Journal of the Neurological Sciences 404 (2019) 36–39

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Letter to the Editor

# An autopsy case of MM2-thalamic subtype of sporadic Creutzfeldt-Jakob disease with Lewy bodies presenting as a sleep disorder mimicking anti-IgLON5 disease

ARTICLE INFO

*Keywords:*
Sporadic CJD
Thalamic form of MM2
IgLON5
Lewy bodies
Sleep disorder

*Dear Editor,*

## 1. Introduction

A thalamic form of MM2 (methionine homozygosity at codon 129 with type 2 abnormal prion protein)-type sporadic Creutzfeldt-Jakob disease (MM2-thalamic-sCJD) is a rare prion-related disorder characterized by prominent insomnia, progressive psychomotor hyperactivity, and cognitive impairment [1]. This phenotype lacks antemortem clinical, laboratory or imaging diagnostic markers; an electroencephalogram (EEG) or brain MRI is often unremarkable, and 14-3-3 protein or altered prion protein is usually not detected in cerebrospinal fluid (CSF). Previous studies showed thalamic hypoperfusion/hypometabolism in several cases of MM2-thalamic-sCJD [2,3], but its disease specificity remains unclear.

While anti-IgLON5 disease is a recently established disorder with autoantibodies against extracellular epitopes of IgLON5 [4]. This is a complex disorder with immunological and neurodegenerative features, characterized by a sleep disorder with rapid eye movement (REM) behavior disorder (RBD), non-REM sleep parasomnia, obstructive sleep apnea syndrome and stridor [4,5]. Other neurological features include bulbar symptoms, gait abnormalities, dysautonomia, and cognitive dysfunction. Some of these symptoms can be seen in both MM2-thalamic-sCJD and Lewy body (LB)-associated disease [6].

We report a case of MM2-thalamic-sCJD with LB presenting as a sleep behavior disorder mimicking anti-IgLON5 disease.

## 2. Case report

A 62-year-old Japanese man had been well until 11 months before admission, when abnormal behaviors developed in sleep. His abnormal behaviors were accompanied by vocalizations, limb movements, and purposeful-looking gestures. Six months before admission, memory loss developed. One month before admission, he visited a sleep clinic and underwent a polysomnography (PSG), which demonstrated abnormal sleep architectures. Percentage of total sleep time (%TST) of Stage N1 was high (76.4%), Stage N2 was low (7.7%), and Stage N3 was not seen. Stage R was slightly decreased (15.9%). Stage N1 completely lacked slow eye movements, N2 lacked sleep spindles, and excessive chin-EMG was seen throughout the sleep stages (Supplementary Fig. 1). The sleep efficiency was 39% (usually > 85%). Apnea hypopnea index was 3.3/h (normal < 5.0) with lowest oxygen saturation of 93%. Stridor with obstructive sleep apnea began from the onset of sleep and developed intermittently at any sleep stage (Fig. 1). Periodic leg movements (PLM) index was 109/h (> 50/h, considered severe). The rapid PLMs (PLM with intervals shorter than 5 s) was frequently recognized. Sleep latency was normal but REM latency was markedly prolonged (391 min, usually 60–120), and arousal index was high (41/h, usually 10–25). These findings were atypical of RBD. He was referred and admitted to our hospital. His family history was unremarkable.

On admission (day 1), the physical examination was unremarkable. On neurologic examination, the patient was awake but disoriented to time. The mini-mental state examination was 16/30, and the frontal assessment battery scale was 9/18. The function of the cranial nerves was normal, except dysphagia. Sensory examination was normal. He had no Parkinsonism. The gait was unsteady and tandem walking was impossible. He had nocturnal hyperhidrosis but no other autonomic symptoms. A videofluoroscopic examination showed saliva pooling in the piriform sinus, aspiration into laryngeal cavity, and poor pharyngeal clearance.

