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A Japanese family with a variant of Gerstmann-Sträussler-Scheinker disease

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Abstract

Objective—A new variant of Gerstmann-Sträussler-Scheinker disease (GSS) was reported, which had a substitution of glutamate to lysine at codon 219 (E219K) in addition to a P102L mutation on the same allele of the PrP gene. However, clinical features were not detailed and pathological studies were not done. Unusual clinical, neuroradiological, and pathological findings are reported for these patients.

Methods and results—Clinical presentations of the patients in the same family were variable; progressive dementia with minimal ataxia in some patients but ataxia without dementia in others. PET studies with ^{18}F -2-fluoro-2-deoxyglucose (FDG) disclosed a relative decrease of FDG uptake in bilateral temporoparietal cortices of a patient with dementia, but in the cerebellar cortices in a patient with ataxia. At necropsy, a patient with dementia had multicentric and diffuse plaques stained with PrP antiserum, but not with haematoxylin and eosin or Congo red, in the cerebral and cerebellar cortices.

Conclusion—Neurological and neuropathological features in the patients were atypical of the classic form of GSS with P102L mutation. The absence of Congo red staining prion protein plaques is probably attributable to E219K polymorphism on the same allele of the PrP gene.

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Keywords: ataxia; dementia; Gerstmann-Sträussler-Scheinker disease; prion protein

Gerstmann-Sträussler-Scheinker disease (GSS)¹ is a genetic form of prion disease, with clinical features characterised by progressive ataxia (ataxic form) or dementia (telencephalic or dementing form). Since Hsiao *et al*² first reported the linkage of human prion protein (PrP) mutation to the development of GSS in 1989, many point mutations in the PrP gene have been found in patients with GSS, including a proline to leucine substitution at codon 102 (P102L), proline to leucine at codon 105 (P105L), alanine to valine at codon 117 (A117V), tyrosine to TAG at codon 145 (Y145Stop), phenylalanine to serine at codon 198 (F198S), and glutamate to arginine at codon 217 (Q217R).²⁻⁸

The clinicopathological features (pheno-

types) of GSS vary according to the type of PrP gene mutation. The most common PrP gene mutation is P102L, which was also found in the original GSS family.⁹ Although mental deterioration may occur later in the course, the predominant feature linked to the P102L mutation is progressive ataxia of a cerebellar type, labelled as ataxic GSS.¹⁰ Histopathologically, diffuse gliosis with neuronal loss and many plaques occurs throughout the brain,¹¹ which can be shown with haematoxylin and eosin staining. There have been no reports using PET of cerebral metabolic changes in patients with GSS.

We found a Japanese family with a new variant of GSS, in which the P102L mutation is accompanied by glutamate to lysine polymorphism at codon 219 (E219K) in the same allele. We recently reported results of the gene analysis in this family.¹² Their phenotypes were not uniform; some of the family members presented with the ataxic form, but the others were characterised by progressive dementia. In this report, we describe detailed clinical, PET, and neuropathological features of patients with this atypical form of GSS.

Report of cases

PATIENT 1 (PROPOSITUS; III-2)

The propositus was a 34 year old right handed man, who was admitted to our hospital in May 1993 because of progressive mental deterioration. He was physically healthy without any prior illness and worked as a high school teacher until three years before the admission. In 1990, he began to have progressive difficulties in speaking and writing, and his gait became unsteady. He was diagnosed as having mild spinocerebellar degeneration (SCD) by a physician in another clinic. During the next few years, his language and cognition became progressively disturbed. He responded only with "yes, yes" to any questions and often lost his way home. He lost his job at the high school in 1993. He became dependent in his daily living six months before admission. He had no episodes of myoclonus, convulsions, or hallucination.

