

A novel familial prion disease causing panautonomic-sensory neuropathy and cognitive impairment

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1. Introduction

Sensory neuropathy is not common in prion diseases and autonomic failure has not been reported to be the initial or the main symptom of prion disease.(1) Here we report a unique familial prion disease with a novel prion gene mutation, pan-autonomic failure, sensory neuropathy and mild cognitive impairment as the initial symptom.

2. Case report

A 34-year-old Japanese female began to have urinary retention of up to 2L at the age of 26 years. At age 30, she developed syncope for 5 min due to orthostatic hypotension. At age 31, she began to show memory disturbances. After the age of 31, she suffered from frequent vomiting and diarrhea.

Her family tree is shown in Fig. 1a. Her mother developed dementia, urinary disturbance and orthostatic hypotension (from 140/100 mmHg lying to 80/45 standing) with frequent syncope attacks at the age of 47 years. She had thermoanesthesia in her lower limbs. One year after onset, she died without a final diagnosis. The grandfather of the present case is told to have developed dementia with urinary disturbance and orthostatic hypotension at the age of 52 years and died at the age of 62 years, but no medical record could be obtained.

The present case had a height of 159.5 cm and a body weight of 39.5 kg. Her cognitive function showed mild decline to 27/30 in mini-mental state examination (MMSE) and 21/30 in Montreal cognitive assessment (MoCA). The muscles in her distal limbs were slightly atrophic, and severe thermoanesthesia and hypoalgesia were present. Her tendon reflexes showed generalized areflexia. Severe orthostatic hypotension was observed from 115/80 mmHg (lying) to 59/35 (standing).

Cerebrospinal fluid (CSF) analysis showed an elevated protein level of 141 mg/dl, and otherwise normal data. Other laboratory data is shown in Table 1 and Fig 1b-e. Compound muscle action potentials and sensory action potentials were not evoked in bilateral tibial and sural nerves, respectively. Sural nerve biopsy revealed moderate loss of myelinated fibers (Fig. 1f) with no deposits of amyloid material. Unlike normal sural nerve (Fig. 1g), prion protein staining of the biopsy revealed ragged deposits in myelin (Fig. 1hi). The serum and CSF neuron-specific enolase (NSE) levels were elevated at concentrations of 35.2 ng/ml and 134.9 ng/ml, respectively. The CSF levels of 14-3-3 and tau proteins were also elevated at 1,125 μ g/ml and 2,994 pg/ml, respectively. Thus, the prion gene was analyzed, revealing a 2 bp deletion (CT) in codon 178 that causes additional variable 25 amino acid at C-terminal from the mutation site to the premature stop codon at codon 195 (Fig. 1j). We examined this mutation by PCR-based restriction

fragment length polymorphism (RFLP) analysis using BssSI restriction enzyme.(2) The BssSI restriction site detects mutation of the present 2 bp deletion (Fig. 1k).

There are no brain autopsy data to confirm prion disease in the proband, therefore she was treated as presumed prion disease. Bi-level positive airway pressure (BiPAP) was initiated for her in order to avoid the sudden death at night, and the patient is living by herself today.

3. Discussion

We experienced the first case with severe pan-autonomic failure, sensory neuropathy, and mild cognitive impairment owing to a novel prion gene mutation. An initial symptom of autonomic failure of has not been reported in prion disease. Hereditary sensory and autonomic neuropathies (HSANs) are inherited peripheral neuropathies.(3) HSAN-I is characterized by a slowly progressive loss of pain and temperature sensation with autosomal dominant inheritance. Causative mutations of HSAN-I identified to date occur in five genes.(4, 5) On the other hand, other HSAN subtypes are autosomal recessive diseases. Cellular prion protein is expressed in axons and Schwann cells of peripheral nerves; thus 108 German HSAN patients were surveyed to determine whether a mutation in prion protein was responsible. However,

no prion protein mutation was found.(6) Thus, the present case may be classified as a new type of HSAN-I with autosomal dominant inheritance and adulthood onset.

20 years disparity in the age of onset and protracted course in the proband are mysterious but difficult to explain because both her mother and grandfather died today.

Scrapie-infected transgenic mice expressing prion protein lacking the glycosylphosphatidylinositol (GPI) membrane anchor, abnormal protease-resistant PrPres was reported deposited as amyloid plaques, rather than the usual nonamyloid form of PrPres and the mutation of the proband is likely producing anchorless PrP protein.(7) This present case provides important clues to the mechanisms underlying prion disease.

