Received: 17 January 2023 | Accepted: 26 February 2023

DOI: 10.1002/epd2.20043

Epileptic Disorders

CASE VIGNETTE

# A super-elderly autopsy case of benign adult familial myoclonus epilepsy with a heterozygous mutation

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**Funding information**
Grant-in-Aid for Exploratory Research KAKENHI, Grant/Award Number: 20K21573; Grant-in-Aid for Scientific Research (B) KAKENHI, Grant/Award Number: 19H03574; Grant-in-Aid for Young Scientists (Start-up), Grant/Award Number: 22K20855; Grant-in-Aid for Young Scientists KAKENHI, Grant/Award Number: 22K15729; Health and Labour Sciences Research Grants on Rare and Intractable Diseases from the Ministry of Health, Labour and Welfare, Japan, Grant/Award Number: JPMH20FC1039

**Keywords:** cerebellum, cortical myoclonus, cortical tremor, giant somatosensory evoked potentials, TTTCA

Benign adult familial myoclonus epilepsy (BAFME) is one of the diseases causing cortical myoclonus.[1] BAFME could be a neurodegenerative disease, because the disease progresses with age and cognitive dysfunction could occur in elderly.[2] Abnormal intronic expansions caused BAFME, and the number of expansions and the seizure onset age are inversely related.[3] Previous electrophysiological and imaging findings have suggested possible abnormalities in the cerebellum, sensorimotor cortex, and thalamocortical networks in BAFME.[4] We report the brain autopsy finding of a case deceased at age 93 and was genetically diagnosed with BAFME type 1. We performed examinations as part of the clinical evaluation after obtaining informed consent.

A 76-year-old right-handed woman was treated in our hospital for hand tremors since age 59. Her two children had very mild hand tremors (Figure 1A). She also had infrequent generalized tonic–clonic seizures since age 62. At age 76, she had moderate tremulous myoclonus in both upper extremities and a postural tremor predominantly in the left hand (Figure 1B). Electrophysiological findings suggested cortical hyperexcitability: enlarged P25 amplitudes (median nerve stimulation, Rt: 12.2 μV, Lt: 15.9 μV) in somatosensory evoked potentials (SEPs) (Figure 1C). Brain MRI at age 76 showed mild diffuse atrophy. Genetic testing revealed a 3.4 kb heterozygous expansion of the TTTCA and TTTTA repeats in *SAMD12*; she was consequently diagnosed with BAFME type 1. Although antiseizure medications successfully treated her epileptic seizures, the tremulous myoclonus continued to progress. At age 84, the SEP P25 amplitude decreased (Rt: 9.3 μV, Lt: 9.9 μV). In the last several years of her life, she had a prominent vocal tremor with a fast frequency and comprehension of

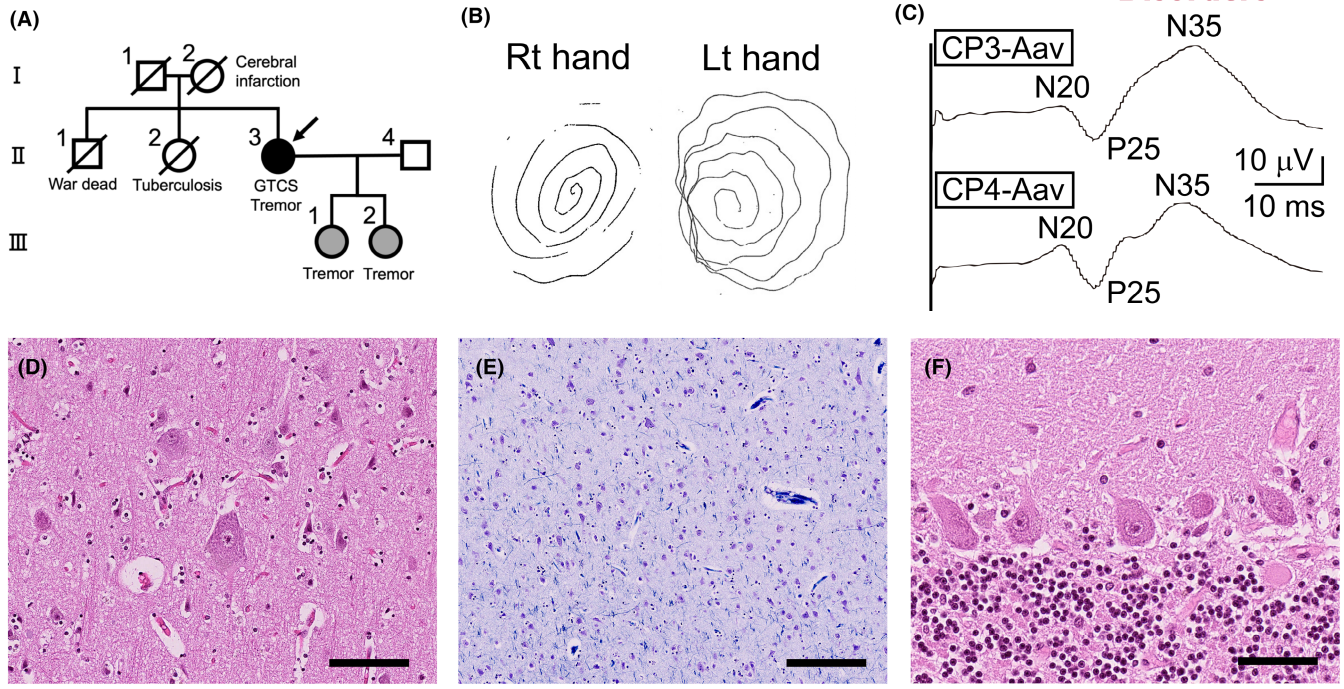


**FIGURE 1** Clinical, electrophysiological, and pathological findings. Pedigree (A). A left-dominant tremor during a spiral drawing (B), and giant SEPs to right (upper row) and left (lower row) median nerve stimulation (C), at age 76. In the autopsy, no remarkable gliosis or neuronal loss was observed in the bilateral primary motor cortex (D), primary sensory cortex (E), or Purkinje cells (F). Scale bars = 100 mm for D, 200 mm for E, and 50 mm for F. GTCS, generalized tonic–clonic seizure; Lt, left; Rt, right; SEP, somatosensory evoked potentials.