The laboratory test-results were unremarkable, including ANA and autoantibodies to MPO-ANCA, TPO, Tg, or GAD. CSF examination showed no abnormal findings. IgG index was 0.54, and oligoclonal bands were not detected. The patient's serum and CSF were determined to be negative for autoantibodies against neuronal surface antigens or synaptic proteins, including NMDA receptor, AMPA receptor, $GABA_{(A)}$ receptor, $GABA_{(B)}$ receptors, LGI1, Caspr2, DPPX, Neurexin3, and IgLON5. 14-3-3 protein was negative in CSF. Abnormal form of prion protein ($PrP^{Sc}$) in CSF were also examined with real-time quaking-induced conversion assay [7] but negative. A whole-body CT, brain MRI, and $^{123}$I-iodoamphetamine ($^{123}$IMP) single photon emission tomography (SPECT) were unremarkable (Fig. 2A,B). $^{123}$I-N-fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane ($^{123}$I-FP-CIT) SPECT on day 3 demonstrated mildly decreased uptake of the tracer (Fig. 2C).

During his hospitalization, the patient was treated with intravenous methylprednisolone (1000 mg/day, 3 days) from day 29, without

https://doi.org/10.1016/j.jns.2019.07.010
Received 29 March 2019; Received in revised form 15 June 2019; Accepted 9 July 2019
Available online 10 July 2019