At the time of admission, general physical examination was normal, but his cognitive function was severely impaired, particularly auditory comprehension. He rarely spoke spontaneously, and his answers to questions consisted of short, repetitive words that were usually unrelated to the questions. His writing was characterised by frequent misspelling and hypergraphia. Verbal and visual memory were

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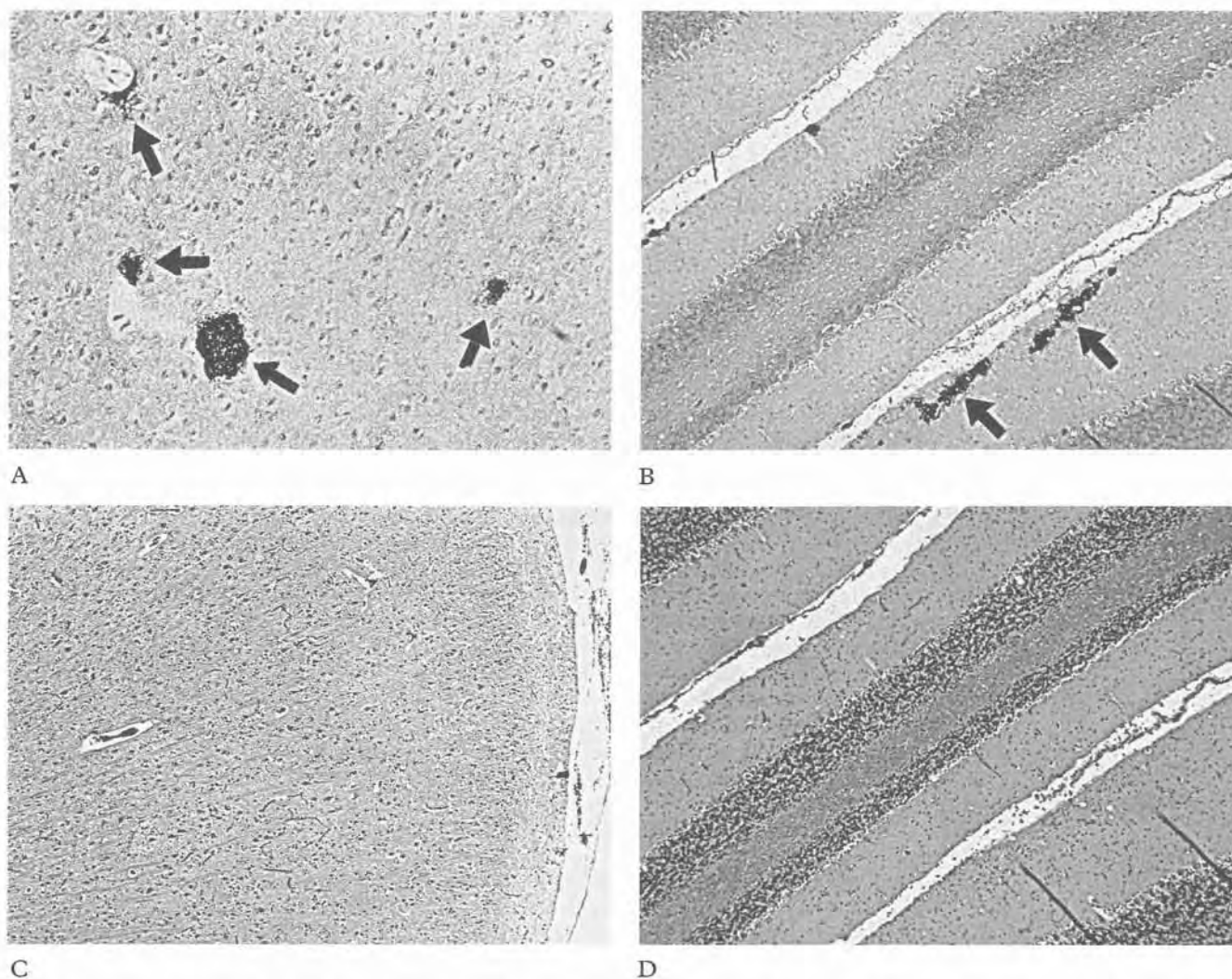


Figure 1 Histological studies of cerebral and cerebellar cortices. Multicentric plaques (arrows) stained with PrP immunohistological stain in (A) the cerebral cortex (originally magnification $\times 94$) and (B) cerebellar cortex (originally $\times 20$). (C) No neuronal loss and spongiform changes with haematoxylin and eosin stain in the cerebral cortex (originally $\times 43$) and (D) cerebellar cortex (originally $\times 20$). Purkinje cells and granular layer of cerebellum are spared.

severely impaired. He had ideomotor apraxia with perseveration. The Wechsler adult intelligence scale revised (WAIS-R) could not be performed because of severely compromised comprehension.

Neurological examination disclosed no nystagmus and no abnormal ocular movements. The muscle tone was diffusely increased and muscle strength was normal. Myoclonus was not evident. The deep tendon reflexes were normal without Babinski's sign. He had mild bilateral limb ataxia and a wide based gait.

Routine laboratory examinations were normal. Results of the CSF examination were all normal. Oligoclonal IgG band and myelin basic protein were not detected. An EEG examination showed a background of 6–7 Hz without asymmetry or periodic synchronous discharges. Brain CT and MRI showed moderate atrophy of the cerebral cortex but a normal cerebellum. A PET study with intravenous injection of ^{18}F -2-fluoro-2-deoxy-D-glucose (FDG) showed that glucose uptake was reduced in the temporoparietal cortices, particularly on the right side, but was normal and symmetric in the cerebellar cortices.

Over the next year, he progressively deteriorated, becoming completely disabled. In May

1994, he died of aspiration pneumonia. Necropsy was performed seven hours after death. The brain weighed 1290 g and was macroscopically normal. It was fixed with 10% formalin for one month. To enhance PrP immunoreactivity, hydrolytic autoclaving pretreatment was used as described previously.¹² For PrP antibodies, we used amyloid plaque core (APC) antiserum and PrP-N antiserum. Anti-APC was prepared with amyloid plaque core fraction from a patient with GSS¹⁰² and anti-PrP-N was prepared from the synthetic peptide of N-terminal 25 amino acids of PrP as described previously.¹³ The immunostaining steps were performed with the peroxidase-antiperoxidase method. The histopathological findings (fig 1) were summarised as follows: (1) no spongy changes and no neuronal loss in the cerebral and cerebellar cortices; (2) mild to moderate gliosis in the cerebral cortices; (3) diffuse plaques in the cerebral and cerebellar cortices, which were not stained with haematoxylin and eosin or Congo red, but with antihuman PrP antiserum; and (4) a normal spinal cord. Cerebral PrP plaques were not recognised with PAS staining, but cerebellar plaques were stained weakly with PAS.

PATIENT 2 (THE FATHER OF THE PATIENT 1; II-1)

The father of patient 1 was 64 years old and right handed. He complained of unsteadiness in walking for the two years before evaluation. At the time of admission for detailed neurological evaluation in July 1993, he had dysdiadochokinesis of the left arm. Tandem gait was impossible. All other neurological functions were normal, including cognitive function. Studies on CSF and an EEG were normal. Brain CT disclosed a small hypodense lesion in the left thalamus and mild brain atrophy. There were multiple ischaemic lesions in the thalamus, basal ganglia, and corona radiata, but no abnormalities in the cerebellum on MRI. An FDG-PET study showed that glucose uptake was decreased predominantly in the cerebellar cortices. Glucose uptake was mildly decreased in the bilateral parietal cortices.

FAMILY HISTORY

Among 12 family members in three generations, five had a history of progressive dementia, ataxia, or both (fig 2). Patient 3 (II-4), a 56 year old, right handed woman, had a five year history of progressive dementia. She complained of unsteady walking. Patient 4 (II-7), a 44 year old, right handed man, had had slowly progressive ataxia for 10 years. Other neurological deficits including myoclonus, spasticity, and cognitive impairments were not evident. His brain CT showed cerebellar atrophy. Patient 5 (I-2) reportedly had ataxic gait and mental deterioration before death. Detailed information about her illness could not be obtained. Another woman (II-6) was diagnosed as having schizophrenia at the age of 30 years. Two years later she died of an

unknown cause, and detailed information was not available.

GENETIC STUDY

Genomic DNA was extracted from peripheral lymphocytes of patients 1, 2, 3, and 4 and the proband's brother (III-1) without neurological deficits. The method of analysis was detailed in a previous report.¹² A P102L mutation of PrP was present in all of the patients. In addition, they all had E219K polymorphism on the same allele. The asymptomatic brother (III-1) had neither the P102L nor E219K mutations. A codon 129 showed methionine/methionine in all cases.

Discussion

The primary clinical features of our patients were either cerebellar ataxia without significant cognitive impairments, or progressive dementia with mild dystonia or ataxia. The differential diagnosis is broad, including familial Alzheimer's disease, familial Pick's disease, familial dementia-parkinsonism, familial diffuse Lewy body disease, metachromatic leukodystrophy, Huntington's chorea, multiple sclerosis, dentorubropallidolusian atrophy, and spinocerebellar degeneration. None of these disorders, however, completely fulfilled the clinical picture and family history of our patients. The detection of the PrP gene mutations established the diagnosis of GSS.

