of Helsinki 2004, Denmark 2004, Mexico 2002, Hong Kong 1984, Venice 1983 and Tokyo 1975, and the Code of Bioethics for health personnel in Mexico City 2002.

Authors contributions

MEPS conceived the idea for the study and wrote the initial draft of the manuscript; OASC edited the manuscript and conducted the literature search; VLG wrote the initial draft of the manuscript and conducted the literature search, FETR carried out data analysis, and manuscript editing; LMO wrote the initial and final drafts of the manuscript, and translated the manuscript; JCLV wrote the initial and final drafts of the manuscript, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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