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Correlation between clinical and radiologic features of patients with Gerstmann-Sträussler-Scheinker syndrome (Pro102Leu)

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A B S T R A C T

Background and purpose: Gerstmann-Sträussler-Scheinker syndrome is a rare hereditary neurodegenerative disorder with clinical heterogeneity. This study is aim to demonstrate the clinical spectrum and radiologic characteristics of patients caused by Pro102Leu mutation in PRNP.

Materials and methods: We retrospect clinical manifestations of five patients from four Japanese families, and comprehensively analyzed their brain MRI, SPECT (N-isopropyl-p-[123I] iodoamphetamine), and PET (18F-2-fluoro-2-deoxy-D-glucose) images.

Results: All patients developed ataxia of lower limbs and trunk, gait disturbance, dysesthesia in legs, and lower limb hyporeflexia. In the early clinical stage before dementia began, no noticeable abnormalities could be observed from brain MRI, but SPECT and PET revealed mosaic-like pattern of blood flow and glucose metabolism of the brain. Predominant abnormalities were found in the occipital and frontal lobes on SPECT and PET analysis, respectively. In SPECT analysis, blood flow of the anterior cerebellar lobes was lower than that of the posterior cerebellar lobes.

Conclusions: Clinical symptoms resulting from failure of dorsal horn of spinal cord and spinocerebellar tracts were observed in all cases. Radiologic findings revealed individual differences of involved region in their brain, which could produce clinical diversity. We identified a downtrend of blood flow in the anterior cerebellar lobes, a projection field of the spinocerebellar tracts, which is an important feature of Gerstmann-Sträussler-Scheinker syndrome.

1. Introduction

Gerstmann-Sträussler-Scheinker syndrome (GSS), first reported in 1936, as a common inherited prion disease, is clinically and genetically heterogeneous [1,2]. According to a recent Japanese report, GSS102 accounts for 16.3% (93/572) of patients with inherited prion disease [3]. GSS102 is characterized clinically by prominent cerebellar signs accompanied by a slowly progressive dementia and pathologic findings of multifocal prion protein (PrP)–positive plaques [4,5]. Spinocerebellar degeneration is known as one of the disease features and has been recognized as associated with dementia. However, dementia frequently appears later during the course of illness, which makes it difficult for neurologists to diagnose in the early stage.

Previously, we demonstrated that GSS102 mainly shows ataxia of the lower limbs and trunk, dysarthria, lower limb paresthesia, and decreased deep tendon reflexes in the early stage, followed by dementia in the advanced stage. On radiologic analysis, we have also described that SPECT imaging shows abnormalities earlier than MRI, manifesting predominantly as decreased blood flow in the occipital lobes but almost normal flow in the cerebellum [6]. In this study, we further examined the higher brain function of patients with GSS102, and evaluated the image findings of MRI, SPECT, and PET.

Abbreviations: GSS, Gerstmann-Sträussler-Scheinker syndrome; GSS102, GSS patients caused by Pro102Leu mutation in *PRNP*

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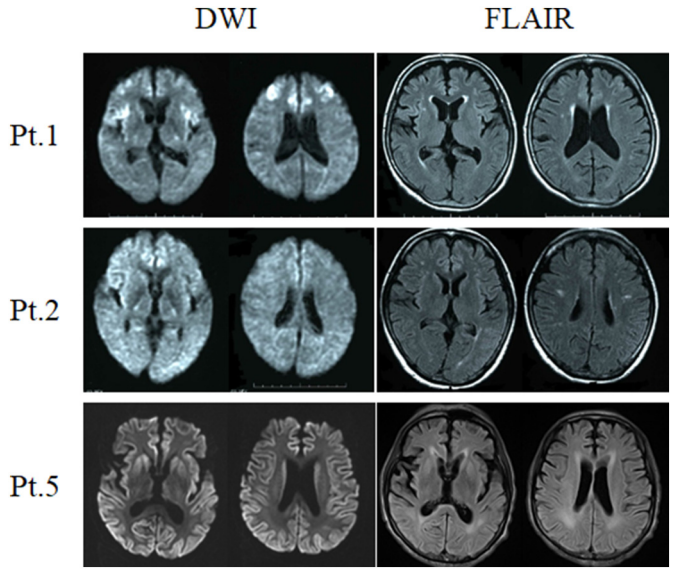

Fig. 1. Brain MRI. DWI and FLAIR image in Patients 1,2,5. They presented abnormal intensity of the cortex and no brain atrophy.