The clinicopathological pattern in our patients with GSS was different from the classic form of those with the P102L mutation alone. Our patients did not always have the same neurological picture; progressive dementia with mild ataxia in patients 1 and 3, but ataxia without significant cognitive impairments in patients 2 and 4. Another family member who may have been affected was diagnosed as having schizophrenia, although we could not confirm the accuracy of the diagnosis or the presence of PrP gene mutations. An asymptomatic brother had a normal PrP gene.

Patient 1 had histopathological findings different from those typically associated with GSS with P102L—that is, numerous plaques, visualised by haematoxylin and eosin staining. The pathological pattern in this patient with GSS and E219K polymorphism accompanied by the P102L mutation on the same allele was marked by cerebral cortices with diffuse plaques which were not stained with Congo red. However, the pathological pattern in patients with GSS and E219K polymorphism accompanied by the P102L mutation on the different allele has shown Congo red staining PrP plaques in cerebral cortices, consistent with that of patients with GSS who had a P102L mutation but not E219K polymorphism (T Kitamoto, unpublished data). These findings indicate that codon 219 polymorphism of the PrP gene may modify the pathological pattern in patients with the classic form of GSS with the codon 102 mutation.

No prior studies have evaluated cerebral metabolic changes in patients with GSS by using PET. Studies with FDG-PET in

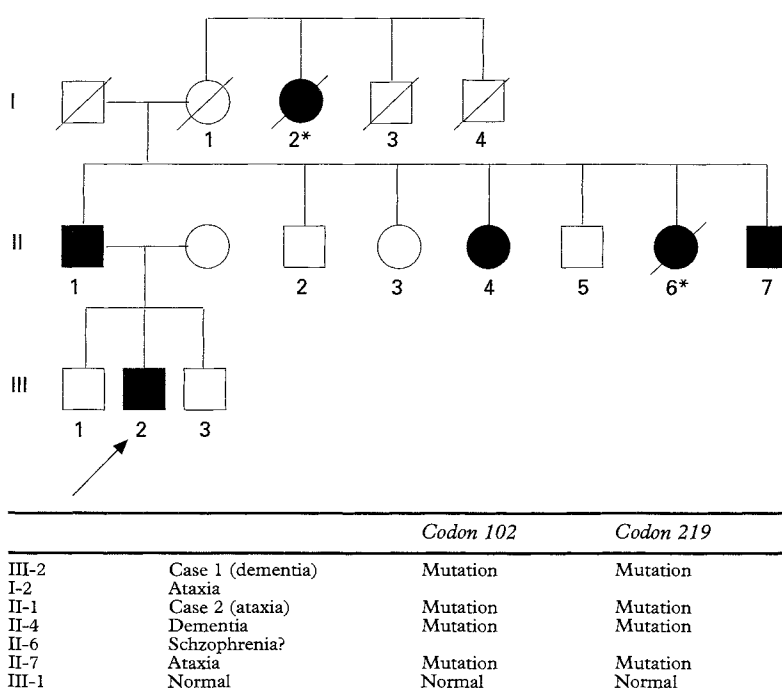


Figure 2 Pedigree of the family. Circle = female; square = male; a black symbol = affected with GSS; a slashed symbol = deceased; *genetic study not available.

patients 1 and 2 showed a variable topographic pattern of metabolic derangements, compatible with the neurological abnormalities in each patient. These results again indicate that phenotypes in GSS may be heterogenous even if patients have the same PrP mutations.

The E219K mutation of the PrP gene that was detected in our patients is found in 6% of the Japanese general population without any neurological deficits, and is considered as a normal polymorphism.¹⁴ Some studies have shown that a particular PrP gene mutation or polymorphism is accompanied by the P102L mutation in patients with classic GSS,^{2,3,15} but no study except ours¹² reported a P102L mutation accompanied by a E219K polymorphism on the same allele. As the open reading frame of the PrP gene is the same throughout the affected members, some factors other than this should be the cause of the atypical phenotype in this family. The codon 219 polymorphism gene may be an important factor influencing the neurological and pathological pattern in patients with GSS with the codon 102 mutation.

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