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Familial Creutzfeldt-Jakob Disease with V180I Mutation

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Creutzfeldt-Jakob disease (CJD) is an uncommon neurodegenerative disorder with an incidence of 1 per 1000,000 per year typically characterized by rapidly progressive dementia, ataxia, myoclonus and behavioral changes. Genetic prion diseases, which develop due to a mutations in the prion protein gene (PRNP), account for an estimated 10 to 15% of all CJD cases. We report a 75-yr-old woman with familial CJD carrying a V180I mutation which features late onset, slow progression, no periodic sharp wave complexes on electroencephalography, and extensive cortical ribboning with spared the cerebellum and the medial occipital lobes posterior to the parieto-occipital sulcus on MRI. To our knowledge, this is the first documented case of a point mutation at codon 180 in South Korea.

Key Words: Creutzfeldt-Jakob Syndrome; Prion Protein Gene; Codon 180

INTRODUCTION

Creutzfeldt-Jakob diseases (CJD) is a rare neurodegenerative disorder with rapidly progressive dementia, cerebellar ataxia, myoclonus, and behavioral changes (1). Human prion diseases have an incidence of 1 or 2 cases per million population per year. Although most CJD cases are sporadic, genetic prion disease, including familial CJD (fCJD), due to mutations in the prion protein gene (PRNP) account for only 10-15% of all CJD cases (2). More than 55 mutations associated with genetic prion disease and more than 20 with fCJD have been identified (3, 4), and showed variations in clinical manifestations depending on each genotype. We report a 75-yr-old woman with a PRNP point mutation causing fCJD due to a substitution of an isoleucine for a valine at codon 180 (V180I). Analysis of associated studies suggests this is the first reported case of fCJD with mutation V180I in South Korea.

CASE REPORT

A 75-yr-old right-handed woman presented with a 8 month history of neuropsychiatric symptoms and progressive dementia. Her family described that her symptoms started with severe depression, including suicidal ideation. She became frequently irritable and would not go outside for fear of getting hit by a car. Further, she suffered from delusions of people on the television staring at her and visual hallucinations such as a thief writing letters on the wall with black paint. Antidepressants did not help her symptoms.

Approximately 4 months before her admittance to the hospital, she developed memory problems. She asked for the same items repeatedly. She did not remember who she was speaking with on the phone, making transitions in conversation as if she had suddenly spoken with a person other than the one she was actually speaking with. Her memory gradually worsened, which led to a diagnosis of dementia at a local psychiatric clinic. Within 2 months, her cognitive decline and behavioral changes were more prominent. She had difficulty finding the bathroom at home and recognizing her family. Her behaviors were stereotypic and disinhibited, such as walking in and out of rooms repeatedly and walking around her house in the nude. She appeared to lack control over her emotions and she became more apathetic and less talkative. Additionally, her motivation diminished until she would only eat and bathe herself.

Four years prior to the onset of her symptoms, she underwent lumbar spine surgery. There was no family history of neurologi-

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cal and psychiatric illness. She had six years of education and no history of alcohol or substance abuse.

Upon admittance, her general physical examination was unremarkable. The cranial nerve examination was normal. Her muscle tone was slightly increased bilaterally in the upper extremities. Bradykinesia and clumsiness in upper limbs were noted. She had mild dysmetria with finger-to-nose test bilaterally. Her gait was slow but nearly normal based, with symmetrical arm swing. Knee jerks were present but diminished and she had a right extensor plantar response.

Laboratory studies including CBC, electrolytes, chemistry, lipid profiles, liver function, thyroid function, tumor markers, autoimmune laboratories and viral antibodies were within normal limits. Electrocardiography and chest radiography were also normal.

On neuropsychological testing, her Korean Mini-Mental State Examination (K-MMSE) score was 14/30. Overall, she showed severely impaired attention, language related functions (comprehension, naming, repetition, praxis, calculation), verbal and visual memory, visuospatial and frontal executive functions (Table 1).

Diffusion weighted and FLAIR axial brain MRIs demonstrated high signal intensities involving bilateral frontal, parietal, temporal and occipital cortices, especially on the right hemisphere. High signal intensities were also seen in the right caudate nucleus and the putamen, but both cerebellum and medial regions posterior to parieto-occipital sulcus were spared (Fig. 1).