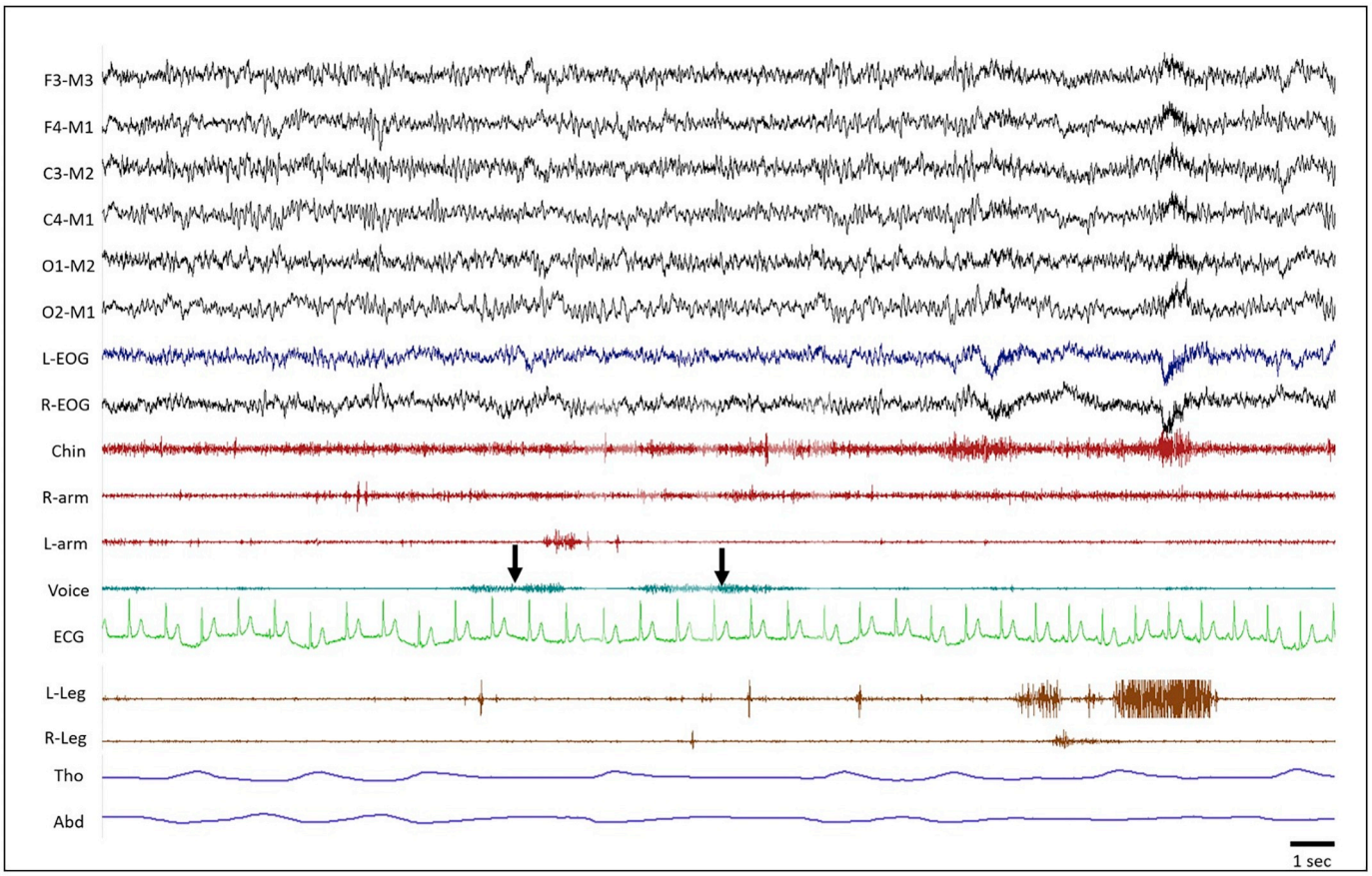


**Fig. 1.** Polysomnogram in the stage N1 performed one month before admission.
Sleep vocalization is seen in non-REM stage N1 (arrows). Slow eye movements are not seen. Note continuous excessive EMG in chin throughout the recording. This polysomnogram is selected from a sleep study performed overnight (Supplementary Fig. 1).
Abd: abdominal respiratory movement; Arm: electromyogram of upper limb; Chin: electromyography of mentalis muscle; ECG: electrocardiogram; EOG: electrooculogram; HR: heart rate; Leg: electromyogram of lower limb; PLM: periodic leg movements; REM: sleep stage of rapid eye movements; REM*: rapid eye movements; Tho: thoracic respiratory movements.

efficacy. On day 47 paroxysmal severe laryngeal stridor and apneic spells developed. A video laryngeal scope revealed bilateral vocal cord palsy. The symptom was easily provoked by mechanical stimulation (suction or insertion of feeding tube), and partially relieved by clonazepam; however, the symptoms had gradually worsened. On day 84 he died of pneumonia.

Autopsy and PrP gene analysis were performed after obtaining informed consent from his family. The brain weighted 1342 g. Macroscopic examination revealed no apparent cerebral cortical atrophy. The hippocampus was well preserved. There was no depigmentation of the substantia nigra and locus ceruleus. Macroscopically, the inferior olivary nucleus was not atrophic but microscopically severe neuronal loss and gliosis were seen bilaterally in the dorsomedial part of inferior olivary nucleus in the medulla oblongata and the dorsomedial nuclei of the thalamus (Fig. 2D,E); it was difficult to identify ambiguous nuclei. Immunohistochemistry using 3F4 anti-prion protein antibody did not detect positive immunoreactivity (Fig. 2F). LB were found in the dorsal motor nucleus of the vagus nerve, reticular formation of medulla oblongata, locus coeruleus, substantia nigra, basal nucleus of Meynert, amygdala and transentorhinal cortex, consistent with limbic type of Lewy-related pathology [8] (Fig. 2G,H, Supplemental Table 1); however, neuronal loss or gliosis was not apparent in the brainstem nuclei including with substance nigra, except inferior olivary nuclei. Only mild gliosis was seen in basal nucleus of Meynert (Fig. 2).

No PrP gene mutation was identified and methionine homozygosity at codon 129 and glutamic acid homozygosity at codon 219 were found. Western blot analysis of protease K-resistant PrP revealed type 2-PrP, with 19 kDa unglycosylated bands, and a positive band was detected by type 2 specific antibodies but not by type 1 specific antibodies (Fig. 2I). A diagnosis of MM2-thalamic-sCJD with LB was made.

## 3. Discussion

This patient presented with progressive insomnia, dementia, dysphagia, and laryngeal stridor with sleep architecture abnormalities. These clinical features have been reported in anti-IgLON5 disease. Therefore, we measured IgLON5 antibodies but the results were negative. Autopsy confirmed MM2-thalamic-sCJD with LB pathology.

This patient had striking features such as vocal cord paralysis and rapid PLM, which were presumed to be due to MM2-thalamic-sCJD, Limbic type of Lewy-related pathology, or the combination of the two pathologies. However, we could not identify pathological changes directly causing these symptoms, and it was difficult to assess loss of small ambiguous nuclei in the specimen obtained from the autopsy material. Hens, we could not determine which pathology mainly contributes to these symptoms. No apparent loss of neurons or gliosis was seen in the substance nigra but LBs were identified; therefore, RBD-like parasomnia and mildly decreased uptake on $^{23}$I-FP-CIT SPECT are likely caused by LB pathology.