2. Materials and methods

We retrospectively studied five GSS patients from four families with genetically confirmed heterozygous Pro102Leu mutation in the *PRNP* gene. Additionally, 4 patients harbored homozygous methionine at codon 129 in *PRNP*, while heterozygous substitution from methionine to valine (Met129Val) was detected in patient 3. Besides, all patients shared a homozygous glutamate at codon 219. All patients were born in Kagoshima Prefecture, locating in the southern part of Japan. The protocol of the following study was reviewed and approved by the Institutional Review Board of Kagoshima University. All patients and family members provided written, informed consents to participate in this study.

2.1. Cognitive and electrophysiological studies

Neurologic examination was performed mainly in our hospital. To evaluate cognitive abnormalities, three methods were applied, consisting of the Mini Mental State Examination (MMSE), the Wechsler Adult Intelligence Scale-Revised (WAIS-R) test, and the Trail Making Test (TMT). Three of the five patients underwent electrophysiologic studies, including nerve conduction study (NCS), needle electromyography (needle EMG), short latency somatosensory evoked potential (SSEP), and electroencephalogram (EEG).

Table 1
Clinical summary of 5 GSS patients with Pro102Leu mutation.

Patient No.	1	2	3	4	5
Year/sex	73/F	62/F	61/F	60/M	59/M
Duration from onset	1y3m	1y11m	2y0m	0y9m	> 2y
Onset symptom	Dysesthesia in lower limbs	Ataxic gait	Ataxic gait	Dysarthria	Character change
Clinical features at initial examination					
MMSE	29	25	24	27	Unable
Dysarthria	−	+	+	+	+
Ataxia in upper limbs	−	+/−	+	+	+
Ataxia in lower limbs	+	+	+	+	+
Weakness of lower limbs	+	+	+	+	+
Pyramidal sign	+	+	+	−	+
Extra-Pyramidal sign	−	−	−	−	−
Areflexia in lower limbs	+	+	+	+	+
Dysesthesia in lower limbs	+	+	+	+	Unknown
Vibration in lower limbs	normal	normal	normal	normal	Unable
WAIS-R (VIQ/PIQ/IQ)	83/84/82	**76/64/69**	91/100/95	84/82/81	N.E.
TMT A	**92**	**80**	27	55	N.E.
TMT B	140	**incomplete**	40	119	N.E.
Codon129	Met/Met	Met/Met	Met/Val	Met/Met	Met/Met
Codon219	Glu/Glu	Glu/Glu	Glu/Glu	Glu/Glu	Glu/Glu
Brain MRI abnormality	+	+	−	−	+
SPECT abnormality	+	+	+	+	+
PET abnormality	+	+	+	+	+
Electrophysiological study					
EEG PSD	–	–	–	–	N.E.
NCS	normal	normal	normal	normal	normal
Needle EMG	normal	normal	normal	N.E.	N.E.
SSEP latency in lower limbs	normal	normal	normal	N.E.	N.E.

MMSE: Mini Mental State Examination.
WAIS-R: Wechsler Adult Intelligence Scale-Revised.
VIQ: Verbal Intelligence Quotient.
PIQ: Performance Intelligence Quotient.
IQ: Intelligence Quotient.
N.E.: Not Exam.
TMT: Trail Making Test.
EEG: electroencephalogram.
PSD: periodic synchronous discharge.
NCS: nerve conduction study.
EMG: electromyography.
SSEP: short latency somatosensory evoked potential.
Bold value means abnormal value.