Cerebrospinal fluid (CSF) examination showed no white blood cells, normal glucose and mildly elevated protein (74.2 mg/dL). An electroencephalography (EEG) on the fifth day of admission revealed intermittent 6-8 Hz of slow wave on right hemisphere. Her second EEG, taken on the eleventh admission date, showed 1-2 Hz of continuous slow waves predominantly on bilateral frontal area. During admission, she had several obsessive-compulsive behaviors such as washing her hands every 30 min and cleaning her genital area repeatedly. She wandered around the ward, however her cognitive and behavioral abnormalities did not change significantly throughout her admission. There were no significant differences on a follow-up brain MRI, conducted 19 days after admission. On the twenty-second day, a third EEG showed 3-5 Hz of continuous slow waves predominantly in the right hemisphere. Thirty-seven days after admission, she was discharged with no apparent clinical degeneration or improvement. After discharge, it was confirmed that the 14-3-3 protein

Table 1. Results of neuropsychological test

Tests	Results
Attention	4/4
Digit span forward/backward	
Language & related functions	
Spontaneous speech	FL
Comprehension	BL
Repetition	13/15
K-BNT	4/15 (0.01%ile)
Reading/Writing	NL/NL
Calculation	6/12
Finger naming/Body part identification	NL
Right-left orientation	NL
Ideomotor/buccofacial Praxis	1/5, 4/5
Visuospatial functions	
Interlocking pentagon/Copy of Rey-CFT	NL/10
Memory	
Seoul Verbal Learing Test-free recall (1st/2nd/3rd trial /20 min delay recall/recognition score)	0/3/3/0/14
Rey-CFT copy/immediate recall/ 20 min delayed recall/ recognition score	10/0/0/12
Frontal/executive function	
Contrasting program/ Go-no-go test	AB/AB
Fist-edge-palm	AB
Alternating hand movement	AB
Luria loop	PSV
Alternating square & triangle	NL
Word fluency: Category items (animal/supermarket)	1/0
Word fluency: Letter (ㄱ/ㅇ/ㅅ)	0/0/0
Stroop (word reading, color reading)	14/112, 20/112
K-MMSE	14/30
CDR/GDS/KDSQ/S-IADL/Barthel ADL	3/6/28/44/10
GDS, CGA-NPI	19/30, 106/144

K-BNT, Korean version of Boston Naming Test; Rey-CFT, Rey Complex Figure Test; K-MMSE, Korean version of Mini-Mental State Examination; CDR, Clinical dementia rating; GDS, Global deterioration scale; KDSQ, Korean Dementia Screening Questionnaire; S-IADL, Seoul-Instrumental activities of daily living; Barthel ADL, Barthel activities of daily living; GDS, Geriatric depression scale; CGA-NPI, Caregiver-administered-Neuro–psychiatric inventory; ND, Not done; NL, Normal; AB, Abnormal; BL, Borderline; FL, Fluent.

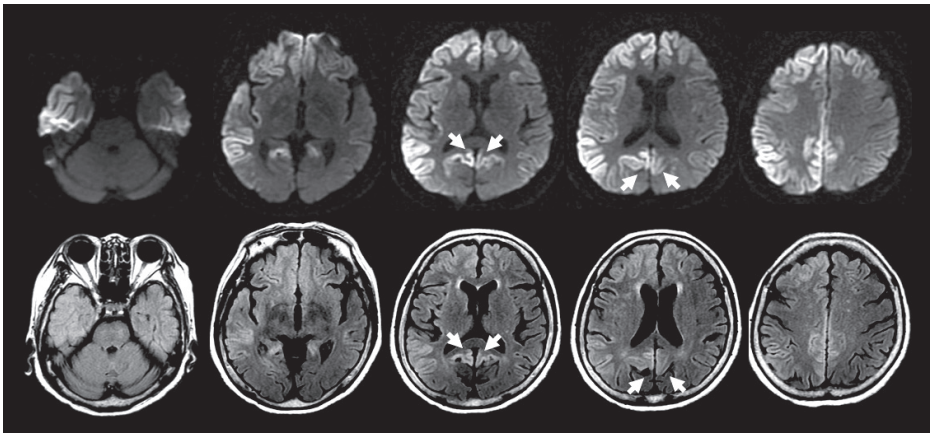

Fig. 1. Diffusion weighted (upper row) and FLAIR (lower row) axial brain MRIs show high signal intensity in diffuse cerebral cortex with dominant involvement of right hemisphere. Cerebellum and medial occipital lobes posterior to the parieto-occipital sulcus indicated by arrows are spared.

