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【 CASE REPORT 】

Spastic Paraplegia with Paget's Disease of Bone due to a *VCP* Gene Mutation

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Abstract:
Hereditary spastic paraplegia (HSP) is a neurodegenerative disorder clinically characterized by slowly progressing spastic paraparesis. We herein report a 50-year-old Japanese woman who presented with slowly progressing spastic paraplegia and a history of Paget's disease of bone (PDB). Genetic testing revealed a mutation of the *Valosin-containing protein* (*VCP*) gene (p.Arg155Cys; c.436C>T). This mutation has not been reported to cause HSP with PDB.

Key words: *VCP* mutation, hereditary spastic paraplegia, Paget's disease of bone, rare mutation

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Introduction

Hereditary spastic paraplegia (HSP) is a neurodegenerative disorder clinically characterized by slowly progressing spastic paraparesis. Autosomal dominant, autosomal recessive, and X-linked inheritance patterns with some sporadic cases at a certain rate have been reported (1, 2). Among them, the most frequent inherited model is autosomal dominant HSP (ADHSP), which includes the SPG4 subtype, the most common HSP (2). A *Valosin-containing protein* (*VCP*) mutation was recently reported to be a cause of HSP. A *VCP* mutation can cause numerous clinical symptoms, including Paget's disease of bone (PDB), which is rare in Asians, in addition to HSP (3, 4).

We herein report an extremely rare case of spastic paraplegia with PDB in a middle-aged woman without a family history of pathognomonic symptoms due to a *VCP* gene mutation.

Case Report

A 50-year-old woman developed slowly progressing weakness of the lower extremities from 6 years ago and leg pain while walking from 4 years ago. She was admitted to our hospital for an examination. She had been diagnosed with PDB pathologically at 36 years old and was being treated using bisphosphonates. She had no family history, but her parents were cousins.

On admission, a physical examination demonstrated arthrogryposis of the ankle joint and shortening of the Achilles tendon. She had no respiratory difficulty or dysphagia. A neurological examination revealed severe spasticity, mild muscle weakness [4/5 on the manual muscle testing (MMT)], painful cramps, hyperreflexia, and pathological reflex of both lower extremities. She exhibited mild muscle weakness (4/5 on the MMT) in her bilateral deltoid, but there were no other abnormalities, including deep tendon reflex and pain or sensory disturbance, in the upper extremities. There was no muscle atrophy in her extremities and no findings suggestive of Parkinsonism. She was unable to stand or walk due to spasticity and joint deformation. Her mini-mental examination score was 29/30 points, Frontal Assessment battery score was 12/18 points, Trail making test-A was 98 seconds, and Trail making test-B was 133 seconds. Although she had no evident higher brain dysfunction, including memory and frontal lobe disturbance, she had slight disinhibition, presenting as talkativeness, stubbornness, and selfishness.

Her blood count was normal. Blood chemistry revealed

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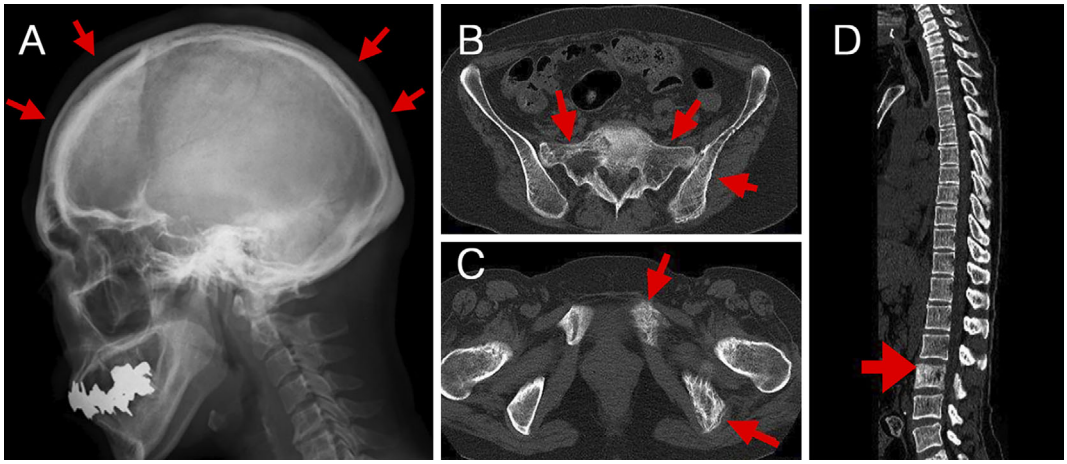

Figure 1. **Pathological changes due to Paget's disease of bone on imaging examinations. Skull radiography revealed mild bone hypertrophy and thickening (A). On computed tomography, thickening of the bone cortex and increased endosteal resorption in the sacroiliac bone (B), ischiopubic (C), and 3rd lumbar vertebra (D) were observed.**

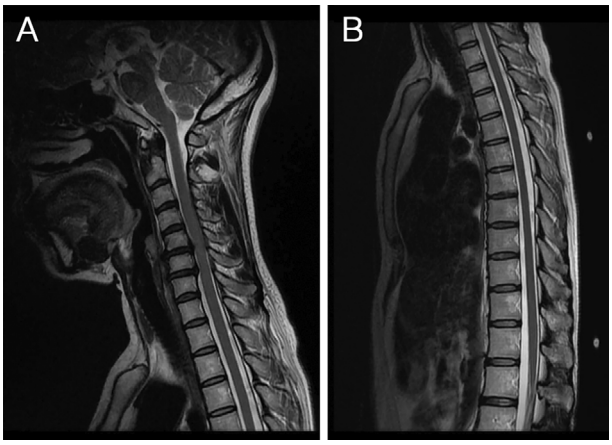

Figure 2. **Magnetic resonance imaging (MRI) of the cervical and thoracic spinal cord. Mild cervical spondylosis of C4/5 and C5/6 was noted (A), but no abnormality was observed in the thoracic region (B).**

high levels of alkaline phosphatase and inorganic phosphorus. The level of creatine kinase was normal (110 U/L, reference value: 45-163 U/L). Vitamin B group levels and an examination of the cerebrospinal fluid were normal (no increase in myelin basic protein or oligoclonal band; white cell count <1, protein 34.8 mg/dL, glucose 60 mg/dL, IgG index 0.43). Serological tests for syphilis and antibody of human T-cell leukemia virus type 1 were negative. On skull radiography, mild bone hypertrophy thickening was observed, but there was no evidence of bone resorption (Fig. 1A). Computed tomography revealed thickening of the bone cortex and increased endosteal resorption in the sacrum, ilium, ischiopubic, and third lumbar vertebra (Fig. 1B-D).

Magnetic resonance imaging (MRI) of the spinal cord demonstrated mild cervical spondylosis of C4/5 and C5/6 (Fig. 2), but brain MRI was normal. There was no specific brain hypoperfusion, including in the frontal and temporal lobes, on N-isopropyl-p-^{123}I iodoamphetamine (^{123}I-IMP) single-photon-emission computed tomography (Fig. 3). Genetic testing confirmed a heterozygous *VCP* gene mutation (p.Arg155Cys; c.436C>T).

Discussion

The clinical classification of HSP proposed by Harding is divided into pure and complex types, depending on the presence of symptoms other than spastic paraplegia (5). Other possible neurological abnormalities include peripheral neuropathy, cognitive dysfunction, epilepsy, and extrapyramidal symptoms (6). Furthermore, as spastic paraplegia includes many different diagnoses, neurophysiological and ophthalmic examinations, screening for metabolic disease, and examinations of the cerebrospinal fluid, the plasma amino acid fraction, lipoprotein fraction, serum vitamin B and vitamin E as well as syphilis, human T-cell leukemia virus type 1, and human immunodeficiency virus tests are needed as auxiliary tests (7-11). However, sporadic cases of spastic paraplegia may have genetic factors, including recessive inheritance, inheritance from asymptomatic carriers, and *de novo* mutations (7-9).

The causative *VCP* gene on chromosome 9p13 encodes a valosin-containing protein (VCP) whose mutation was recently reported to cause inclusion body myopathy (IBM) with PDB and frontotemporal dementia (IBMPFD) (3). VCP belongs to the AAA-ATPase family and functions as a molecular chaperone that mediates many cellular activities (12). Regarding neurological disorders, VCP functions in the ubiquitin-proteasome pathway, the disturbance of which causes neurodegeneration (13). In particular, spastic paraplegia is considered to be caused by the loss of function of VCP protein and by the indirect effects of a *VCP* mutation through other spastic paraplegia-associated proteins (spastin or paraplegin), which also belong to the AAA-ATPase family (14).

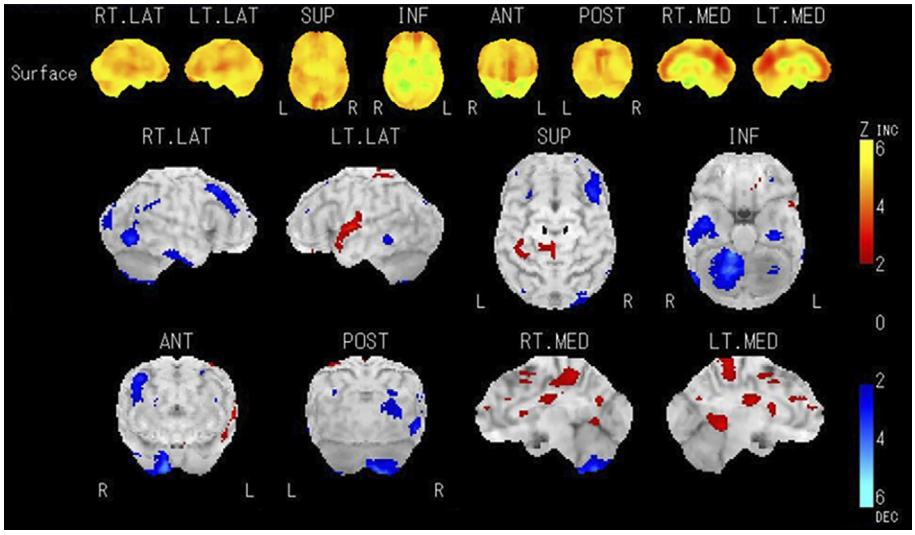

Figure 3. **Results of N-isopropyl-p-^{123}I iodoamphetamine (^{123}I-IMP) SPECT. No specific decrease in cerebral blood flow was observed in the 3D stereotactic surface projection analysis. SPECT: single photon emission computed tomography**

VCP mutations cause many disease subtypes that can vary within the same gene mutation or family; familial or sporadic amyotrophic lateral sclerosis (ALS), Parkinson syndrome, and peripheral neuropathy have been reported in addition to IBMPFD and HSP (15, 16). Although diseases caused by *VCP* gene mutations are generally autosomal dominant, there are many previous reports of sporadic disease cases and of HSP (17). In our case, there was no family history suggesting a *VCP* mutation, although there was a genetic risk due to cousin marriage. However, while it was difficult perform genetic tests and neurological examinations on relatives, including the parents, this case was considered to be a *de novo* mutation.

PDB is rare in Asians compared with Caucasians, especially in Japan, with an incidence of 2.8 per million (4). The incidence of PDB in the United States is estimated to be at least 1%, with the highest incidence reported in the northeast (18). Although approximately half of the patients with *VCP* mutations in the United States and Europe have PDB (19, 20), a Japanese group reported that only one out of seven Japanese patients with *VCP* mutations had a bone sclerotic region suggesting PDB (21). Of note, epidemiological studies of PDB conducted in Auckland, where the incidence rate of Paget's disease is high, revealed that the prevalence of PDB among people of Asian origin was similar to that among people of European origin and concluded that there is no marked difference in the genetic risk of PDB in Asians (22). Thus, the differences in the prevalence of PDB between Asians and Europeans cannot be explained by genetic factors alone and may be related to environmental factors. The variation in phenotypes caused by a *VCP* mutation may also be related to environmental factors. As our patient had radiological evidence of bone lesions, increased alkaline phosphatase, and a pathological diagnosis of PDB, her case was considered to be markedly rare in Japan. However, we were unable to find possible environmental factors from the medical history.

Other mutations that can cause PDB are found in the *SQSTM1* (23), *TNFRSF11A* and *TNFRSF11B* genes (24). Mutations in *SQSTM1* in particular can cause frontotemporal lobe degeneration (25), Alzheimer's disease (26), amyotrophic lateral sclerosis (25), and distal myopathy with rimmed vacuoles (27), in addition to PDB (25), which overlap with the symptoms caused by *VCP* mutations. Sequestosome1, encoded by *SQSTM1*, is presumed to selectively degrade ubiquitinated proteins through autophagy (28). Dysfunction of the ubiquitin-proteasome pathway in the autophagy system may be associated with bone, muscle, and nervous system phenotypes.

The *VCP* p.Arg155Cys variant was not found in normal controls (GnomAD version 3). High conservation of the arginine residue at codon 155 among different species (human, Rhesus monkey, mouse, elephant, chicken, and *Xenopus tropicalis*) was confirmed by the UCSC genome browser (https://genome.ucsc.edu/). *In silico* predictions of the pathogenicity of this variant were "probably damaging (score 0.99)" by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and "deleterious (score -5.08)" by PROVEAN (http://provean.jcvi.org/index.php). This variant in our case was also reported to be pathological and cause IBMPFD (29). A clinical analysis of the 31 *VCP* p.Arg155Cys mutation cases showed that 39% were IBM only, 3% PDB only, 0% FTD only, 26% IBM and PDB, 16% IBM and FTD, 0% PDB and FTD, and 16% IBM with PDB and FTD (30). Although our patient had no major symptoms of IBM or ALS, such as muscle atrophy, an increased creatine kinase level, selective muscle weakness of the quadriceps or flexor digitorum profundus, or fasciculation, it was difficult to completely rule out IBM or ALS. Although we were unable to perform the motor evoked poten-

tial test to detect pyramidal tract dysfunction due to the lack of infrastructure, if such symptoms develop during follow-up, needle electromyography will be added.

In conclusion, HSP with PDB was considered to be caused by the *VCP* mutation p.Arg155Cys, which to our knowledge has not been previously reported. The subtype of HSP with PDB was previously reported in one family in the Netherlands, but the causative mutation was p.Arg159Cys (14). The accumulation of individual case reports is necessary to clarify the pathogenesis and clinical phenotypes.

The authors state that they have no Conflict of Interest (COI).

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