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Rapidly Progressive Parkinsonism and Dementia with No Insomnia due to the *PRNP* D178N Mutation

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Dera Editor,

Hereditary prion diseases are fatal progressive neurodegenerative disorders caused by mutation in the prion-related protein (*PRNP*) gene.[1] There are three major clinical phenotypes: familial Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), and Gerstmann-Straussler-Scheinker disease.[1] An aspartate-to-asparagine substitution due to mutation at codon 178 (D178N) of *PRNP* is known to cause either the FFI or CJD phenotype depending on the genotype of codon 129.[2] However, recent studies suggest that the clinical manifestations of D178N mutants are highly variable independently of the genotype of codon 129.[3] Here we report a family carrying the *PRNP* D178N mutation and having hereditary prion disease with an atypical presentation.

A 68-year-old female presented with gait disturbance and frequent falls with a 2-month history (III-2) (Fig. 1A). A neurological examination revealed moderate bradykinesia, mild rigidity, mild dysphagia, and moderate postural instability. She had a score of 32 on the Unified Parkinson's Disease Rating Scale (UPDRS) part III. She reported having experienced troublesome constipation and the sensation of residual urine for the past few years. Her sleeping partner reported to have witnessed her dream enactment behaviors, sleep apnea, and inspiratory stridor. However, the patient denied insomnia, and there was no myoclonus or ataxia. MRI including diffusion-weighted imaging (DWI) showed mild leukoaraiosis (Fig. 1B and C). Heterogeneous decrease in dopamine transporter binding were observed on ^{18}F-N-(3-fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl)nortropane (CIT) positron-emission tomography (PET). ^{18}F-fluorodeoxyglucose (FDG) PET showed subtle hypometabolism of the midbrain (Fig. 1D and E). There was no therapeutic response to levodopa at 600 mg/day for 2 months, during which she developed visual hallucination, and overt dementia developed 1 month later. She had received 12 years of education, and had a score of 10 on the Mini Mental Status Examination (MMSE). She became bedridden 5 months after the initial visit, and was repeatedly admitted for dilated cardiomyopathy, fever, and stercoral colitis. She died at 15 months after her initial visit.

Similar symptoms manifested in the proband's mother and sister (II-2 and III-4) (Fig. 1A) prior to their deaths. Her sister presented cognitive decline and bradykinesia at the age of 62 years. She reported a urinary frequency, sensation of residual urine, constipation, inspiratory stridor, snoring, and dream enactment behaviors, but no insomnia. Her MMSE score was 17 and she had 12 years of education, and mild parkinsonism was documented by a UPDRS part III score of 16. There was no sign of myoclonus or ataxia. She became bedridden after 3 months and died 9 months later. Brain MRI revealed mild brain atrophy (Fig. 1F and G). No amyloid deposition was seen in florbetaben PET, and diffuse cortical hypometabolism was observed on FDG PET (Fig. 1H and I). Her cerebrospinal fluid (CSF) was negative for 14-3-3 protein. Sanger sequencing of the DNA of the proband and her sister for *PRNP* identified the c.532G>A (D178N) mutation (Fig. 1J) with the methionine-methionine geno-

