Clinical Neurology and Neurosurgery 202 (2021) 106490

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Case Report

Early sensory disturbances and seizures are common manifestations of familial Creutzfeldt-Jakob disease due to E200K *PRNP* mutation: Case report from two Peruvian families

Elison Sarapura-Castro [a,b,c,*], Carlos Cosentino [d,e], Jonathan Landman [f], Avi Landman [g], Luis Torres [d,e], Yesenia Nuñez [d], Sabina Capellari [h,i], Piero Parchi [h,j], Mario Cornejo-Olivas [a,k]

[a] Neurogenetics Research Center, Instituto Nacional de Ciencias Neurologicas, Lima, Peru
[b] Northern Pacific Global Health Research Fellows Training Consortium, Seattle, USA
[c] Master's Program in Clinical Epidemiology and Biostatistics, Universidad Científica del Sur, Lima, Peru
[d] Movement Disorders Unit, Instituto Nacional de Ciencias Neurologicas, Lima, Peru
[e] School of Medicine, Universidad Nacional Mayor de San Marcos, Lima, Peru
[f] Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA
[g] University of Central Florida / HCA Healthcare Consortium, USA
[h] IRCCS Istituto Delle Scienze Neurologiche Di Bologna, Bologna, Italy
[i] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[j] Department of Experimental Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy
[k] Center for Global Health, Universidad Peruana Cayetano Heredia, Lima, Peru

ARTICLE INFO

Keywords:
Genetics
Creutzfeldt-Jakob disease
Dementia
Seizure
Sensory disturbance

1. Introduction

Familial Creutzfeldt-Jakob disease (fCJD) is an autosomal dominant disorder characterized by rapidly progressive dementia, myoclonus, ataxia, and other motor signs. fCJD comprises 10–15 % of all prion diseases and is linked to single-nucleotide or insertional pathogenic variants within the prion protein gene, *PRNP*. The most frequent mutation associated with fCJD is the c.598 G > A variant causing a glutamate to lysine change at codon 200 (E200K) [1]. We report the first description of five cases of fCJD occurring in two Peruvian families (Fig. 1A and D) carrying the E200K mutation.

2. Case report

2.1. Proband-family 1 (II-2)

A 52-year-old female experienced tingling in both arms, followed by a short-term memory loss, irritability, and confabulations. She then gradually developed dysarthria, dysphagia, drooling, difficulty in walking and sudden, episodic jerking movements of the arms. On admission, 11 months from onset, she was disoriented with an ataxic gait, bilateral dysmetria, dysdiadochokinesia, right-sided spasticity, bilateral upgoing plantar reflex and generalized action-type myoclonus. During hospitalization, she promptly became bed-bound with akinetic mutism and developed several generalized seizures.

Complete blood count (CBC) and basic metabolic panel (BMP) were all normal. The 14−3-3 protein was undetectable in the cerebrospinal fluid (CSF). An electroencephalogram (EEG) showed periodic triphasic

* Corresponding author at: Neurogenetics Research Center, Instituto Nacional de Ciencias Neurologicas, 1271 Ancash St. 15003, Lima, Peru.
E-mail address: elison.sarapura.c@incngen.org.pe (E. Sarapura-Castro).

https://doi.org/10.1016/j.clineuro.2021.106490
Received 3 November 2020; Received in revised form 8 January 2021; Accepted 9 January 2021
Available online 12 January 2021
0303-8467/© 2021 Elsevier B.V. All rights reserved.

sharp wave complexes (PSWCs) (Fig. 1B). Brain MRI axial DWI sequence showed bilateral hyperintensities of the basal nuclei and frontal and temporal cortical regions (Fig. 1C). Genetic testing performed by direct sequencing revealed the heterozygous E200K mutation with homozygosity for methionine (Met) at codon 129 in the *PRNP* gene. The disease duration, from onset to death by respiratory complications, was 17 months.

2.2. Proband-family 2 (III-4)

A 46-year-old male experienced a rapidly progressive disease starting with a nocturnal cold sensation in the right lower limb. Over the next