Thalamic hypoperfusion was not seen on $^{123}$IMP-SPECT on admission, but histopathological examination performed 12 weeks later demonstrated severe neuronal loss and gliosis in the dorsomedial nuclei of the thalamus. The mechanism of discrepancy between regional cerebral

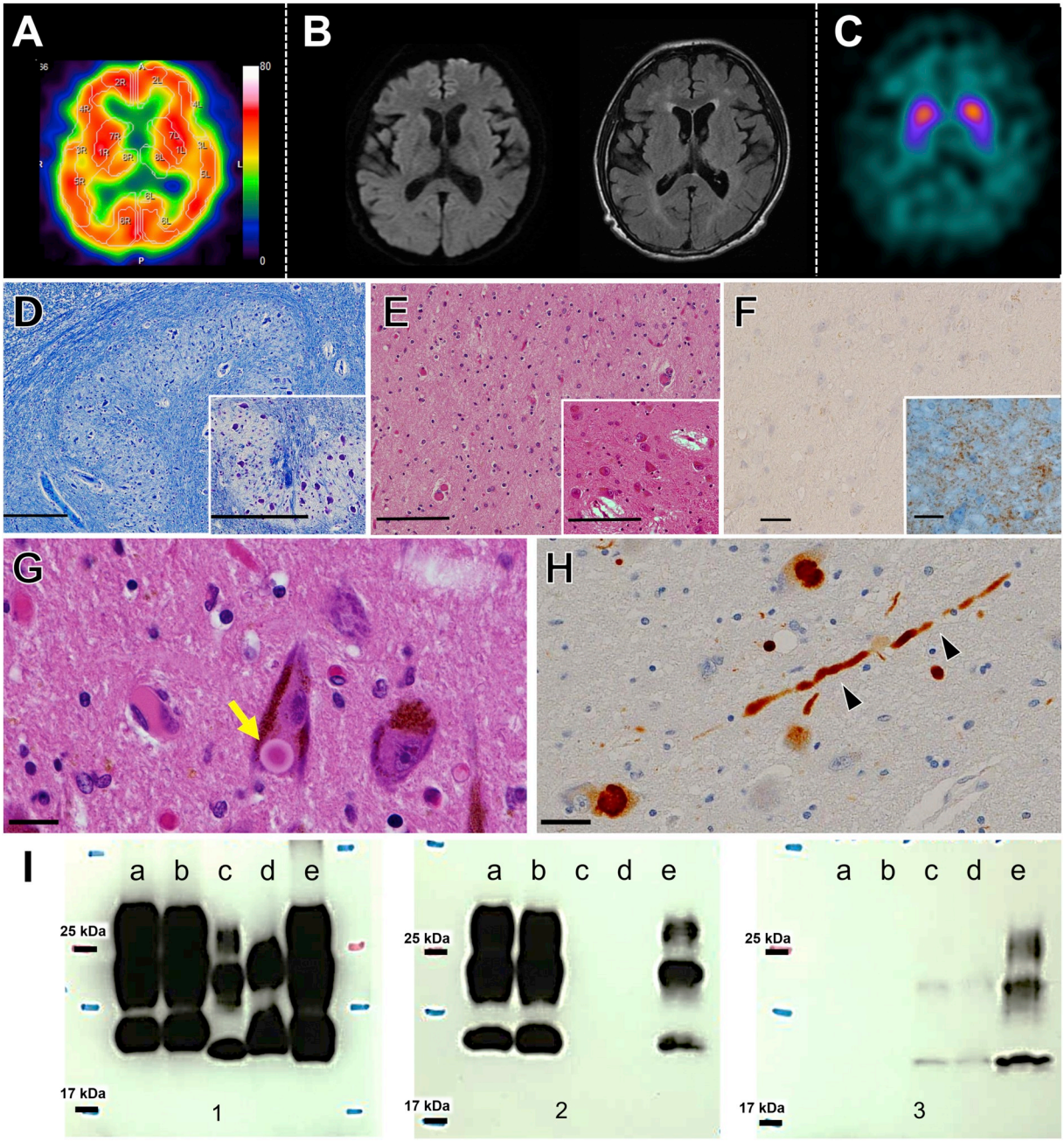


**Fig. 2.** Radiological, pathological, and Western-blotting findings in this patient.
$^{123}$I-IMP-SPECT (A) obtained on day 4 is unremarkable. Brain MRI (B) obtained on day 3 does not show increased DWI/FLAIR signals in the cerebral cortex or basal ganglia. $^{123}$I-FP-CIT SPECT (C) demonstrates mildly decreased bilateral striatal uptake. Specific binding ratio (SBR) is 3.76 (R), and 3.68 (L). Microscopic examination of the brain shows neuronal loss and gliosis in the dorsomedial part of the inferior olive nucleus (D, Klüver-Barrera staining. Scale bar = 200 μm), and dorsomedial nuclei of bilateral thalami (E, H-E staining, Scale bar = 100 μm). The insets in D and E show the age-matched normal control. PrP immunostaining using 3F4 antibody shows no apparent staining in thalamus (F, 3F4 staining, Scale bar = 100 μm). The inset in F is positive control of CJD case. Lewy bodies are seen in the substantia nigra (G, arrow, H-E staining. Scale bar = 50 μm). Lewy neuritis with slight gliosis are recognized in basal nucleus of Meynert (H, arrowhead, phosphorylated-α-synuclein immunohistochemistry, Scale bar = 100 μm). A Western-blotting analysis with the 3F4 antibody (I-1), type 1 specific antibody (Tohoku-1, I-2), and type 2 specific antibody (Tohoku-2, I-3) shows the presence of type 2 protease resistant core of the disease-associated prion protein in this patient (c). Immunostaining studies were performed using cryopreserved brain tissue obtained from a patient with MM1-type sporadic CJD (a), MM1-type sporadic CJD (b), this patient (c), MV2-type sporadic CJD (d), and MM2 + 1 cortical type sporadic CJD (e).
CJD: Creutzfeldt-Jakob disease; DWI: diffuse weighted image; FLAIR: fluid-attenuated inversion recovery; $^{123}$I-FP-CIT: $^{123}$I-N-fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane; $^{123}$I-IMP: $^{123}$I-iodoamphetamine; L: left; M: methionine; R: right; SPECT: single photon emission computed tomography; V: valine.