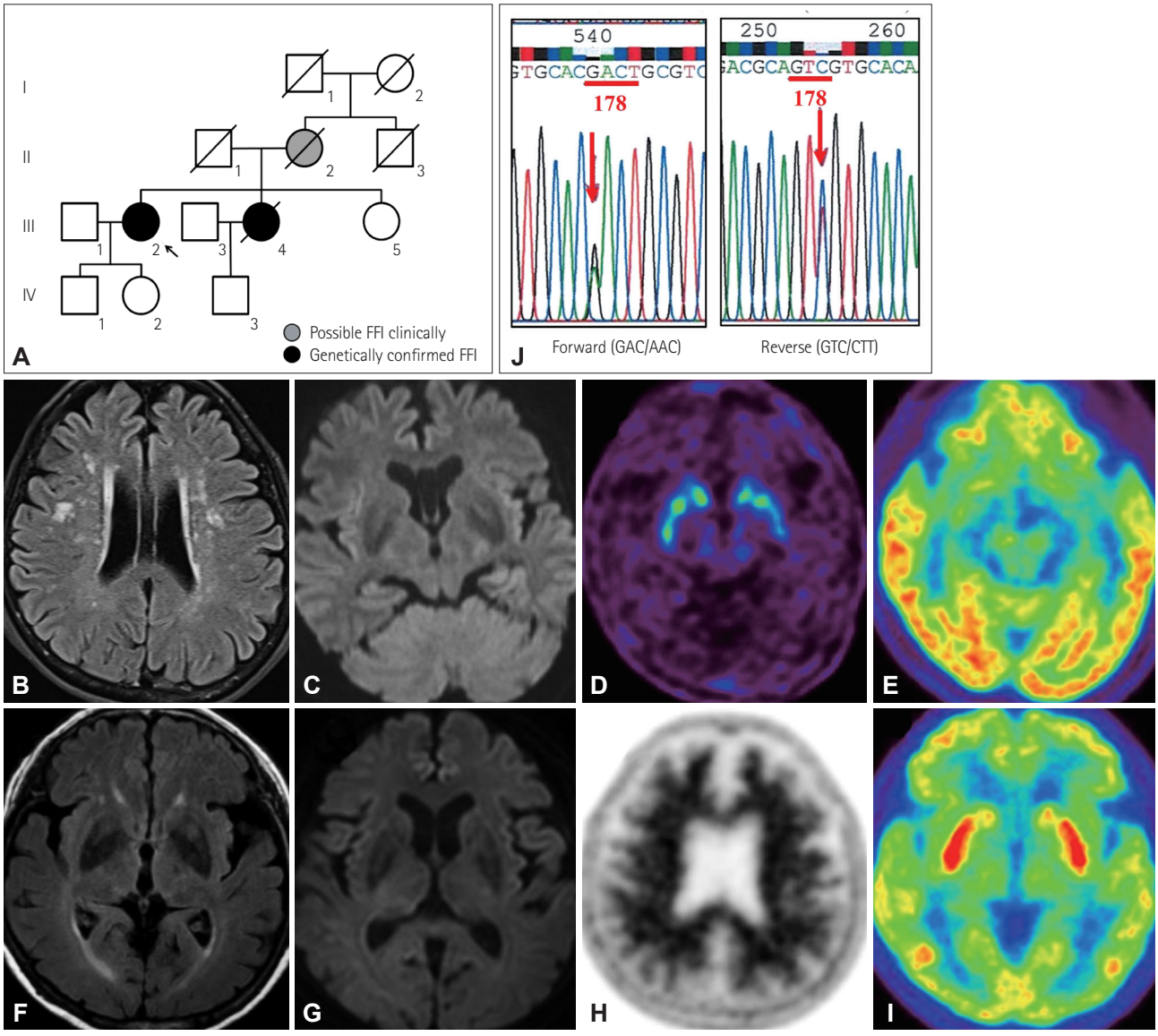

Fig. 1. Genetic and neuroimaging findings of the patients. A: Pedigree of the family. Arrow denotes the proband. B–E: Neuroimaging findings for patient III-2. B: FLAIR MRI showing mild leukoaraiosis. C: Normal DWI MRI. D: Patchy heterogeneous decreases in dopamine transporter binding in a 18F-N-(3-fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl)nortropane (CIT) PET image. E: Subtle hypometabolism of the midbrain. F–I: Neuroimaging findings for patient III-4. F: No definite abnormalities were found in FLAIR MRI. G: Normal DWI MRI. H: Negativity for amyloid deposition in florbetaben PET. I: Diffuse cortical hypometabolism was seen in ^{18}F-fluorodeoxyglucose PET. J: Sanger sequencing for patient III-2 revealing a heterozygous G-to-A substitution at position 532 (c.532G>A, D178N). DWI: diffusion-weighted imaging, FFI: fatal familial insomnia, FLAIR: fluid-attenuated inversion recovery, PET: positron-emission tomography.

type at codon 129 (129MM).

In patients carrying the *PRNP* D178N mutation, it has generally been considered that the homozygous methionine at codon 129 of *PRNP* results in FFI and that the presence of valine at codon 129 manifests as familial CJD. The present family exhibited rapidly progressive parkinsonism and dementia associated with the *PRNP* D178N mutation and the 129MM genotype. Due to the absence of insomnia, the sisters could not be classified as the typical FFI phenotype. However, the absence of DWI abnormalities and 14-3-3 protein elevation was also atypical for classification as CJD phenotype.[1] Recent reports suggest that the clinical phenotype of the D178N mutation is highly variable, with it now being considered as a continuous clinical spectrum between FFI and CJD, regardless of the genotype of codon 129.[3,4] Our literature review of previous case reports revealed heterogeneous manifestations of the *PRNP* D178N mutation (Supplementary Table 1 in the online-only Data Supplement). A particularly interesting observation was that most cases were negative for CSF 14-3-3 protein and the cortical ribbon sign in DWI. Because of its variable presenta-

tion, a more systemic consensus for the clinical diagnosis of hereditary prion disease is warranted.[4] Despite the atypical presentations of the present cases, their rapidly progressive course, severe autonomic dysfunction, and family history suggesting autosomal dominant inheritance led to suspicion of hereditary prion disease. Genetic testing for *PRNP* should be considered in patients with any rapidly progressive neurological conditions. In conclusion, these cases reflect the phenotypic variability in prion disease caused by the D178N mutation.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.4.579.

Ethics Statement

All procedures in this study involving human participants were performed in accordance with the ethical standards of the Institutional Review Board of Asan Medical Center and with the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

Sun Ju Chung, a contributing editor of the *Journal of Clinical Neurology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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