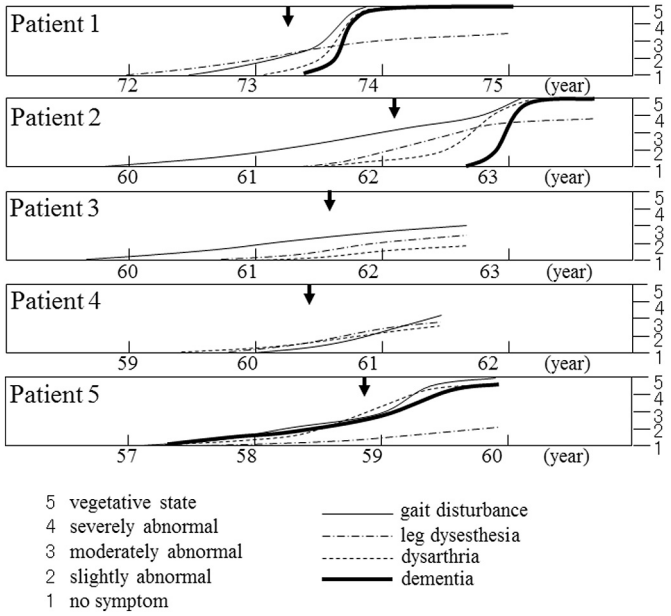

Fig. 2. Clinical course of 5 patients with GSS102. For gait disturbance, slightly abnormal means with difficulty in ambulation but still able to walk without support, moderately abnormal means able to walk with support, and severely abnormal means unable to walk even with support. For dementia, slightly abnormal means having some problems with intellectual function but able to perform activities of daily living without help, moderately abnormal means able to perform activities of daily living but with help, and severely abnormal means unable to perform most activities of daily living. For dysarthria, slightly abnormal means difficulty with smooth speech, moderately abnormal means definite speech problem but able to talk to some degree, and severely abnormal means unable to talk. For leg dysesthesia, slightly abnormal means dysesthesia with slight pain, moderately abnormal means dysesthesia with moderate pain, and severely abnormal means dysesthesia with severe pain. Initial date of examination is indicated by an *arrow*.

2.2. Radiological studies

Brain MRI (1.5 T or 3.0 T), N-isopropyl-p-[123I] iodoamphetamine SPECT, and 18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) PET were performed in all patients during their initial examination. MRI, SPECT, and PET were performed within approximately one month in all patients. SPECT and PET were analyzed using the 3-dimensional stereotactic surface projection (3D-SSP) method [7]. Normalization was performed by whole-brain voxel averaging. SPECT data from normal control subjects were obtained from sex-matched individuals of 60 to 69 years (13 cases) or of 70 to 79 (10 cases) years, applying standard measurements at National Center of Neurology and Psychiatry. Fluorodeoxyglucose (FDG)-PET scans in normal control subjects were based on standard measurements at Fujimoto General Hospital, and were obtained from 10 males and females at each age level. The stereotactic images were generated from 3D-SSP data using 3-dimensional brain scanning focus method software (Nihon-Mediphysics Co., Hyogo, Japan). We also analyzed quantities of blood flow and brain metabolism in each brain area using the stereotactic extraction estimation (SEE) method to detect details of small segments of the brain [8].

3. Results

3.1. Clinical and electrophysiological features

Five patients ranged from 59 to 73 years old, and their onset age were younger than 60 years, except for patient 1, who developed symptoms older than 70 years old. The period from onset to first examination ranged from 9 months to longer than 2 years. Initial symptoms varied significantly, encompassing lower limbs dysesthesia (1 case), gait disturbance (2 cases), dysarthria (1 case), and character change (1 case).

Patients 1 and 2 are sisters from the same pedigree, but both presented with distinct clinical manifestations from typical GSS. Their first physical examination revealed muscle weakness, ataxia, dysesthesia in lower limbs, areflexia of lower limbs, and positive Babinski reflex. They spoke normally without contradiction and had no abnormalities in their daily intellectual activities. However, 3 and 6 months later, respectively, cognitive dysfunctions appeared and progressed quickly leading to bedridden within the following 3 months. Both patients presented with high intensity of the cortex in the anterior part of frontal lobes, and the internal part of temporal lobes on FLAIR and DWI images (Fig. 1). Their disease progression and appearance of MRI images were comparable to sporadic Creutzfeldt-Jakob disease (CJD). Patient 5 presented with high intensity of the cortex too. Other patients presented almost normal findings and no atrophy of brain.

In the three patients who underwent electrophysiological studies, no notable abnormalities were found in NCS, needle EMG, or SSEP. In the EEG study, no periodic synchronous discharge, which was described in typical prion disease, was observed. The clinical and genetic features, higher brain functions, radiological and electrophysiological findings are summarized in Table 1.

3.2. Cognitive studies

Cognitive tests for patient 5 were not available because of his progressing dementia. We could not recognize any cognitive impairment through MMSE during initial neurologic examination in the other four patients. Decreased borderline intelligence was observed in patient 2 using the WAIS-R after she developed cognitive dysfunction. Further WAIS-R analysis suggested decreased long-termed memory by visuals in patient 1, and dysfunction of visual information processing in patient 2. With TMT, patient 1 showed a borderline decrease, while patient 2 had an obvious decrease. No remarkable abnormalities were identified in patients 3 and 4 by means of any cognitive tests. Their clinical courses are described in Fig. 2.