blood flow (CBF) and pathology remains unclear, but it can be explained by long interval between CBF study and autopsy. We did not follow-up SPECT study in this patient, thus we do not know changes in CBF at the late stage of the disease. $^{123}$IMP-SPECT at the early stage may be limited in term of detection of thalamic hypoperfusion in patients with MM2-thalamic-sCJD. Further study will be required to conclude it.

Sleep behavior disorder may develop in MM2-thalamic-sCJD/familial fatal insomnia, RBD, or anti-IgLON5 disease, but some of the features may distinguish one from the others. Severe insomnia,

wakefulness-invading movements, and disappearance of sleep spindles/slow wave sleep are seen in FFI [9], while rapid PLM or stridor develops more frequently in anti-IgLON5 disease than other disorders [4,5]. Rapidly progressive insomnia, movement disorders and abnormal EEG findings are more likely suggestive of MM2-thalamic-sCJD, thus PSG may help to discriminate (Supplemental Table 2).

Vocal cord paresis is rare in CJD [10,11] and antemortem diagnosis of MM2-thalamic-sCJD is difficult, but it is important to note that MM2-thalamic-sCJD coexisting with LB pathology can represent as a sleep behavioral disorder with marked laryngeal stridor.

## Study funding

This work was supported in part by the Japan Epilepsy Research Foundation [JERFTENKAN 17002, TI].

## Ethics committee

This study was approved by Institutional Review Boards of Kitasato University (B17-351).

## Authors' contributions and disclosures

Y. Hongo, T. Iizuka: study concept or design, data acquisition, analysis or interpretation of the data, and drafting/revising the manuscript. A. Kaneko, H. Suga, K. Namba, Y. Inoue, K. Nishiyama: data acquisition, analysis or interpretation of the data, and drafting/revising the manuscript. A. Uchino, S. Murayama: analysis or interpretation of the pathological data and drafting/revising the manuscript.

## Disclosures

Y. Hongo, A. Kaneko, H. Suga, A. Uchino, K. Namba reports no disclosures; T. Iizuka received a grant from Japan Epilepsy Research Foundation; S. Murayama received grants from Japan Ministry of Education, Culture, Sports, Science and Technology Japan ministry of health, labor and welfare, national center of neurology and psychiatry, national center for geriatrics and gerontology, and Tokyo Metropolitan Geriatric Hospital, Institute of Geriatrics; Y. Inoue received honoraria from Eisai Co., Ltd., MSD KK, and Takeda Pharmaceutical A Co., Ltd.; K. Nishiyama received grants from Daiichi Sankyo Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., and Eisai Co., Ltd..