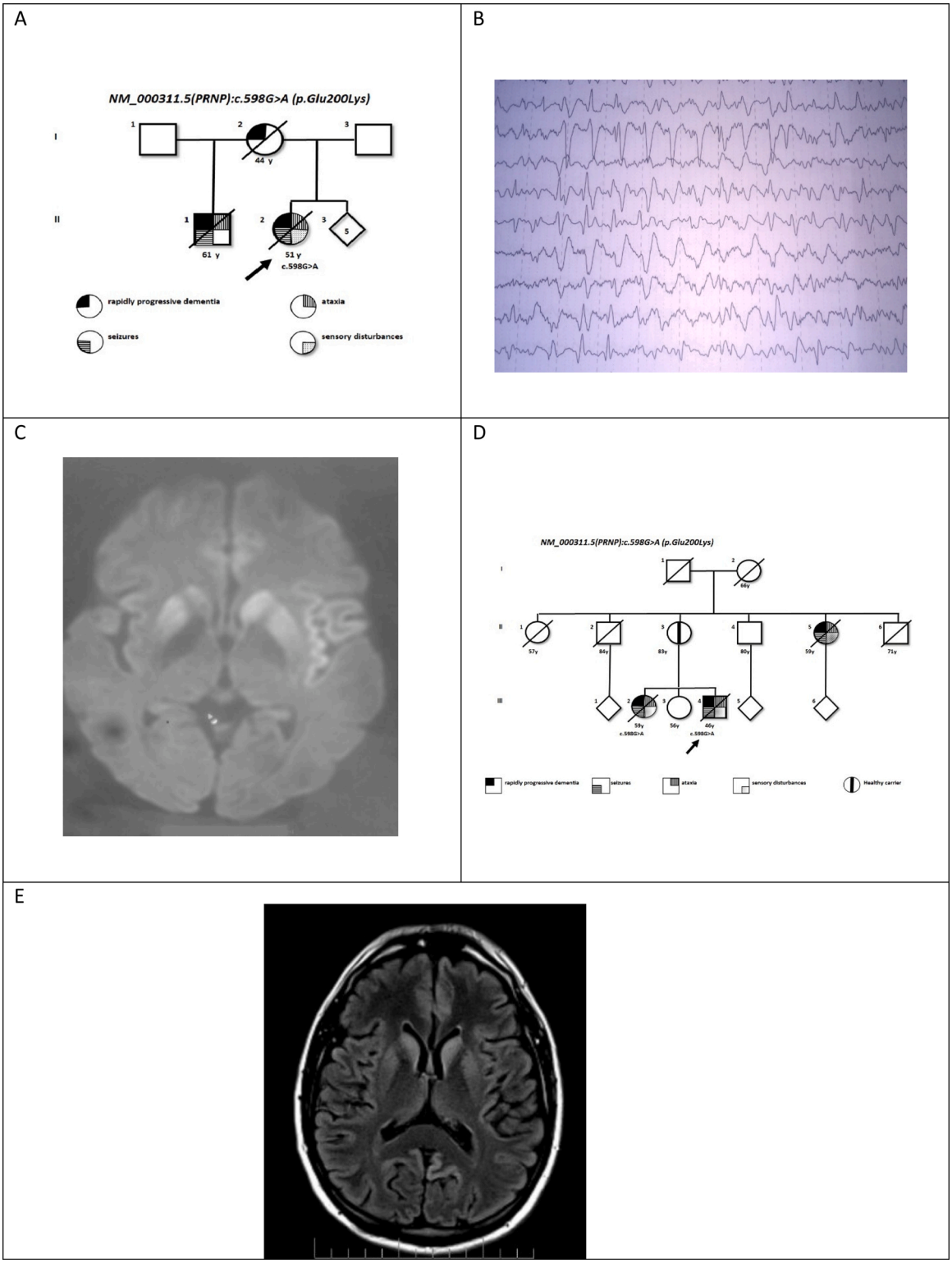


Fig. 1. (A) Pedigree of family 1. (B) EEG of case II-2 from family 1 showed periodic triphasic sharp wave complexes (PSWCs). (C) Brain MRI-DWI of case II-2 from family 1 with hypersignal in bilateral caudate nuclei, putamen, and insular cortices with left predominance. (D) Pedigree of family 2. (E) Brain MRI-FLAIR of case III-4 from family 2 with hyperintensities in the caudate nuclei, putamen, and brain cortex (including insular region).

two months, he experienced short-term memory loss and paroxysmal paranoia followed by gait disturbances, dysarthria, dystonic posture of the upper limbs and excessive daytime sleepiness. Two weeks before admission, he complained of blurry vision. On admission, he was disoriented in time and dysarthric. Motor examination revealed mild right-sided spasticity, upgoing plantar reflexes, clonus, and hyperreflexia. He had an ataxic gait, bilateral dysmetria, and dysdiadochokinesia. Over the next two weeks, he developed generalized seizures and became bed-bound with akinetic mutism. No myoclonus was reported.