her speech was difficult. Throughout the course, she had no apparent cerebellar ataxia or cognitive decline. She died of aspiration pneumonia at age 93. A general autopsy was performed, at which time the brain weighed 982 g. Diffuse pyogenic pneumonia was observed in both lungs. Histologically, gliosis was unremarkable in the brain, where no neuronal loss in the bilateral primary motor cortices (Figure 1D), primary sensory cortices (Figure 1E), or Purkinje cells (Figure 1F) was observed. Halo-like amorphous materials around the cytoplasm of Purkinje cells, seen in homozygous mutation cases,[3] were not evident.

This super-elderly[5] case was genetically diagnosed as heterozygous BAFME type 1, with consistent clinical and electrophysiological findings. The autopsy revealed no degenerative findings at a very old age 93. Although BAFME is the second most common disease underlying progressive myoclonus epilepsy in Japan,[6] to the best of our knowledge, there have been no autopsy reports of cases over 90 years of age. Previous postmortem pathology of three cases from a Dutch family with heterozygous BAFME type 3[7,8] and one South African case[9] without identified genetic abnormalities showed loss, dendrite decrease, and morphological abnormalities (somatic sprout) of Purkinje cells in the cerebellum. Mild somatic sprouts of Purkinje cells have also been reported in homozygous Japanese BAFME type 1, whereas no apparent pathological changes in the cerebellum in few cases of heterozygous Japanese BAFME type 1.[3] Compared with these cases, our case was clinically mild in terms of onset age, cerebellar ataxia, and cognitive decline (Table S1). The relatively small number of expansions (3.4 kb) might be related to the severity.[3] However, the myoclonus at age 76 was moderate rather than mild, as compared to other Japanese BAFME cases,[10] and it is unclear whether the case was actually mild, because there have been no detailed reports of BAFME over 90 years of age. Additionally, this case showed decreased SEP amplitude at age 84, which was interpreted as a decrease of the hyperexcitability of the sensorimotor cortex, in contrast to the autopsy findings. This may be due to the inability to assess interneurons or neuronal networks with the current pathological techniques, or the decreased but still giant SEP amplitude did not result in pathological degeneration.

The pathological findings of this case suggest that heterozygous Japanese BAFME type 1 cases could involve no degenerative changes, even in the super-elderly. According to our current pathological analysis, its phenotype may be different from homozygous BAFME type 1 and other types of BAFME. Further studies on genotype–phenotype associations and pathological demonstration of neurodegeneration are warranted.

## ACKNOWLEDGMENTS

We would like to acknowledge Dr. Hiroyuki Ishiura (Department of Neurology, The University of Tokyo

Hospital) and Dr. Shoji Tsuji (Department of Molecular Neurology, The University of Tokyo Hospital Institute of Medical Genomics, International University of Health and Welfare) for the genetic analysis of BAFME.

## FUNDING INFORMATION

This study was supported by Health and Labour Sciences Research Grants on Rare and Intractable Diseases from the Ministry of Health, Labour and Welfare, Japan (JPMH20FC1039), a Grant-in-Aid for Scientific Research (B) KAKENHI Grant Number 19H03574, a Grant-in-Aid for Exploratory Research KAKENHI Grant Number 20K21573, a Grant-in-Aid for Young Scientists KAKENHI Grant Number 22K15729, a Grant-in-Aid for Young Scientists (Start-up) KAKENHI Grant Number 22K20855 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

## CONFLICT OF INTEREST STATEMENT

Maya Tojima, Katsuya Kobayashi, Takefumi Hitomi, Haruka Ishibashi, Daisuke Yoshii, Makoto Sainouchi, Takashi Ayaki, Akihiro Shimotake, Takakuni Maki, Akiyoshi Kakita, and Ryosuke Takahashi report no disclosures relevant to this manuscript. Kiyohide Usami and Akio Ikeda are current members of The Department of Epilepsy, Movement Disorders, and Physiology. Since June 2018, this department is the Industry-Academia Collaboration Courses supported by Eisai Co. Ltd., Nihon Kohden Corporation, Otsuka Pharmaceutical Co., and UCB Japan Co. Ltd.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Tojima M, Kobayashi K, Hitomi T, Ishibashi H, Yoshii D, Sainouchi M, et al. A super-elderly autopsy case of benign adult familial myoclonus epilepsy with a heterozygous mutation. Epileptic Disord. 2023;25:110–113. https://doi.org/10.1002/epd2.20043

**Test yourself**

1. Which type of tremor was present in this case?
   A. Resting tremor
   B. Postural tremor
   C. Intention tremor
2. What are the repeated sequences of bases that are abnormally expanded in benign adult familial myoclonus epilepsy (BAFME)?
   A. CAG
   B. ATTCT
   C. TTTTA and TTTCA
3. What is the location of the pathological abnormal findings reported in a homozygous BAFME type 1 and other types of BAFME?
   A. Cerebellum
   B. Hippocampus
   C. Thalamus

*Answers may be found in the supporting information.*