## Acknowledgements

We particularly thank Dr. Josep Dalmau for examining autoantibodies against neuronal surface antigens or synaptic proteins. We are also grateful to Dr. Katsuya Satoh for analyzing 14-3-3 protein and abnormal prion protein in CSF. We would like to thank Dr. Tetsuyuki Kitamoto for gene study and Western blot assay of brain tissue in this case.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.07.010.

## References

[1] P. Parchi, A. Giese, S. Capellari, P. Brown, W. Schulz-Schaeffer, O. Windl, et al., Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects, Ann. Neurol. 46 (2) (1999) 224–233.
[2] T. Hamaguchi, T. Kitamoto, T. Sato, H. Mizusawa, Y. Nakamura, M. Noguchi, et al., Clinical diagnosis of MM2-type sporadic Creutzfeldt-Jakob disease, Neurology 64 (4) (2005) 643–648.
[3] P. Cortelli, D. Perani, P. Montagna, R. Gallassi, P. Tinuper, F. Provini, et al., Pre-symptomatic diagnosis in fatal familial insomnia: serial neurophysiological and 18FDG-PET studies, Brain 129 (Pt 3) (2006) 668–675.
[4] L. Sabater, C. Gaig, E. Gelpi, L. Bataller, J. Lewerenz, E. Torres-Vega, et al., A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study, Lancet Neurol. 13 (6) (2014) 575–586.
[5] C. Gaig, F. Graus, Y. Compta, B. Hogl, L. Bataller, N. Bruggemann, et al., Clinical manifestations of the anti-IgLON5 disease, Neurology 88 (18) (2017) 1736–1743.
[6] A. Iranzo, J. Santamaria, E. Tolosa, The clinical and pathophysiological relevance of REM sleep behavior disorder in neurodegenerative diseases, Sleep Med. Rev. 13 (6) (2009) 385–401.
[7] R. Atarashi, K. Satoh, K. Sano, T. Fuse, N. Yamaguchi, D. Ishibashi, et al., Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion, Nat. Med. 17 (2) (2011) 175–178.
[8] I.G. McKeith, D.W. Dickson, J. Lowe, M. Emre, J.T. O'Brien, H. Feldman, et al., Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium, Neurology 65 (12) (2005) 1863–1872.
[9] S. Abu-Rumeileh, V. Redaelli, S. Baiardi, G. Mackenzie, O. Windl, D.L. Ritchie, et al., Sporadic fatal insomnia in Europe: phenotypic features and diagnostic challenges, Ann. Neurol. 84 (3) (2018) 347–360.
[10] P. Montagna, P. Gambetti, P. Cortelli, E. Lugaresi, Familial and sporadic fatal insomnia, Lancet Neurol. 2 (3) (2003) 167–176.
[11] S. Iwata, A. Nakamura, N. Nakamura, I. Sakashita, H. Fukunaga, 2 cases of Creutzfeldt-Jacob disease with bilateral vocal cord paralysis, Rinsho Shinkeigaku 28 (3) (1988) 333–337.

Yu Hongo[a,*], Takahiro Iizuka[a], Atsushi Kaneko[a], Hiroki Suga[a], Akiko Uchino[a], Shigeo Murayama[b], Kazuyoshi Namba[c], Yuichi Inoue[c,d], Kazutoshi Nishiyama[a]

[a] *Department of Neurology, Kitasato University School of Medicine, Sagamihara, Japan*

[b] *Department of Neurology and Neuropathology (the Brain Bank for Aging Research), Tokyo Metropolitan Geriatric Hospital & Institute of Gerontology, Tokyo, Japan*

[c] *Neuropsychiatric research institute, Japan Somnology center, Tokyo, Japan*

[d] *Tokyo Medical University, Tokyo, Japan*

*E-mail addresses:* hongo_yu@yahoo.co.jp (Y. Hongo), takahiro@med.kitasato-u.ac.jp (T. Iizuka), a.kaneko@kitasato-u.ac.jp (A. Kaneko), h.suga@kitasato-u.ac.jp (H. Suga), akikou@med.kitasato-u.ac.jp (A. Uchino), smurayam@bbarjp.net (S. Murayama), namba@somnology.com (K. Namba), inoue@somnology.com (Y. Inoue), nishiyk@med.kitasato-u.ac.jp (K. Nishiyama).

[*] Corresponding author at: Department of Neurology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan.