Neurological Sciences (2019) 40:429–431
https://doi.org/10.1007/s10072-018-3603-z

LETTER TO THE EDITOR

Decreasing ^{123}I-ioflupane SPECT accumulation and ^{123}I-MIBG myocardial scintigraphy uptake in a patient with a novel homozygous mutation in the *ZFYVE26* gene

Kishin Koh[1] · Mai Tsuchiya[1] · Takamura Nagasaka[1] · Kazumasa Shindo[1] · Yoshihisa Takiyama[1]

Received: 17 April 2018 / Accepted: 10 October 2018 / Published online: 16 October 2018

Dear editor,

Hereditary spastic paraplegia (HSP) is a group of neurodegenerative disorders characterized by weakness and spasticity of the lower extremities. HSP is divided into a pure form and a complicated one including mental retardation, ophthalmologic abnormalities, ichthyosis, cerebellar ataxia, thin corpus callosum, and extrapyramidal signs. In general, autosomal recessive HSP (ARHSP) tends to be the complicated form. In ARHSP, SPG11 is the most common type, SPG15 being the second. SPG11 and SPG15 overlap in clinical and brain MRI findings including spastic paraplegia associated with cognitive impairment, ophthalmologic abnormalities, thin corpus callosum, and leukodystrophy.

^{123}I-ioflupane single-photon emission computed tomography (^{123}I-ioflupane SPECT) and ^{123}I-metaiodobenzylguanidine myocardial scintigraphy (^{123}I-MIBG myocardial scintigraphy) are usually used for the diagnosis of Parkinson disease (PD) and Parkinson syndrome. Decreasing ^{123}I-MIBG myocardial scintigraphy uptake indicates postganglionic sympathetic nerve denervation in a lot of diseases including Parkinson disease. To date, the ^{123}I-ioflupane SPECT findings in SCA15 patients have rarely been reported, and no results of ^{123}I-MIBG scintigraphy have been reported [1, 2]. We describe here a Japanese SCA15 patient with a novel homozygous *ZFYVE26* mutation with decreasing ^{123}I-ioflupane SPECT accumulation and ^{123}I-MIBG myocardial scintigraphy uptake.

Case report

We present a 36-year-old woman who visited our hospital because of gait disturbance and cognitive impairment. She experienced difficulty in running in kindergarten, spastic gait in junior high school, and instability on standing at age 27. Her parents were not related, but they came from the same town. She exhibited severe cognitive impairment, i.e., the Mini Mental State Examination score was 12/30 and Raven's colored progressive matrices were 2/36. She also showed slurred speech, rigidity and ataxia in her upper limbs, and severe leg spasticity. She could not stand up by herself. She did not show autonomic disturbance like constipation, urinary incontinence, dysuria, or sweat dysfunction. Her blood pressure was within normal range, and she did not exhibit orthostatic hypotension clinically. The following examinations were all normal: complete blood cell count, routine chemistry, urinalysis, and electrocardiography.

Brain MRI revealed thin corpus callosum, bilateral atrophy of the frontal and temporal lobes, and leukodystrophy (Fig. 1a). ^{123}I-ioflupane SPECT showed the specific binding ratio (SBR) was −0.04 on the right and −0.221 on the left (normal, > 4.5), respectively (Fig. 1b). ^{123}I-MIBG myocardial scintigraphy revealed the heart to mediastinum (H/M) ratio was 1.48 (normal, > 2.2) in the early and 1.34 (normal, > 2.2) in the delayed phase, and the washout ratio was 44.2% (normal, < 22) (Fig. 1c).

We diagnosed her as having complicated HSP due to the neurological signs and neuroimaging findings. She did not show any changes of the neurological symptoms or radiological findings even though we prescribed levodopa (per os, 200 mg/day).