3.3. SPECT and FDG-PET analysis

SPECT analysis using 3D-SSP suggested decreased cerebral blood flow of the cortex in a mosaic-like pattern. All 5 patients showed a blood flow decrease in the anterior cingulate gyri, parahippocampal gyri, and thalamus. Patient 1 had a significant decrease in the frontal lobes, whereas a predominant decrease of blood flow in the occipital lobes was recognized in patients 1 and 2. Patients 3 and 4 showed more remarkable decrease of blood flow in cerebellum than others, particularly in the anterior lobes. Besides, patient 5 showed a more obvious blood flow decrease in the frontal lobes (Fig. 3).

Using FDG-PET, decreased glucose uptake of the cerebral cortex was observed in a mosaic pattern resembling SPECT findings. In three patients (patients 1, 2, and particularly 5) FDG-PET revealed decreased glucose uptake in the frontal lobes. Besides, a remarkable decrease in glucose uptake was observed mainly in the precuneus of the posterior inside area in the parietal lobes. However, decreased glucose uptake in the cerebellum was only found in patient 3 and 4 (Fig. 4).

We also evaluated SPECT and PET findings with the SEE method, and presented the proportion of voxel count which Z score was greater than 1.0 in each lobes of the cerebral cortex. SPECT analysis suggested predominantly decreased blood flow, most commonly in the occipital lobes, followed by the temporal and frontal lobes. PET analysis suggested predominantly decreased glucose uptake in the frontal lobes. Patient 5 with dementia showed decreased blood flow predominantly in the frontal lobes and grossly low glucose uptake (Fig. 5). Patients 1 and 2, whose disease was progressing, exhibited more evident glucose uptake decrease in the frontal lobes than other patients. Particularly,

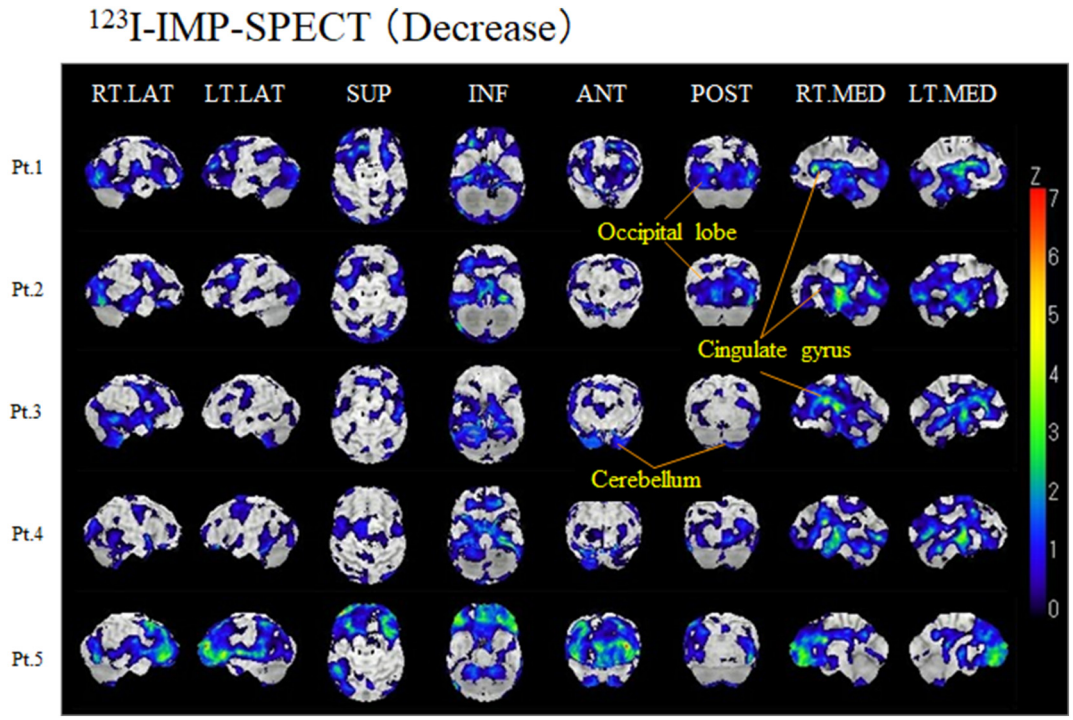

Fig. 3. IMP-SPECT (Decrease). SPECT images in 5 patients with GSS102 analyzed by the 3D-SSP method. Decreased regional CBF adjusted to global mean CBF in the GSS patients compared to controls. Image shows six views taken: right lateral (RT. LAT), left lateral (LT. LAT), anterior (ANT), posterior (POST), right medial (RT. MED), and left medial (LT. MED). Colors indicate degree of CBF perfusion: red, severely decreased; yellow, moderately decreased; green and blue, mildly decreased. Areas with low blood flow are indicated. Areas with Z scores > 2 had a statistically significant decrease in blood flow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

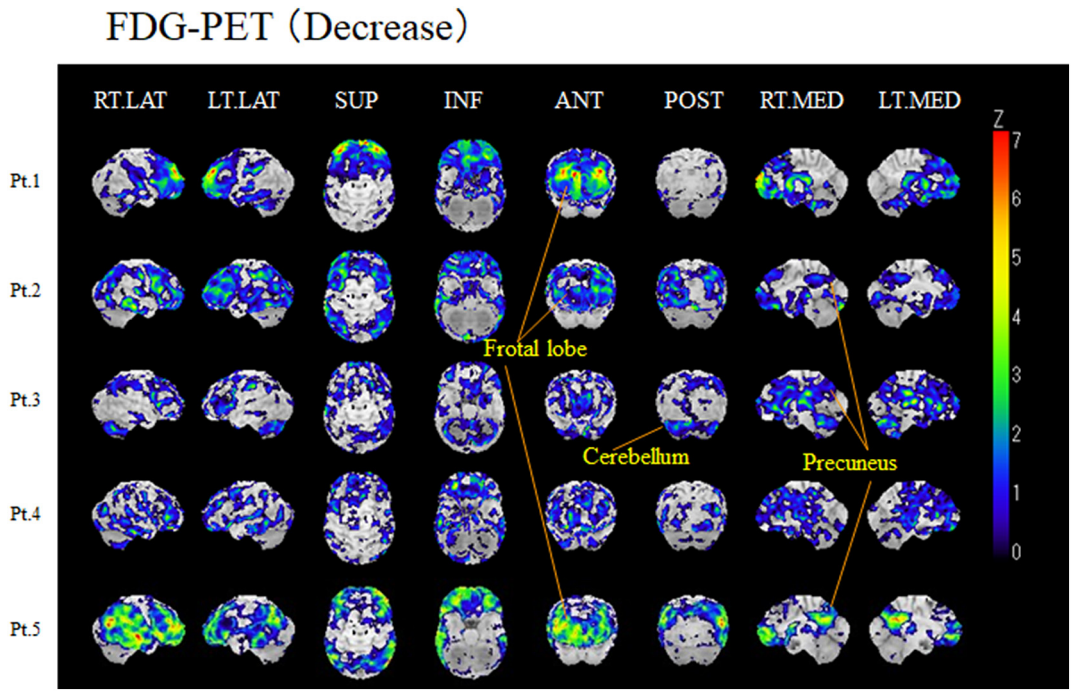

Fig. 4. FDG-PET (Decrease). PET images in 5 patients GSS102 analyzed by the 3D-SSP method. Decreased regional glucose uptake adjusted to global mean of that in the GSS patients compared to controls. Image shows six views taken as same as SPECT. Colors indicate degree of glucose uptake.
Areas with low glucose uptake are indicated. Areas with Z scores > 2 had a statistically significant decrease in glucose uptake.

patient 2, who developed dementia earlier than other patients, exhibited a broader area of low glucose uptake.