Labs including CBC and BMP were within normal ranges. Nerve conduction study (NCS) and electromyography (EMG) were normal. Protein 14-3-3 was undetectable in CSF. An EEG showed a typical pattern of PSWC. Brain MRI axial FLAIR sequence showed abnormal bilateral hyperintensities in the basal nuclei, frontotemporal and occipital cortical regions (Fig. 1E). DNA analysis showed a heterozygous E200K mutation and homozygosity for p. Met129 in the *PRNP* gene. The patient expired 12 months after disease onset. Post-mortem brain tissue pathology with spongiform encephalopathy confirmed the diagnosis of CJD.

3. Discussion

We report the first two Peruvian fCJD families linked to the E200K-*PRNP* variant. Clusters of E200K-fCJD cases are documented in Slovakia, Libyan Jews, Chile, Italy, and Japan. E200K-fCJD cases from Spain and Chile have been associated with a founder effect from descendants of Sephardic Jews [1]. In Latin America, isolated cases have been reported in Argentina and Brazil. The proband of family 1 (II-2) was of Chilean ancestry, moreover the Latino family names of both families suggest a relationship between these two families and the Mediterranean European cluster.

Age at onset, disease duration, and results of diagnostic studies are quite consistent among fCJD cases linked to the E200K-*PRNP* variant reported to date. Table 1 summarizes the clinical features of the five affected cases from both families. The age at onset in these cases varied from 46 to 61 years falling within the range of previous reports [33–84 years], whereas the disease duration varied from 8 to 17 months. A previous report documented a greater variability in disease duration ranging from 1 to 78 months in E200K fCJD [2]. PSWCs recorded in our cases are typical EEG findings in both sporadic CJD (sCJD) and fCJD linked to the MM(V)1 subtype. CSF was negative for the 14-3-3 protein in both probands, and positive in case II-1 from family 1. Lower sensitivity 14-3-3 protein of about 68.7 % has been reported in in E200K-fCJD cases [3]. The homozygosity for p. Met129, as seen in both probands, is a common feature in most of E200K-fCJD cases described to date.

Early sensory disturbances (ESD) are infrequent symptoms and could mark the initial stage of both fCJD and sCJD. ESD were present in 4/5 of our cases, but they previously reported in only 15–30 % of E200K-fCJD cases [4–6], suggesting a distinctive progression pattern of the disease in these two families. Paresthesia, numbness, cold and pressure sensations may represent the phenotypic expression of a dysfunction of the central or peripheral somatosensory system. ESD are not always associated with other ingravescent neurological and psychiatric symptoms. They may remain isolated for some time in some cases of sCJD due to polyneuropathy, likely related to prion protein deposition [7]. Any associated neuropathy was ruled out by NCS and EMG in cases II-5 and III-4 from family 2. Other sensory changes such as pruritus have been associated with lower diffusion MRI imaging in the thalamus, putamen, claustrum/insula, and other regions. Restricted diffusion and FLAIR sequences hyperintensities in the striatum and the insular cortex might explain at least in part the development of ESD in both probands (Fig. 1C and E). The timing of appearance of ESD coinciding with that of memory impairment, the evidence of FLAIR and DWI hyperintensities on somatosensory regions such as insula, the asymmetrical distribution of ESD with associated pyramidal signs in majority our cases seem to

Table 1
Clinical features of Peruvian affected family members with E200 K-fCJD.

Family 1	Sex	AAO	Symptom at onset	Clinical features	Investigations	DD
II-1	M	61	Insomnia	Rapidly progressive dementia, ataxia, myoclonus, and seizures.	Brain MRI: Hyperintense signal in bilateral caudate nuclei and pallidum. EEG: PSWCs. Protein 14-3-3: Positive. Genetic test: Not done	8
II-2 (P)	F	52	Tingling in both arms	Described in detail in text	Brain MRI: Hyperintense signal in bilateral caudate nuclei, putamen, and insular cortices. EEG: PSWCs. Protein 14-3-3: Negative. NCS and EMG: Not done. Genetic test: Positive for E200K/codon 129 MM.	17
Family 2	Sex	AAO	Symptoms at onset	Clinical features	Investigations	DD
II-5	F	59	Pressure sensation in the right lower limb	Rapidly progressive dementia, insomnia, ataxia, myoclonus, and seizures	Brain MRI: Hyperintense signal in bilateral putamen and cerebral cortices. EEG: PSWCs. Protein 14-3-3: Not data. NCS and EMG: Normal. Genetic test: Not done.	11
III-2	M	59	Numbness in right shoulder	Rapidly progressive dementia, ataxia, myoclonus, and seizures.	Brain MRI and EEG: "Suggestive of CJD". Protein 14-3-3: No data. NCS and EMG: Not done. Genetic test: Positive for E200K/codon 129: No data	14
III-4 (P)	M	46	Nocturnal cold sensation in the right lower limb	Described in detail in text	Brain MRI: Hyperintense signal in bilateral caudate nuclei, putamen, and cerebral cortices. EEG: PSWCs. Protein 14-3-3: Negative. NCS and EMG: Normal. Genetic test: Positive for E200K/codon 129 MM	12

*P: Proband, M: Male, F: Female, AOO: Age at onset (years), PSWCs: periodic triphasic sharp wave complexes. DD: Disease duration (months).

support a prion-related aetiology and a central pathways origin in our cases. However, we cannot rule out other aetiologies capable to disturb the sensory pathways.

