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Late-Onset Dystonia With *THAP1* Mutation (DYT6) in South Korea: A Case Report and Literature Review

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Dear Editor,

The most common gene mutation that causes primary dystonia is DYT1, followed by DYT6. DYT6 dystonia was first reported in two Amish-Mennonites families in 1997.[1] In 2009, a mutation in the thanatosis-associated protein domain-containing protein 1 (*THAP1*) gene was identified as the cause of DYT6 dystonia, and since then more than 30 mutations have been reported, mostly in Caucasians.[2] The penetrance of *THAP1* mutations is about 60%.[2] The prevalence rate of *THAP1* mutations in primary dystonia is 0.6%–4.7% in Europe, Brazil, and Asia.[3] DYT6 often presents in late childhood or adolescence, but several cases with an onset after 40 years old have also been reported.[4-7] Here we report the first case of late-onset dystonia with *THAP1* mutation in South Korea.

A 54-year old male presented with retrocollis and dysarthria, which first appeared at 42 years old and subsequently progressed. He had no family history of neurological disorders (Supplementary Fig. 1 in the online-only Data Supplement). He had no cognitive impairment. An examination revealed spasmodic speech with perioral dystonia, severe retrocollis from the upper back to the neck, and dystonia in the bilateral upper limbs (Supplementary Video 1 in the online-only Data Supplement). He scored 34 on the Bruke-Fahn-Marsden Dystonia Rating Scale. He presented normal saccadic/pursuit eye movements and no abnormality in deep tendon and pathologic reflexes. The findings of routine laboratory tests and brain magnetic resonance imaging were normal. Medication therapy using clonazepam, trihexyphenidyl, nortriptyline, baclofen, levodopa, benztropine, carbamazepine, topiramate, and pramipexole was attempted but provided no benefit. Botulinum toxin A injection was also not effective in treating his cervical dystonia. Dystonia gene panel testing revealed a known pathogenic variant of *THAP1* (c.505C>T, p.Arg169*, heterozygote).[8] The patient was reluctant to undergo deep brain stimulation (DBS).

This case was the first of a patient with DYT6 dystonia in South Korea. DYT6 often involves the craniosegmental region and has less tendency to become generalized.[2,6] The mean age at DYT6 onset is 16.1 years, which is older than that of DYT1.[2] Early-onset dystonia cases tend to involve multiple sites at onset that gradually become generalized, while later-onset cases tend to have focal or segmental dystonia, which is often sporadic and occurs without a family history.[4-7] Although antidystonic oral medications and botulinum toxin A injection have been reported to be effective in treating DYT6,[6] they were of no benefit to the current patient. DBS of the globus pallidus internus (GPi-DBS) has been reported to be as effective in DYT6 as in DYT1.[4,5]

Few studies have investigated patients with late-onset DYT6 (older than 40 years), with 21 late-onset cases reported among seven studies.[3-7,9,10] Details about the clinical manifestations, family history, and treatment response of the patients are provided in Table 1. Late-onset DYT6 often presents as cervical or laryngeal dystonia, and remains as focal or segmental dystonia. It can also present as blepharospasm or oromandibular dystonia. Among the above-

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Table 1. Literature review of DYT6 cases with onset at 40 years or older

Reference	Onset age (years)	Sex	Onset site	Spread	Family history	Treatment
Groen et al.[4]	54	M	Cervical, truncal, and bilateral arm	Segmental	No	GPi-DBS(+)–good improvement of cervical dystonia
	50	F	Cervical	Focal	No	NA
Houlden et al.[9]	57	M	Writer's	Segmental	No	NA
Söhn et al.[10]	46	F	Cervical	Focal	No	NA
Danielsson et al.[5]	42	F	Cervical	Focal		Botulinum toxin, benzodiazepines, gabapentin, and nonsteroidal anti-inflammatory drug GPi-DBS(+)–no improvement
	40	F	Cervical	Focal		Botulinum toxin, benzodiazepines GPi-DBS(+)–good improvement
Xiao et al.[6]	53	M	Leg	Generalized	Yes	NA
	49	F	Cervical	Focal	Yes	NA
	53	F	Cervical	Focal	Yes	NA
	43	F	Cervical	Focal	No	Botulinum toxin
	51	F	Larynx	Focal	No	Botulinum toxin
	62	F	Larynx	Focal	No	Botulinum toxin
	69	F	Upper face	Focal (blepharospasm)	No	NA
	62	F	Larynx	Focal	No	NA
	50	F	Upper face	Focal (blepharospasm)	No	NA
	61	M	Jaw	Focal (masticatory)	No	Botulinum toxin
	58	F	Cervical	Focal	No	NA
	48	F	Larynx	Focal	No	NA
	66	F	Larynx	Focal	No	NA
Dobričić et al.[3]	41	M	Larynx	Focal	No	NA
Holla et al.[7]	45	M	Arm	Generalized (face, trunk, and right toe)	No	Botulinum toxin, baclofen, clonazepam, and tetrabenazine
Current report	42	M	Cervical	Segmental (face, arm, and trunk)	No	No benefits from antidystonic medication and botulinum toxin

DBS, deep brain stimulation; GPi, globus pallidus internus; NA, not available.

mentioned studies, most patients (15/18) had no family history. Five patients responded well to botulinum toxin injection. GPi-DBS was performed on three patients, two of whom showed improvement.

The onset age and site and spread of dystonia may vary even within the same mutation site and family.[3,5,6] The genetic mutation identified in the current patient was previously reported in a patient with an onset at 5 years old.[8] Further studies on modifiers that affect clinical variations of DYT6 are needed.

Supplementary Video Legend

Video 1. The patient presented with severe retrocollis and dystonia of the perioral area and bilateral upper limbs.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.0241.

Ethics Statement

This study was approved by the Seoul National University Hospital Ethics Committee (IRB No. 2206-013-1328).

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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