By contrast, we could not recognize any significant reduction of blood flow in the cerebellum with SPECT analysis. However, further analysis with SEE showed a downward trend in the anterior lobes in 4 cases, suggesting a prominent difference from the cerebellar posterior lobes (Fig. 6). Furthermore, using PET analysis, we could only recognize significant hypometabolism in the cerebellum of Patient 3,

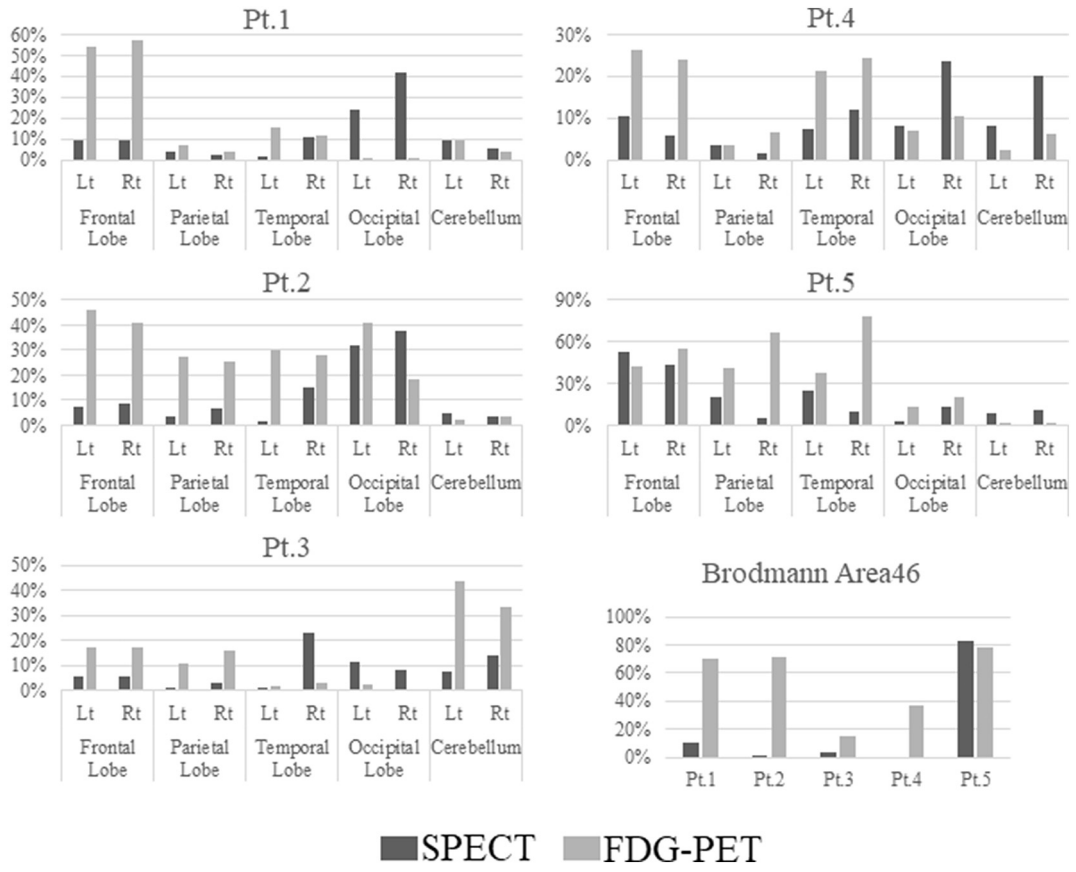

Fig. 5. SEE analysis of SPECT and PET. Extent ratio; proportion of voxel count with Z score > 1.0 in cerebral cortex of each lobes and Brodmann area 46 in SPECT and FDG-PET, respectively.

which was further validated with SEE (Fig. 6).

4. Discussion

We performed comprehensive radiologic analysis of five Japanese patients with GSS102. In patients with early stage GSS102, we found extensive hypometabolism in the cerebral cortex on FDG-PET analysis. We also identified a variety of involved regions in their cerebrum, which may lead to corresponding clinical diversity. Using SPECT analysis, we found new evidence for a downtrend of blood flow in the anterior cerebellar lobes, a projection field of the spinocerebellar tracts, which is an important feature of GSS.

Of the five patients, although their initial symptoms varied, neurologic findings revealed ataxia in lower limbs and trunk, dysesthesia in legs, and hyporeflexia/areflexia in lower limbs. The appearance order of clinical manifestations was different from each other in the present patients, whereas rapid progression followed by dementia was observed commonly. These clinical features were comparable to those of our previous report [6]. Patients 1 and 2, who exhibited abnormalities in brain MRI, suffered dementia and became bedridden in a short period after initial examination. For both patients, the WAIS-R study indicated deterioration of processing ability for information related to vision and ability of long-term memory. Meanwhile, TMT also indicated mild abnormal findings, but MMSE was normal. These findings could account for abnormalities in their occipital lobes, where hypoperfusion and hypometabolism were identified in SPECT and PET, respectively.

