A Case of 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 (PBD). Genetic testing revealed a mutation of the VCP gene (p.Arg155Cys; c.436C>T). This mutation has not been reported to cause HSP with PBD.

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 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 high levels of alkaline phosphatase and inorganic phospho-
single-photon-emission computed tomography (Fig. 3). Ge-
lobes, on N-isopropyl-p-123I iodoamphetamine (123I-IMP)
brain hypoperfusion, including in the frontal and temporal
(Fig. 2), but brain MRI was normal. There was no specific
demonstrated mild cervical spondylosis of C4/5 and C5/6
ischiopubic, and third lumbar vertebra (Fig. 1B-1D).

Computed tomography revealed thickening of the bone cor-
x and increased endosteal resorption in the sacroiliac bone (B), ischiopubic (C), and
3rd lumbar vertebra (D) were observed.

Discussion

The clinical classification of HSP proposed by Harding is
divided into pure and complex types, depending on the pres-
ence of symptoms other than spastic paraplegia (5). Other
possible neurological abnormalities include peripheral neu-
opathy, cognitive dysfunction, epilepsy, and extrapyramidal
symptoms (6). Furthermore, as spastic paraplegia includes
many different diagnoses, neurophysiological and ophthal-
mic examinations, screening for metabolic disease, and ex-
aminations 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 aux-
ilary tests (7-11). However, sporadic cases of spastic para-
plegia may have genetic factors, including recessive inheri-
tance, 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 re-
cently 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 mo-
olecular 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 paraple-
gia 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 fam-
ily (14).

VCP mutations cause many disease subtypes that can vary
within the same gene mutation or family; familial or spo-
radic 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 to perform genetic tests and neurological examinations on relatives, including the parents, this case was considered to be a de novo mutation.

PBD is rare in Asians compared with Caucasians, especially in Japan, with an incidence of 2.8 per million (4). The incidence of PBD 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 PBD (19, 20), a Japanese group reported that only one out of seven Japanese patients with VCP mutations had a bone sclerotic region suggesting PBD (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 PBD in Asians (22). Thus, the differences in the prevalence of PBD 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 PBD, 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/phil2/) 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 IBM/FD (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 potential 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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References
1. Christian N, Dupre N, Gan-Or Z, et al. Clinical and genetic study of hereditary spastic paraplegia in Canada. Neurology Genetics 3: e122, 2017.
2. Schule R, Wiethoff S, Martus P, et al. Hereditary spastic paraplegia: Clinicogenetic lessons from 608 patients. Ann Neurrol 79: 646-658, 2016.
3. Watts GD, Wymer J, Kovach MJ, et al. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nature genetics 36: 377-381, 2004.
4. Hashimoto J, Ohno I, Nakatsuoka K, et al. Prevalence and clinical features of Paget’s disease of bone in Japan. Journal of bone and mineral metabolism 24: 186-190, 2006.
5. Harding AE. Classification of the hereditary ataxias and paraplegias. Lancet (London, England) 1: 1151-1155, 1983.
6. de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, Bortholin T, Oliveira ASB. Hereditary Spastic Paraplegia: Clinical and Genetic Hallmarks. Cerebellum (London, England) 16: 525-551, 2017.
7. Klebe S, Stevanin G, Depienne C. Clinical and genetic heterogeneity in hereditary spastic paraplegias: from SPG1 to SPG72 and still counting. Revue neurologique 171: 505-530, 2015.
8. Finsterer J, Loscher W, Quasthoff S, Wanschitz J, Auer-Grumbach M, Stevanin G. Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance. Journal of the neurological sciences 318: 1-18, 2012.
9. Lo Giudice T, Lombardi F, Santorelli FM, Kawarai T, Orlacchio A. Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. Experimental neurology 261: 518-539, 2014.
10. Salinas P, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. The Lancet Neurology 7: 1127-1138, 2008.
11. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. Acta Neuropathol 126: 307-328, 2013.
12. Meyer H, Bug M, Bremer S. Emerging functions of the VCP/p97 AAA-ATPase in the ubiquitin system. Nature cell biology 14: 117-123, 2012.
13. Wang Q, Song C, Li CC. Molecular perspectives on p97-VCP: progress in understanding its structure and diverse biological functions. Journal of structural biology 146: 44-57, 2004.
14. de Bot ST, Schelhaas HJ, Kamsteeg EJ, van de Warrenburg BP. Hereditary spastic paraplegia caused by a mutation in the VCP gene. Brain 135 (Pt 12): e223; author reply e224, 2012.
15. Johnson JO, Mandrioli J, Benatar M, et al. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron 68: 857-864, 2010.
16. Gonzalez-Perez P, Cirilli ET, Drory VE, et al. Novel mutation in VCP gene causes atypical amyotrophic lateral sclerosis. Neurology 79: 2201-2208, 2012.
17. Koppers M, van Blitterswijk MM, Vlam L, et al. VCP mutations in familial and sporadic amyotrophic lateral sclerosis. Neurobiol Aging 33: 837.e837-813, 2012.
18. Altman RD, Bloch DA, Hochberg MC, Murphy WA. Prevalence of pelvic Paget’s disease of bone in the United States. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research 15: 461-465, 2000.
19. Weihl CC, Pestronk A, Kimonis VE. Valosin-containing protein disease: inclusion body myopathy with Paget's disease of the bone and fronto-temporal dementia. Neuromuscular disorders: NMD 19: 308-315, 2009.
20. Kimonis VE, Fulchiero E, Vesa J, Watts G. VCP disease associated with myopathy, Paget disease of bone and frontotemporal dementia: review of a unique disorder. Biochimica et biophysica acta 1782: 744-748, 2008.
21. Shi Z, Hayashi YK, Mitsuhashi S, et al. Characterization of the Asian myopathy patients with VCP mutations. European journal of neurology 19: 501-509, 2012.
22. Sankaran S, Naot D, Grey A, Cundy T. Paget’s disease in patients of Asian descent in New Zealand. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research 27: 223-226, 2012.
23. Layfield R, Hocking LJ. SQSTM1 and Paget’s disease of bone. Calcified tissue international 75: 347-357, 2004.
24. Sparks AB, Peterson SN, Bell C, et al. Mutation screening of the TNFRSF11A gene encoding receptor activator of NF kappa B (RANK) in familial and sporadic Paget’s disease of bone and osteosarcoma. Calcified tissue international 69: 151-155, 2001.
25. Rubino E, Rainero I, Chio A, et al. SQSTM1 mutations in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Neurology 79: 1556-1562, 2012.
26. Cuyvers E, van der Zee J, Bettens K, et al. Genetic variability in SQSTM1 and risk of early-onset Alzheimer dementia: a European early-onset dementia consortium study. Neurobiol Aging 36: 2005, e2015-e2022, 2015.
27. Bucelli RC, Arzhaouyi K, Pestronk A, et al. SQSTM1 splice site mutation in distal myopathy with rimmed vacuoles. Neurology 85: 665-674, 2015.
28. Komatsu M, Waguri S, Koike M, et al. Homeostatic levels of p62 control cytoplasmic inclusion body formation in atrophy-deficient mice. Cell 131: 1149-1163, 2007.
29. Kim EJ, Park YE, Kim DS, et al. Inclusion body myopathy with Paget disease of bone and frontotemporal dementia linked to VCP p.Arg155Cys in a Korean family. Arch Neurol 68: 787-796, 2011.
30. Al-Obeidi E, Al-Tahan S, Surampalli A, et al. Genotype-phenotype study in patients with valosin-containing protein mutations associated with multisystem proteinopathy. Clin Genet 93: 119-125, 2018.