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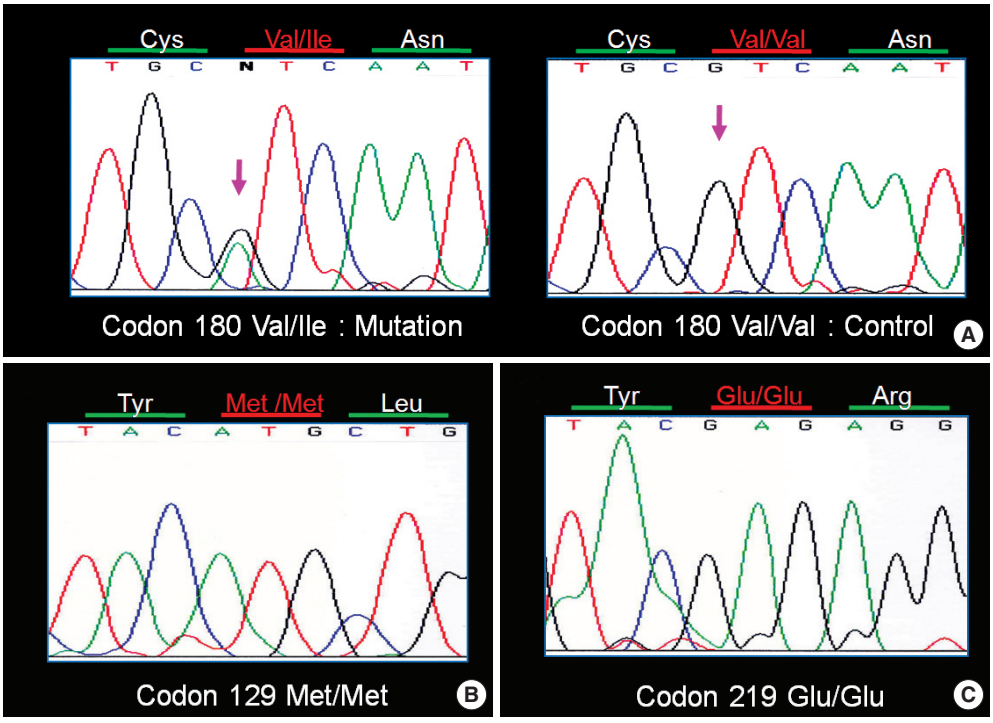

Fig. 2. (**A**) DNA sequence at codon 180 of PRNP gene from the patient (left) and a control (right). The Letter "N" indicates a point mutation causing a substitution of GTC (Val) by ATC (Ile) at codon 180. Sequence in a control is homozygous for GTC (Val) at codon 180. (**B**) Homozygosity for methionine at codon 129 and (**C**) homozygosity for glutamate at codon 219 are also identified in the sequence analysis of PRNP gene mutation of the patient.

in CSF was positive and sequencing of PRNP revealed a V180I mutation with methionin homozygosity at codon 129 and glutamate homozygosity at codon 219 (Fig. 2). Her family did not want a follow-up examination. At last contact with the family, she was still alive 18 months after onset.

DISCUSSION

Our case with rapidly progressive dementia over 8 months superimposed on mild parkinsonism and cerebellar ataxia met WHO possible sCJD criteria at the time of presentation (5). Furthermore, extensive abnormal high signal intensities involving cerebral cortices on both diffusion weighted brain MRIs and FLAIR images strongly suggested sCJD (6, 7). Although an EEG with periodic sharp and wave complexes (PSWC) is present in only about 60% of sCJD cases (8, 9) and not necessary for diagnosing probable sCJD by either WHO or UCSF criteria (10), which allow the use of 14-3-3 or MRI, respectively, our patient's non-diagnostic EEG and lack of progression during her admission led us to consider an alternative diagnosis such as a genetic prion disease.

More than 55 different PRNP mutations have been associated with genetic prion diseases, including fCJD, and the clinical phenotype varies depending on the underlying mutation (3). Worldwide, the most common mutation is E200K (glutamate to lysine), the phenotype of which often is indistinguishable from that of sCJD (4).

fCJD due to the V180I, as our patient's, is extremely rare, with all reported cases have come from Japan with one from France (11, 12), and two in the United states in a non-Asian (Geschwind et al. unpublished results) (13). To our knowledge this is the first reported case in South Korea.

Jin et al. described characteristic clinical features of the fCJD associated with V180I as follows: 1) late onset, 2) slow progression, 3) frequent higher cortical dysfunction, 4) low positive rate of 14-3-3 protein, and 5) no PWSC on EEG (14). In addition, Jin noted that the MRI in fCJD with V180I showed extensive cortical ribboning and sparing of the cerebellum and the medial occipital lobes posterior to the parieto-occipital sulcus on DWI sequences in the early stage of the disease (14).

Possibly due to the late age of onset and imcomplete penetrance, patients with genetic prion diaease often have no family history of dementia. The age of onset of our case was 74, which is slightly older than the mean age of onset for sCJD. This might be the cause of negative family history of dementia for our case.

Our patient showed relatively slow progression during 37 day admission period, even still alive 18 months after onset, cortical dysfunction on neuropsychological test, and no PSWC on repeated EEGs. Her MRIs were compatible with those of previous reports about fCJD with V180I. Therefore, her clinical features, despite positive 14-3-3 protein, generally correspond with those of the previous reported cases with fCJD with V180I (14).

There have been several studies to investigate the influence of the polymorphism of codon 129 to clinical characteristics and neuropatholgic patterns in sCJD, iatrogenic CJD and variant CJD (15). However, the contribution of codon 129 polymorphism to V180I has not been established. Furthermore, there is no report about V180I with the polymorphism at codon 219.

This case may have clinical implications. That is, fCJD with V180I should be considered in all patients with late onset rapidly progressive dementia who showed rather atypical manifestations with characteristic MRI features than those of sCJD despite a negative family history.

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