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Figure legend

- a) Family tree showing the proband (arrow) and her mother and grandfather suffering from the same disease.
- b) DWI MR image showing neither cerebral atrophy nor abnormal signal intensities.
- c) ^{99m}Tc -ECD SPECT showing a decrease in cerebral blood flow in the right parietal and bilateral occipital lobes in eZIS analysis.
- d) Before the sweating test, her body temperature was 36.5 °C.
- e) At 35 min after the sweating test, her body temperature became 37.6 °C, but she showed no sweating response.
- f) The peripheral nerve biopsy was taken from the left sural nerve. Glutaraldehyde-osmium fixed and Epon embedded semithin cross-sections were stained with toluidine blue and were subjected to light microscopic examination. Sural nerve biopsy showing moderate loss of myelinated fibers with toluidine blue staining.
- g) Normal sural nerve stained with an antibody for prion protein showing myelin staining. The biopsy specimen was fixed in 10% formalin, and embedded in paraffin. For immunohistochemistry, 4.5- μm sections were incubated in 0.3% H_2O_2 for 30 min to bleach endogenous peroxidase activity, and then treated by “hydrolytic

autoclaving” to enhance the immunoreactivity of prion protein. Slides were incubated at 4 °C overnight with anti-prion protein antibody (clone 3F4, Millipore, Temecula, CA) diluted at 1:500. Positive staining was visualized by the avidin-biotin-peroxidase complex method with diaminobenzidine as the chromogen.

- h) Prion protein staining of the sural nerve biopsy from the proband at low magnification.
- i) Prion protein staining of the sural nerve biopsy from the proband showing a ragged depositions (arrowheads) in myelin around residual axons at high magnification.
- j) Direct PCR sequencing of the prion gene of the proband showing the 2-bp CT deletion. Forward sequence is upper and reverse sequence is lower. It showing mutation site at codon 195.
- k) PCR-RFLP analysis with the restriction enzyme BssSI, showing only 567-bp PCR products in normal controls 1 and 2, but 567 and 280 bands in the proband with BssSI digestion (upper). The BssSI restriction site detects mutation of the present 2-bp deletion (lower).