In general, neuropathological examination suggest widespread spongiform change with numerous eosinophilic amyloid plaques (Kuru plaques) in the cerebral and cerebellar cortices. Numerous PrP immunopositive plaques and diffuse synaptic-type PrP deposition were extensively observed, particularly in the cerebral and cerebellar cortices [9]. A mosaic pattern decrease in cerebral blood flow and glucose uptake was identified through SPECT and PET image analysis, respectively. SPECT and PET were able to detect abnormalities earlier than brain MRI. FLAIR and DWI image (MRI) showed widespread cerebral cortical hyperintensity. We only found obvious blood flow reduction in the frontal lobes of patient 5, who had dementia. Using PET analysis, we observed decreased glucose uptake at the anterior parts of the frontal and parietal lobes (superior parietal lobes, precuneus) in the cases with rapid progression of dementia (patients 1 and 2), or with recognized dementia (patient 5), which is correlated with the results of TMT. Discrepancies of findings between SPECT and PET might be associated with the difference in their sensitivity of disease progression. We could not recognize any atrophy and decreased blood flow in the thalamus in our patients, which was recent described in a GSS102 patient with long disease duration in Japan [10]. Further analysis of patients 1, 2, and 5, using PET and SEE, revealed that Brodmann area 46 was occupied with a number of Z score > 1.0 voxels. These findings were clearly different from the other 2 patients (Fig. 5). Brodmann area 46 is believed to be the main site of working memory and has a role in sustaining attention [11]. SPECT image did not show any correlation with TMT, but patients with progressing dementia had a definite decrease in Brodmann area 46 as well. Taken together, the sensitivity of SPECT and PET might be comparable once a GSS patient had dementia, but PET was more correlated with the clinical findings than SPECT, while image variety would be associated with the initial symptoms and clinical courses.

Patient 3 is the only patient who harbors a heterozygous Met129Val variant in PRNP. This is a low frequency variant, presenting in Human Genetic Variation Database (97/2304 in Japan, http://www.hgvd.genome.med.kyoto-u.ac.jp/) and Exome Aggregation Consortium (208/8638 in East Asia, http://exac.broadinstitute.org/). Our

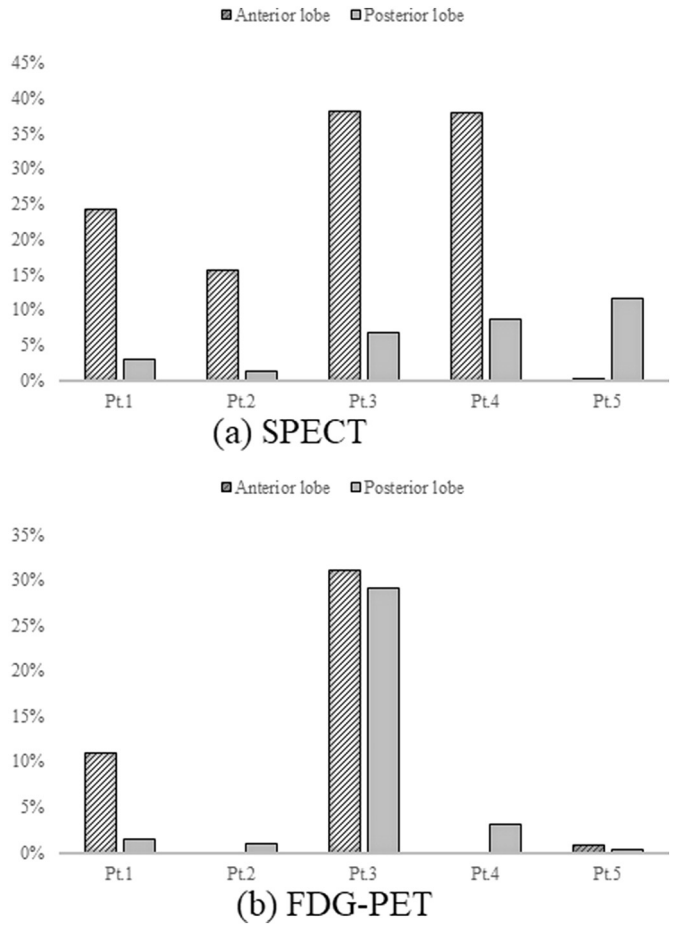

Fig. 6. Extent ratio (Z score > 1) in cerebellar, anterior lobes versus posterior lobes in SPECT and PET.

