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Two FMR1 premutation cases without nuclear inclusions

Verónica Martínez-Cerdeño, PhD[1,2], **Mirna Lechpammer, MD, PhD**[1], **Paul J Hagerman, MD**[2,3], and **Randi Hagerman, MD**[2,4]

[1]Department of Pathology and Laboratory Medicine, UC Davis School of Medicine; Institute for Pediatric Regenerative Medicine and Shriners Hospitals for Children of Northern California

[2]MIND Institute, UC Davis Medical Center

[3]Department of Biochemistry and Molecular Medicine, UC Davis School of Medicine

[4]Department of Pediatrics, UC Davis Medical Center

Observation

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive neurodegenerative disorder that affects carriers of a *FMR1* premutation. Premutation of 55–200 CGG-repeats translate into increased *FMR1* mRNA inducing a toxic gain of function and/or translation of CGG repeats into a polyglycine-containing protein, FMRpolyG [1,2]. Symptoms include ataxia and intention tremor[1]. Pathology includes eosinophilic ubiquitin-positive intranuclear inclusions, which contain *FMR1* mRNA and numerous proteins in neurons and astrocytes[3-5]. It is unclear if all carriers with neurological symptoms present with FXTAS and/or inclusions[6,7]. We report by first time, two carriers who had neurological symptoms but did not have FXTAS or intranuclear inclusions.

All 28 postmortem premutation cases analyzed presented with intranuclear inclusions and were diagnosed with FXTAS, except two (Supplementary Figure 1). An 82 y/o male premutation carrier with 66 CGG repeats (case 1) and an 87 y/o male premutation carrier with 65 CGG repeats (case 2).

Corresponding author: Verónica Martínez-Cerdeño, PhD, 2425 Stockton Boulevard; Sacramento, California, 95817, Phone: (916) 453-2163, vmartinezcerdeno@ucdavis.edu.

Author contributions:

Dr. Martínez-Cerdeño - Study concept and design, acquisition of data, analysis and interpretation, study supervision, and writing of the manuscript.

Dr. Lechpammer - Acquisition of data, analysis and interpretation, and critical revision of the manuscript for important intellectual content.

Dr. P. Hagerman - Critical revision of the manuscript for important intellectual content.

Dr. R. Hagerman - Study concept and design and critical revision of the manuscript for important intellectual content.

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PJH holds patents for assays of CGG-repeat expansion and for FMRP ELISA; he is also in non-remunerative collaborations with Pacific Biosciences, Inc. and Roche Diagnostics.

Authors otherwise declare no conflict of interest.

Case 1

At 77 he experienced memory loss and later developed shuffling gait and dementia. He needed a wheelchair and became severely demented and incontinent. He never had tremor. He had mild atrophic changes in cerebral hemispheres, enlarged ventricles, and decreased size amygdala and hippocampus. Presented with diffuse arteriolosclerosis consistent with hypertension and diabetes, multifocal remote infarcts involving cortex, hippocampus and basal ganglia, and subacute hypoxic/ischemic changes, loss of purkinje cells, loss of ependymal lining and subependymal gliosis, loss of pyramidal neurons in CA1, diffuse white matter gliosis, and increased Iba1-positive microglia (Figure 1). Clinical symptoms are compatible with the presence of severe brain vascular pathology including multifocal infarctions that indicative of a vascular cause of dementia.

Case 2

He had a stroke at 76, ataxia and mild cognitive deficits in his 80s. He never had tremor but developed motor coordination problems in his hands related to muscle weakness. He had 4 daughters who are all carriers. His niece had a son with mild FXS. This case was included in the manuscript by Greco and colleagues in 2006. Microscopic findings included severe small vessel disease (arteriolosclerosis) with hyalinization of intraparenchymal vessel walls, perivascular clearing, hemosiderin deposits, and micro-hemorrhages indicative of severe hypertension. Rare neurons contained Tau+ neurofibrillary tangles, with loss of cortical and CA1 neurons and of Purkinje cells. Evidence of global hypoxic/ischemic changes, diffuse white matter gliosis, focal loss of ependymal lining and subependymal gliosis, and increased number of Iba1+ ramified microglia throughout white matter (Figure 1). Clinical symptoms are compatible with severe small vessel disease (arteriolosclerosis) and acute intraparenchymal microhemorrhages.

