eNeurologicalSci 25 (2021) 100380

Contents lists available at ScienceDirect

eNeurologicalSci

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

A Japanese family with P102L Gerstmann–Sträussler–Scheinker disease with a variant Creutzfeldt-Jakob disease-like phenotype among the siblings: A case report

ARTICLE INFO

Keywords
Gerstmann
Sträussler
Scheinker disease
P102L
Creutzfeldt-Jakob disease

Dear Editor,

Gerstmann–Sträussler–Scheinker's disease (GSS) is an exceedingly rare inherited prion disease. A point mutation at codon 102 of the prion protein gene, resulting in the substitution of proline to leucine (P102L), is the most common causative mutation in Japan. P102L Gerstmann–Sträussler–Scheinker's disease (GSS102) is characterized by middle-aged onset and slow progression of cerebellar ataxia with dementia, with autosomal dominant inheritance, and high penetrance [1]. We initially suspected that the first patient presented herewith had a variant prion disease because he had rapidly developed juvenile dementia, an abnormal signal in the thalamus called the hockey stick sign on MRI, and no family history at disease onset.

We report a total of three cases from the same Japanese family of P102L GSS102 who had different clinical signs and courses.

1. Case report

1.1. Patient 1

A 32-year-old man became less attentive and unable to drive successfully in May,2002. Four months later, he began to behave abnormally, such as calling out to a ceramic dog or television and urinating on the balcony. He could not put on his pants or socks. On admission, the patient's general physical examination results were normal. Neurological symptoms were also assessed. His cognitive function was severely impaired, and his Mini-Mental State Examination (MMSE) score was 4. His cranial nerves were normal. Muscle tone was generally increased, and there was no muscular weakness. Myoclonus was found in the limbs. Bilateral tendon reflexes were increased and Babinski's sign was positive. He had neither gait disturbance nor cerebellar ataxia. Routine laboratory examination results were normal. Results of cerebrospinal fluid (CSF) examination were normal, including normal levels of total tau (t-tau) and 14–3-3 protein. EEG examination showed periodic synchronous discharge. Brain diffusion MRI showed high signals in the occipital, frontal cortex, and thalamus. A hyperintensity in the thalamic and dorsal thalamic nuclei, called the hockey stick sign, was observed (Fig. 1). This sign was considered to be a characteristic of variant Creutzfeldt-Jakob disease (vCJD) at that time [2], as it had been described in a series of vCJD reports in Europe in 2002. The patient has never traveled to Europe but has visited Taiwan and South Korea. The patient was initially considered to have vCJD because he had an early disease onset and no family history. However, his hometown was Fukuoka, a GSS102 accumulation area in Japan, and genetic testing confirmed that he had a mutation in codon 102 of the prion protein from proline to leucine, resulting in GSS102. He progressively deteriorated, became convulsive, ataxic, and had fever and tachycardia, and gradually developed akinetic mutism. In May,2003, the patient died of heart failure. No family member at that time, including his parents (father was 69 years old, mother 65 years old), had GSS102. One older brother committed suicide at the age of 33 years.

1.2. Patient 2

A 53-year-old man (patient 1's older brother, Fig. 2) presented with dysarthria and gait disturbance in January 2017. One year later, his symptoms progressed, and he was unable to walk. On admission, general physical examinations were normal. His cognitive function was mildly impaired, and his MMSE score was 21. He presented with lateral gaze-evoked nystagmus, saccadic eye movement, and ataxic dysarthria. Muscle tone was normal, and no myoclonus was noted. The upper limb reflex was normal, but the lower limb reflex disappeared. He had a gait disturbance due to cerebellar ataxia.

1.3. Patient 3

A 56-year-old woman (patient 1's older sister, Fig. 2) developed dysarthria and gait disturbance in January 2017. One year later, the symptoms progressed, and she was unable to walk. General physical examination results were normal at the time of admission. Her cognitive function was normal, and she had an MMSE score of 28. She presented with lateral gaze-evoked nystagmus, saccadic eye movement, and ataxic dysarthria. Muscle tone was normal, but the proximal muscles of the lower extremities were weak. Myoclonus was not observed in her limbs. The upper limb reflex was increased, but the lower limb reflex had

https://doi.org/10.1016/j.ensci.2021.100380
Received 31 July 2021; Received in revised form 12 October 2021; Accepted 10 November 2021
Available online 16 November 2021