Then, we performed whole-exome analysis to detect the causative gene mutation for HSP. We found a novel

✉ Yoshihisa Takiyama
ytakiyama@yamanashi.ac.jp

[1] Department of Neurology, Graduate School of Medical Science, University of Yamanashi, Yamanashi, Japan

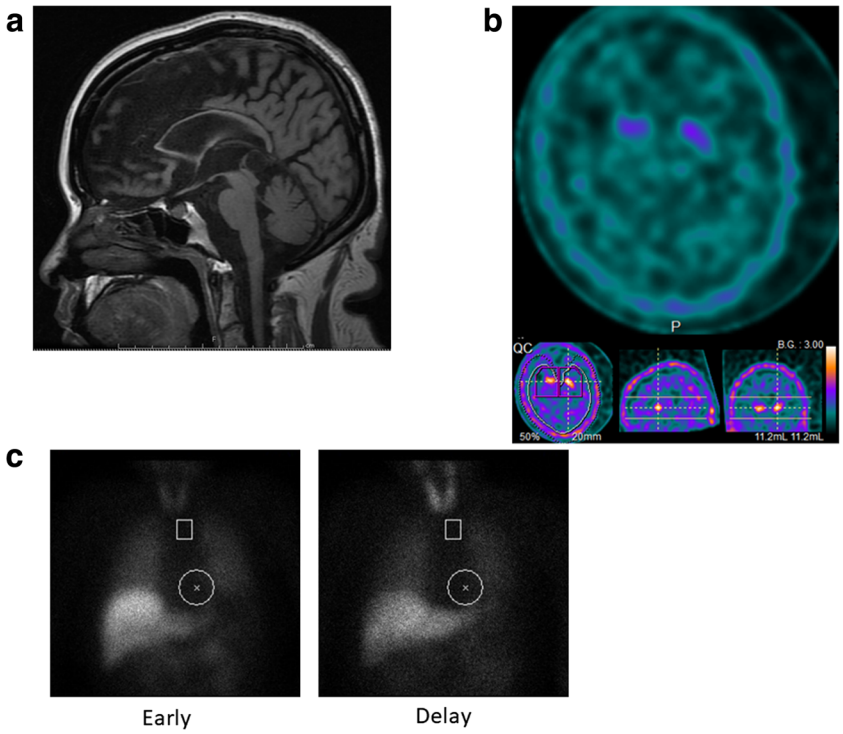

Fig. 1 **a** Brain MRI (T1WI) showed thin corpus callous. **b** ^{123}I-ioflupane SPECT revealed low SBR values; − 0.04 on the right and − 0.221 on the left (normal, > 4.5). The three insets show regions of interest. **c** ^{123}I-MIBG scintigraphy revealed the heart to mediastinum (H/M) ratio was 1.48 (normal, > 2.2) in the early and 1.34 (normal, > 2.2) in the delayed phase, and the washout ratio was 44.2% (normal, < 22). Squares and circles showed the regions of interest in the mediastinum and heart, respectively

homozygous mutation (c.4539delG, p.Arg1513Argfs*26) in the *ZFYVE26* gene responsible for SPG15. We confirmed the patient carried the homozygous mutation and each of the parents carried the heterozygous mutation by Sanger sequencing. Furthermore, whole exome sequencing revealed a homozygous haplotype for 11.6 Mb around the *ZFYVE26* gene.

Discussion

In this study, we found a novel homozygous mutation of c.4539delG in the *ZFYVE26* gene responsible for SPG15. This mutation of around 11.6 Mb was found to be a homozygous haplotype. The parents did not know that they were related, but the homozygous region around *ZFYVE26* indicated that they were. Their hometown was a bit isolated, the latter increasing the chance of patients having homozygous mutations. The neurological and brain MRI findings in our patient, i.e., leg spasticity, extrapyramidal signs, cerebellar ataxia, cognitive impairment, thin corpus callosum, and leukodystrophy, are consistent with those in SPG15 patients reported previously [1–3].

We performed ^{123}I-MIBG myocardial scintigraphy and ^{123}I-ioflupane SPECT to detect degeneration of nigrostriatal pathways and autonomic dysfunction. Our patient showed bilateral nigrostriatal loss on ^{123}I-ioflupane SPECT, which has only been described in two reports to date [1, 2]. These studies involved ^{123}I-2β-carbometoxy-3-β(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane (^{123}I-FP-CIT-SPECT) and ^{123}I-ioflupane SPECT. Thus, we confirmed reduction of the nitrostriatal dopamine transporter in this study. Three reports including ours indicate that SPG15 involves extrapyramidal signs caused by degeneration of the basal ganglia. Our patient did not exhibit levodopa effectivity, which was similar to that of an earlier report [1]. On the other hand, one report indicated effectivity for levodopa treatment [2]. More investigation is needed to clarify what caused this difference in the efficacy of the treatment.

In the present study, we first showed decreasing ^{123}I-MIBG myocardial scintigraphy uptake in SCA15. ^{123}I-MIBG myocardial scintigraphy has been performed to detect local myocardial sympathetic nerve damage, and it can detect an early stage of subclinical disturbance of the autonomic nervous system. To date, although a few reports have mentioned urinary dysfunction in a late stage of SPG15 [4], it was not clarified whether or not SPG15 shows autonomic disturbance throughout the disease course.

According to research involving ^{123}I-MIBG myocardial scintigraphy in PD, decreasing ^{123}I-MIBG myocardial scintigraphy uptake tends to increase with disease severity [5]. Furthermore, decreasing ^{123}I-MIBG uptake reflects cardiac sympathetic dysfunction in PD [6]. These findings indicated that decreasing ^{123}I-MIBG myocardial scintigraphy uptake presages dysfunction of the autonomic nervous system. Thus, we should carefully investigate the autonomic nerve disturbance in SPG15.

Acknowledgements We wish to thank all the participants.

Funding information This work was supported by Grants-in-Aid from the Research Committee for Ataxic Disease (Y.T.), and the Ministry of Health, Labor and Welfare, Japan, JSPS KAKENHI Grant Numbers JP18K07495 (Y.T.) and JP17K17772 (K.K.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and grants for AMED under Grant Number JP17ek0109078 (Y.T.).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Shicks J, Synofzik M, Pétursson H, Huttenlocher J, Reimold M, Schöls L, Bauer P (2011) Atypical juvenile parkinsonism in a consanguineous SPG15 family. Mov Disord 26:564–566
2. Mallaret M, Lagha-Boukbiza O, Biskup S, Namer IJ, Rudolf G, Anheim M, Transchant C (2014) SPG15: a cause of juvenile atypical levodopa responsive parkinsonism. J Neurol 261:435–437
3. Renvoisé B, Chang J, Singh R, Yonekawa S, FitzGibbon EJ, Mankodi A, Vanderver A, Schindler A, Toro C, Cahl WA, MAhuran DJ, Blackstone C, Pierson TM (2014) Lysosomal abnormalities in hereditary spastic paraplegia types SPG15 and SPG11. Ann Clin Transl Neurol 1:379–389
4. Goizet C, Boukhris A, Maltete D, Guyant-Maréchal L, Truchetto J, Mundwiller E, Hanein S, Jonveaux P, Roelens F, Loureiro J, Godet E, Foriani S, Melki J, Auer-Grumbach M, Fernandez JC, Martin-Hardy P, Sibon I, Sole G, Orignac I, Mhiri C, Coutinho P, Durr A, Brice A, Setavanin G (2009) SPG15 is the second most common cause of hereditary spastic paraplegia with thin corpus callosum. Neurology 73:1111–1119
5. Saiki S, Hirose G, Sakai K, Kataoka S, Hori A, Saiki M, Kaito M, Higashi K, Taki S, Kakeshita K, Fujino S, Miaki M (2004) Cardiac ^{123}I-MIBG scintigraphy can assess the disease severity and phenotype of PD. J Neurol Sci 220:105–111
6. Oka H, Toyoda C, Yogo M, Mochio S (2011) Reduced cardiac ^{123}I-MIBG uptake reflects cardiac sympathetic dysfunction in de novo Parkinson's disease. J Neural Transm 118:1323–1327