Both cases lacked intranuclear inclusions and had a low premutation range (65 and 66 CGGs). Although they had neurological symptoms, they did not have classical features of FXTAS. These cases demonstrate that not all individuals with the premutation develop intranuclear inclusions and FXTAS. The reason for the lack of inclusions is likely a low number of *FMR1* CGG repetitions. However, we examined 2 additional cases with less than 70 repetitions (an 85 y/o female with 63 CGG and 69 y/o male with 67 CCG) that presented with inclusions in the cerebral cortex and cerebellum and were clinically categorized as FXTAS.

We hypothesize that having a low CGG repeat number makes it less likely to develop FXTAS. However, other additional factors such as genetic or environmental factors may predispose a person with a low CGG repeat number to develop FXTAS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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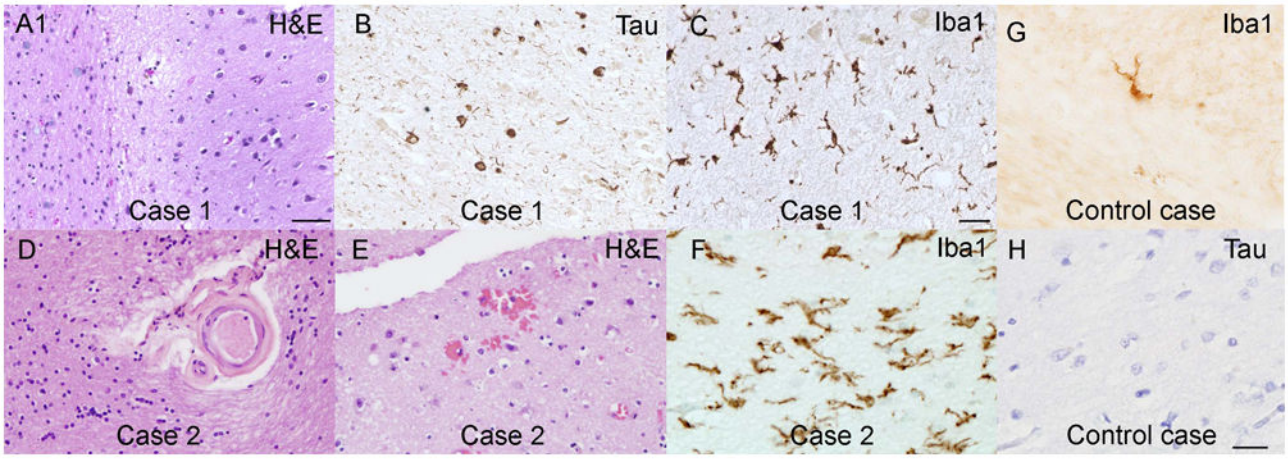

Figure 1.

A-C. Case 1. (A) H&E. Intraparenchymal blood vessels show thickening and hyalinization of the vessel walls, perivascular clearing and patchy white matter rarefactions. B) Tau+ dystrophic neurites in the neuropil and Alzheimer type neuritic plaques and also some neurofibrillary tangles. (C) Iba1+ activated microglial cells. **D-F**. Case 2 (D) Hyalinized intraparenchymal vessel walls and perivascular clearing. (E) Micro-hemorrhages indicative of severe hypertension. (F) Diffuse white matter gliosis and increased number of Iba-1 ramified microglia throughout white matter. **G-H**. Control case (no premutation). (G) Iba 1 staining show a reduced number of microglial cells with a non-activated morphology. (H) Tau staining does not show any label. Scale bar: 50 μm.