Seizures were reported in all affected cases from both families. It contrasts with the 9–40 % of seizures previously reported in E200K-fCJD cases [4,8–10]. PSWCs was the most common EEG feature in our cohort. Insular cortex involvement (epileptogenic zone) might explain the seizures in our cases. However, seizures could also occur later in the disease due to metabolic disorders or sepsis.

4. Conclusion

ESD and seizures were significant clinical features in our E200K-fCJD cases. Although we could not generalize for other affected families, E200K fCJD should be considered in the differential diagnosis in patients presenting with rapidly progressive dementia, ESD and seizures in conjunction with MRI-specific changes and a positive family history.

Funding

Research funds of Instituto Nacional de Ciencias Neurologicas. Research reported in this publication was partially supported by the Fogarty International Center of the National Institutes of Health under Award Number D43TW009345. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Ethical approval

This manuscript was approved by the local ethical committee of Instituto Nacional de Ciencias de Ciencias Neurologicas, Lima, Peru.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

We thank both families for their kind collaboration on this manuscript. Renee Newby for grammar, Richard S. Rodriguez for pedigree drawing, and Diego Veliz-Otani for critical review of the manuscript.

References

[1] H.S. Lee, N. Sambuughin, L. Cervenakova, J. Chapman, M. Pocchiari, S. Litvak, et al., Ancestral origins and worldwide distribution of the PRNP 200K mutation causing familial Creutzfeldt-Jakob disease, Am. J. Hum. Genet. 64 (4) (1999) 1063–1070.

[2] L.T. Takada, M.-O. Kim, R.W. Cleveland, K. Wong, S.A. Forner, I.I. Gala, et al., Genetic prion disease: experience of a rapidly progressive dementia center in the United States and a review of the literature, Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet. 174 (1) (2017) 36–69.

[3] F. Lattanzio, S. Abu-Rumeileh, A. Franceschini, H. Kai, G. Amore, I. Poggiolini, et al., Prion-specific and surrogate CSF biomarkers in Creutzfeldt-Jakob disease: diagnostic accuracy in relation to molecular subtypes and analysis of neuropathological correlates of p-tau and Aβ42 levels, Acta Neuropathol. (Berl.) 133 (4) (2017) 559–578.

[4] J. Chapman, P. Brown, L.G. Goldfarb, A. Arlazoroff, D.C. Gajdusek, A.D. Korczyn, Clinical heterogeneity and unusual presentations of Creutzfeldt-Jakob disease in Jewish patients with the PRNP codon 200 mutation, J. Neurol. Neurosurg. Psychiatry 56 (10) (1993) 1109–1112.

[5] G. Schelzke, H.A. Kretzschmar, I. Zerr, Clinical aspects of common genetic Creutzfeldt-Jakob disease, Eur. J. Epidemiol. 27 (2) (2012) 147–149.

[6] A. Krasnianski, U. Heinemann, C. Ponto, J. Kortt, K. Kallenberg, D. Varges, et al., Clinical findings and diagnosis in genetic prion diseases in Germany, Eur. J. Epidemiol. 31 (2) (2016) 187–196.

[7] S. Baiardi, V. Redaelli, P. Ripellino, M. Rossi, A. Franceschini, M. Moggio, et al., Prion-related peripheral neuropathy in sporadic Creutzfeldt-Jakob disease, J. Neurol. Neurosurg. Psychiatry (2018).

[8] S. Appel, J. Chapman, O.S. Cohen, H. Rosenmann, Z. Nitsan, I. Blatt, Seizures in E200K familial and sporadic Creutzfeldt-Jakob disease, Acta Neurol. Scand. 131 (3) (2015) 152–157.

[9] Z. Meiner, R. Gabizon, S.B. Prusiner, Familial creutzfeldt-jakob disease. Codon 200 prion disease in Libyan Jews, Medicine (Baltimore) 76 (4) (1997) 227–237.

[10] P. Brown, L.G. Goldfarb, C.J. Gibbs, D.C. Gajdusek, The phenotypic expression of different mutations in transmissible familial Creutzfeldt-Jakob disease, Eur. J. Epidemiol. 7 (5) (1991) 469–476.