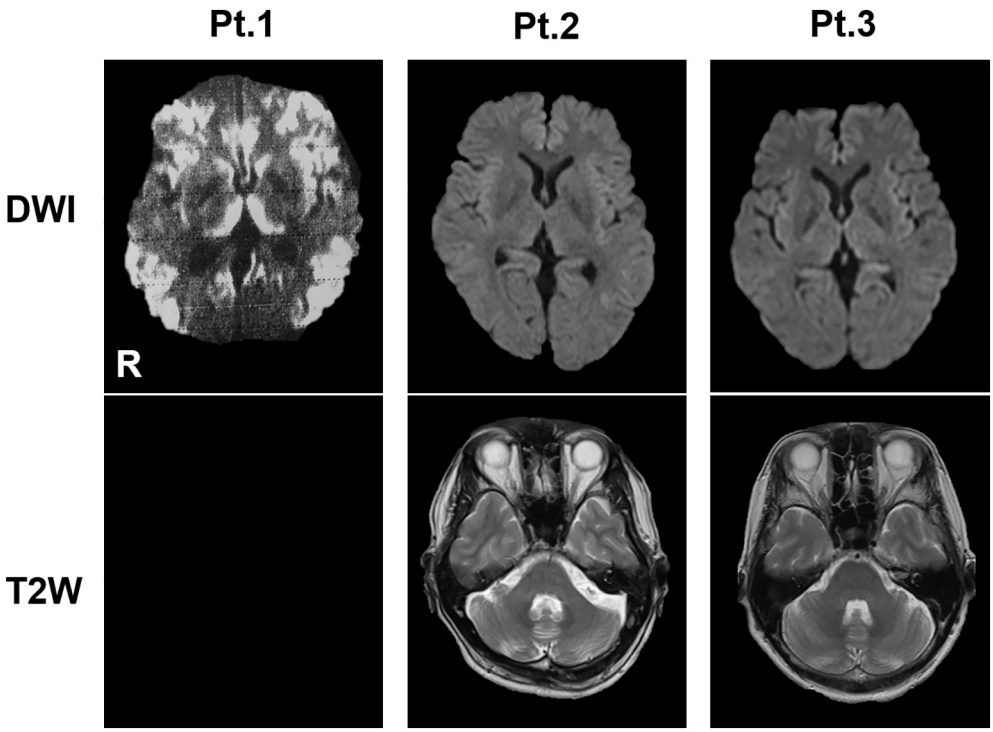

Fig. 1. Brain MRI on admission. DWI image in patient 1. DWI and T2W image in patients 2, 3. Only Pt 1 MRI revealed high signals in the occipital and frontal cortices, and in the thalamus. Pt 2 and Pt 3 MRI had no abnormal signals, but the cerebellum in Pt 2 had mild atrophy. (MRI, Magnetic resonance imaging. DWI, diffusion weighted image, T2W, T2 weighted image).

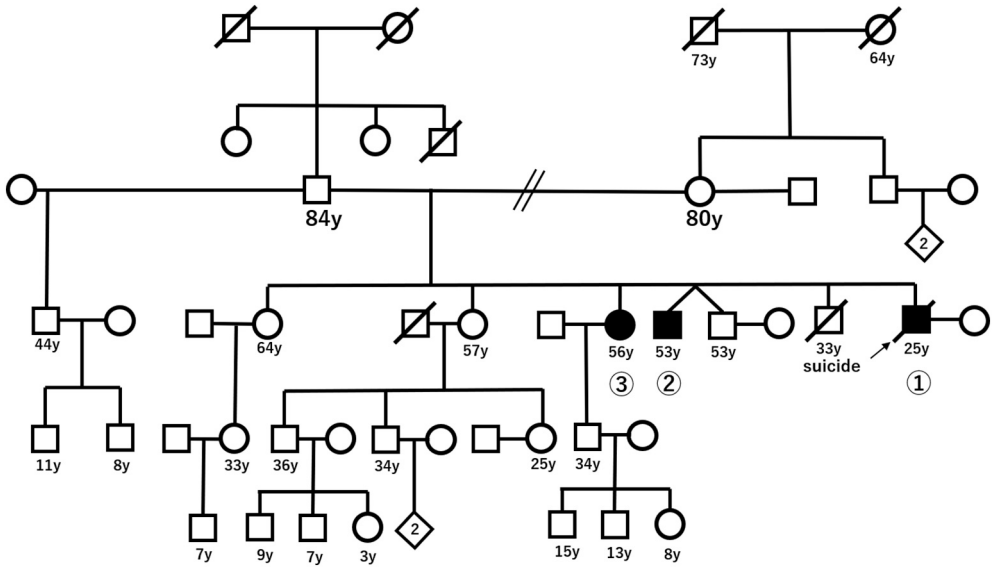

Fig. 2. Proband's pedigree. Squares indicate men, circles indicate women, rhombus indicate gender unknown, black symbols indicate affected individuals, diagonal lines across symbols indicate deceased individuals, and the arrow indicates the proband.

disappeared. She had gait disturbance due to limb ataxia, muscular weakness in both lower limbs, and pain.

Both patients 2 and 3 showed similar neurological findings. Routine laboratory examination and CSF examination were normal, including t-tau and 14–3-3 protein levels. EEG examination results were normal. Brain MRI displayed no abnormal signals, but the cerebellum showed mild atrophy in Patient 2 (Fig. 1). Genetic testing confirmed a prion protein codon 102 proline mutation to leucine, which led to the diagnosis of GSS102.

Patient 2 was unable to walk three years after onset and he began to use a wheelchair. His cognitive function declined, making it difficult to get to the hospital. Symptoms in patient 3 progressed slowly, and three years after onset, she was unable to walk and used a wheelchair. Pain in the lower extremities worsened, and analgesics were ineffective. Her cognitive function declined, and her comprehension deteriorated. Increased pain in her lower limbs made her depressed and have hallucinations, and she had delusions of jealousy and theft. She became violent with her family. She was admitted to a mental care hospital.