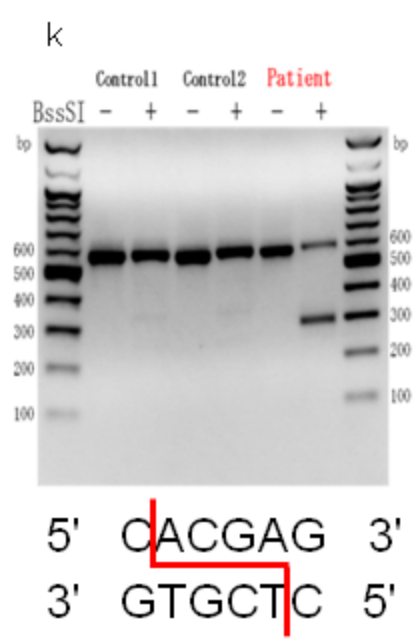
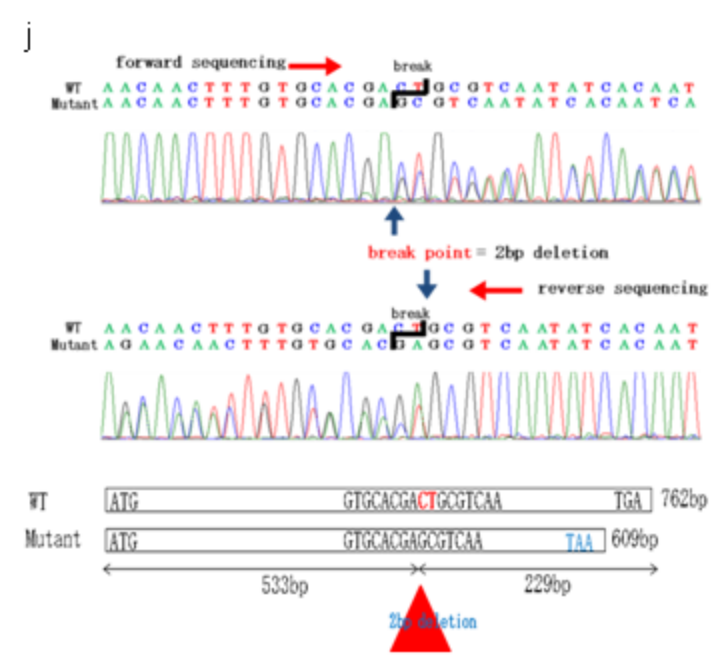
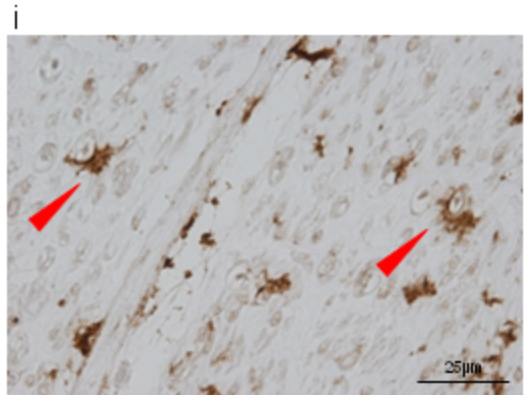
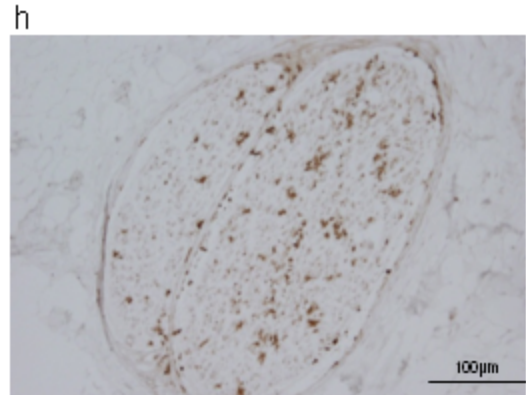
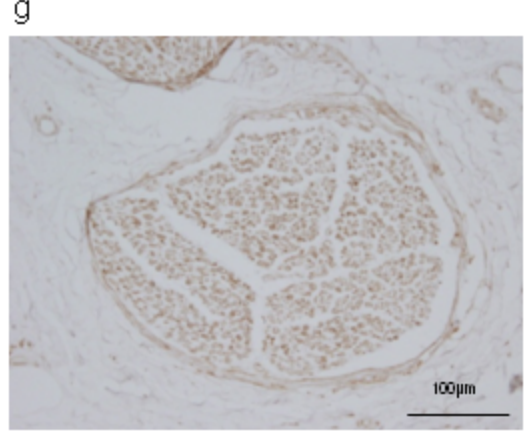
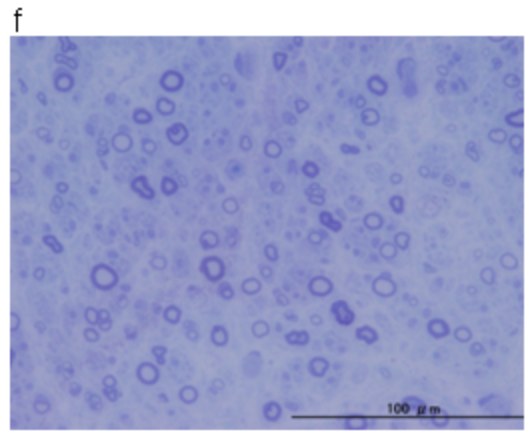
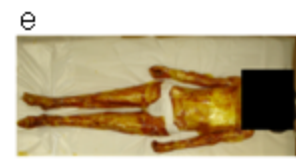
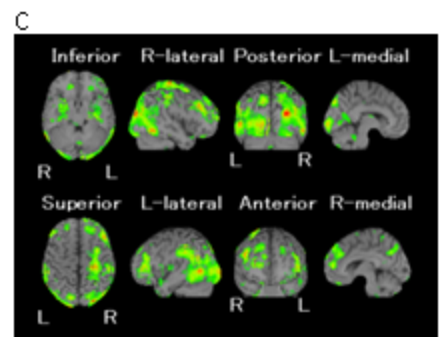
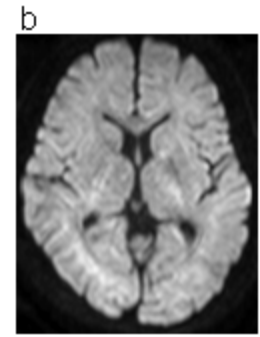
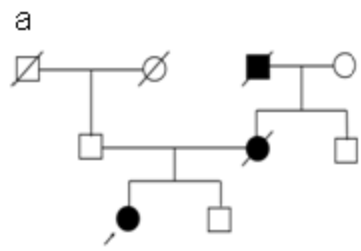


Table 1 Comparison of this present case and her mother

| | Present patient | Her mother |
|--|--|--|
| Onset (year) | 26 | 48 |
| Progress | living | death in 49 |
| MMSE | 27 | 21 |
| FAB | 21 | n.e. |
| OH (mmHg) | 115/80 (lying) 59/35 (standing) | 124/88 (lying) 76/54 (standing) |
| Urinary retention | 2000ml | 300ml |
| Sweating test | general anhidrosis | general anhidrosis |
| CVRR (CV%) | 1.01 | 0.98 |
| brain MRI | no specific finding | mild atrophy in parietal lobe |
| SPECT | Decrease of cerebral blood flow in the right parietal and bilateral occipital lobes | n.e. |
| CSF 14-3-3 protein ($\mu\text{g}/\text{mL}$) | 1,125 | (+) |
| CSF tau protein (pg/mL) | 2994 | n.e. |
| prion gene analysis | 2bp deletion | n.e. |

MMSE: mini-mental state examination

FAB: Frontal assessment battery

OH: Orthostatic hypotension

CVRR: The coefficient of variation for R-R interval

MRI: magnetic resonance image

SPECT: Single photon emission computed tomography

CSF: Cerebrospinal fluid