polymerase chain reaction-restriction fragment length polymorphism analysis has indicated that 102Leu was coupled with 129Met in the same allele (data not shown). It has been reported that amyloid PrP deposits are more numerous in P102L-Met129 than in P102L-Val129 [12], and genotype at 129 residue might also result in clinical and radiological diversities [9,13]. Although patient 3 was a typical GSS102 in clinic, a distinct trend of blood flow and metabolism was recognized in the cerebellum using both SPECT and PET (Fig. 4, Fig. 6 b). We thus speculate that in a GSS102 patient, this Met129Val variant may increase the variant burden of PRNP, and result in additional subclinical or clinical central nervous system dysfunctions.

The dorsal spinocerebellar tract begins from the second order neuron, referred to as Clarke's nucleus in the base of the dorsal horn of the spinal cord, then projects to the anterior lobes of the cerebellum through the dorsal part of ipsilateral lateral funiculus. Degeneration of the dorsal spinocerebellar tract has been reported in GSS [14], while its projection area, the cerebellum anterior lobes, would exhibit a more significant blood flow decrease than the posterior lobes. Patient 4 presented with lower perfusion of SPECT in the cerebellar anterior lobes than other patients, which might explain the dysarthria in addition to his lower limb ataxia. Additionally, it has been described that distribution of PrP deposits in the dorsal spinal horn was similar to that of presynaptic markers, and a decrease in Clarke's nucleus also was observed [14]. Further, the PrP accumulation, moving into synapses, also was reported in Creutzfeld-Jakob disease of the brain [15]. We identified lower limb predominant ataxia in these patients, which might result from failure of transmission to the spinocerebellar tracts due to PrP deposits in the dorsal spinal horn, degeneration of spinocerebellar tracts, or cerebellar anterior lobes dysfunction.

Generally, FDG-PET is more sensitive compared to CBF-SPECT regarding synaptic activity of brain. Using SEE analyses, SPECT showed more significant hypoperfusion in the anterior cerebellar lobes in four patients, but FDG-PET showed hypometabolism in only one patient with Met129Val variant (Fig. 6). The reason of this discrepancy is not clear and require further study. On the other hand, Patient 1 showed more significant hypometabolism of anterior cerebellar lobes (Fig. 6 b), and a similar tendency was observed on SPECT. This downtrend of blood flow in the anterior cerebellar lobes may be an important feature of GSS.

Peripheral neuropathy was sometimes suspected originally in the clinic because these patients presented with hyporeflexia or areflexia in the lower limbs, other than hyperreflexia, despite a pyramidal tract sign observed concurrently. No notable abnormality was observed in NCS and SSEP of patients 1 and 2, which indicated that their muscle weakness was associated with brain involvement. It has been proposed that the presence of lower limb areflexia without central and peripheral conduction abnormalities is highly suggestive or possibly pathognomonic of GSS102 [16]. Deep tendon reflexes generally are a simple monosynaptic stimulation of alpha motor neurons through the Ia fibers, which is evoked by the muscle spindle stimulated by extension of the muscle. Deposits of PrP were found predominantly in the dorsal horn, particularly in the lumbar spinal cord and substantia gelatinosa containing various interneurons [14]. Interneuron dysfunction might impair regulation of reflex control, leading to areflexia of the lower limbs. In addition, the PrP deposits in the posterior horn could affect the synapse of thermal nociception transmission, thus leading to dysesthesia and numbness in the lower limbs. The absence of synapse for vibration perception in the posterior horn and cerebellar PrP aggregates, may explain why vibration perception and SSEP of the lower limbs was normal.

Using a series of radiological analyses, this study identified a downtrend of blood flow in the anterior cerebellar lobes and a projection field of the spinocerebellar tracts, which turned out to be important features of Gerstmann-Sträussler-Scheinker syndrome. We also obtained evidences of interaction between the clinical diversity of GSS102 and their dysfunctional regions of brain. The SPECT findings of Patients 3 and 4, presented with hypoperfusion of anterior cerebellar lobes and mosaic pattern in cerebral cortex, would be useful in clinical practice for GSS102 patients. Whereas cerebellar ataxia is present, it is important for the diagnosis of GSS102 that the posterior cerebellar lobe has normal findings.

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