Her parents (father was 84 years old, mother 80 years old) have not been genetic testing and neurological examination. But according to the

patient's husband, her parents are still alive, no gait disturbance, and dementia.

2. Discussion

GSS is an exceedingly rare disorder and our understanding of its transmission is limited. Since patient 1 showed a rapid cognitive decline and the hockey stick sign on MRI with no family history, he was initially suspected to have variant CJD. However, he was diagnosed with GSS102 by genetic testing. We assumed that his parents would develop CJD in later years. Fourteen years later, his two siblings showed typical GSS102 symptoms that were different from those of patient 1. Twenty-one percent of GSS102 cases have been reported to present as rapidly progressing CJD, such as in patient 1 [3]. GSS102 is affected by codon 129 polymorphisms with specific phenotypic effects, but other additional factors may influence phenotypic variation [4,5]. Previous studies have shown that there is a large difference in the age of onset in the cases of identical twins with GSS102 [6]. Apolipoprotein E variant is also considered as another influencing factor [7]. GSS102 is inherited in an autosomal dominant fashion and is said to have a high penetrance, but only 76% of Japanese GSS102 cases have a family history [8]. In this family, both parents were over 75 years old, which is older than the oldest GSS102 case in Japan [8]. Both parents have not developed GSS102 at this time, but one daughter and two boys have developed the disease in the form of autosomal dominant inheritance. Since the family in this case is from Hakata in Japan, where GSS102 cases accumulate [9], we considered that the parents may develop the disease at an unusually old age. There also may be unknown inhibitors of the onset of GSS102 in this family. Since GSS102 presented different clinical symptoms within the same family, genetic testing is necessary for a definitive diagnosis in GSS102 cases presenting with CJD-like symptoms and no family history.

References

[1] B. Ghetti, P. Piccardo, B. Frangione, et al., Prion protein amyloidosis, Brain Pathol. 6 (1996) 127–145, https://doi.org/10.1111/j.1750-3639.1996.tb00796.x.

[2] M. Zeidler, R.J. Sellar, D.A. Collie, et al., The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease, Lancet. 355 (2000) 1412–1418, https://doi.org/10.1016/s0140-6736(00)02140-1.

[3] M. Higuma, N. Sanjo, Y. Shiga, et al., Relationships between clinicopathological features and cerebrospinal fluid biomarkers in Japanese patients with genetic prion disease, PLoS One 8 (2013) 18, https://doi.org/10.1371/journal.pone.0060003.

[4] J. Smid, A.S. Neto, M.C. Landemberger, et al., High phenotypic variability in Gerstmann-Sträussler-Scheinker disease, Arq. Neuropsiquiatr. 75 (2017) 331–338, https://doi.org/10.1590/0004-282x20170049.

[5] M. Bianca, S. Bianca, I. Vecchio, et al., Gerstmann-Sträussler-Scheinker disease with P102L-V129 mutation: a case with psychiatric manifestations at onset, Ann. Genet. 46 (2003) 467–469, https://doi.org/10.1016/s0003-3995(03)00017-0.

[6] H. Honda, K. Sasaki, H. Takashima, et al., Different complicated brain pathologies in monozygotic twins with Gerstmann-Sträussler-Scheinker disease, J. Neuropathol. Exp. Neurol. 76 (2017) 854–863, https://doi.org/10.1093/jnen/nlx068.

[7] T.E.F. Webb, M. Poulter, J. Beck, et al., Phenotypic heterogeneity and genetic modification of P102l inherited prion disease in an international series, Brain. 131 (2008) 2632–2646, https://doi.org/10.1093/brain/awn202.

[8] I. Nazki, T. Hamaguchi, N. Sanjo, et al., Prospective 10-year surveillance of human prion diseases in Japan, Brain. 133 (2010) 3043–3057, https://doi.org/10.1093/brain/awq216.

[9] H. Murai, Y. Nakamura, T. Kitamoto, et al., Clinical and epidemiological survey of gerstmann-sträussler-scheinker disease with codon 102 mutation in Japan, J. Neurol. Sci. 357 (Suppl. 1) (2015) E114, https://doi.org/10.1016/j.jns.2015.08.364.

Kazumichi Ota[a,*], Yoshihiko Nakazato[a], Ryu Yokoyama[a], Hitoshi Kawasaki[a], Naotoshi Tamura[a], Akira Ohtake[b,c], Megumi Saito-Tsuruoka[b,c], Toshimasa Yamamoto[a]

[a] *Department of Neurology, Faculty of Medicine, Saitama Medical University, Saitama 350-0495, Japan*

[b] *Department of Clinical Genomics, Faculty of Medicine, Saitama Medical University, Saitama 350-0495, Japan*

[c] *Center for Intractable Diseases, Saitama Medical University Hospital, Saitama 350-0495, Japan*

[*] Corresponding author at: Department of Neurology, Saitama Medical School, 38 Morohongo Moroyama, Iruma-gun, Saitama 350-0495, Japan.

E-mail address: kota24@saitama-med.ac.jp (K. Ota).