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Clinical presentation of a patient with *SLC20A2* and *THAP1* deletions: differential diagnosis of oromandibular dystonia

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Oromandibular dystonia is a rare, focal dystonia that is characterized by forceful contractions of the face, jaw, and/or tongue [1]. These contractions cause difficulty with the opening and closing of the mouth, which leads to mastication impairment and speech problems. Idiopathic basal ganglia calcification (IBGC) is a rare, autosomal-dominant disease that is accompanied by abnormal calcium deposition in the brain [2]. IBGC is clinically characterized by dystonia, parkinsonism, tremor, ataxia, dementia, psychosis, and seizures [2]. IBGC is classified into five subgroups, IBGC1 - IBGC5, and this classification is based on causative genes/loci. Wang and colleagues [3] identified *SLC20A2* mutations as a genetic cause of IBGC3. We recently discovered *SLC20A2* and *THAP1* deletions in a familial form of basal ganglia calcification in which dystonia was the most predominant clinical manifestation [4, 5]. We provide a video presentation of a previously reported case from this previously described family (patient III-3 in the previous report [5]) [6]. We also include a summary of the clinical features associated with the type of oromandibular dystonia that arises from known genetic causes (Table).

A right-handed man developed abnormal movements of his trunk and arms at the age of 26 years. His initial symptoms were writer's cramp and involuntary posturing of his shoulders and trunk; these symptoms were more prominent on his right-side. His symptoms remained stable until he was 50-years-old, which was when he developed progressive dysarthria with speech-induced involuntary jaw opening, mild short-term memory loss, and gait impairment. His family history was notable for dystonia, chorea, and postural tremor. A brain CT showed calcifications in the occipital cortex, subcortical white matter, basal ganglia, thalamus, and

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the cerebellum. The esupp video shows the patient during two examinations; one was conducted when he was 77-years-old, and the other was conducted when he was 80-years-old.. The patient provided written consent before filming. The video displays that the patient had speech-induced jaw opening dystonia, severe dysarthria, chorea, right shoulder postural dystonia, and writer's cramp. His gait deteriorated between his first and second examinations. He eventually developed severe cognitive impairment and behavioral problems. He died at the age of 85 years.

An autopsy identified patchy, multifocal calcifications in the periventricular regions, basal ganglia, anterior thalamus, visual cortex, and the cerebellum. Genetic testing revealed that the patient carried *SLC20A2* and *THAP1* deletions [4].

To date, eighteen genetic disorders with known causative gene mutations have been reported to be associated with oromandibular dystonia (Table. Of these, only neurodegeneration with brain iron accumulation 1 (NBIA1) is known to cause calcification in the brain. NBIA1 is caused by *PANK2* mutations and is clinically characterized by dystonia, dysarthria, pyramidal signs, cognitive impairment, pigmentary retinopathy, dysphagia, chorea, psychiatric symptoms, developmental delay, oculomotor abnormalities, and parkinsonism. Typical symptomatic disease onset for NBIA1 usually occurs before the age of 10 years. However, a minority of patients exhibit atypical clinical features, such as a later symptomatic disease onset (between 15–40 years), prominent speech problems, psychiatric symptoms, and a more gradual disease progression. Calcifications in the brains of NBIA1 patients generally can be observed in the basal ganglia. Our patient and his family [5,6] can be clinically distinguished from NBIA1 patients based on the more extensive distribution of brain calcification in their brains.

Currently,, no patients carrying *SLC20A2* mutations have been reported to present with oromandibular dystonia [3]. However, oromandibular dystonia is one of the prominent features of patients with *THAP1* mutations. The oromandibular dystonia seen in this case and in that of others previously reported [5,6] could presumably be caused solely by a mutation in the *THAP1* gene. Additional functional studies to confirm this hypothesis are warranted. Genetic testing, especially for *THAP1*, should be considered in individuals that have extensive basal ganglia calcifications and a family history of dystonia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Neurogenetic disorders that have been associated with oromandibular dystonia

Disorders	Genes	Typical age at onset	Clinical characteristics	Brain calcification	References related to oromandibular dystonia
Ataxia-telangiectasia	<i>ATM</i>	Infantile	CA, choreoathetosis, OMA, oculocutaneous telangiectasias, immunodeficiency, risk of cancer	Not reported	Carrillo, et al. ^{eref 1}
CLN3	<i>CLN3</i>	Infantile-juvenile	Visual loss, MR, seizures, extrapyramidal signs, dysarthria, deterioration of motor skills, Psy	Not reported	Wisniewski, et al. ^{eref 2}
Cerebrotendinous xanthomatosis	<i>CYP27A1</i>	Late childhood	Juvenile cataract, tendon xanthomas, CI, Pyr, CA, mental retardation, seizure, diarrhea, seizure, Psy, peripheral neuropathy, dysarthria, dysphagia, osteopenia, dystonia	Not reported	Lagarde, et al. ^{eref 3} Posada, et al. ^{eref 4} Alcalay, et al. ^{eref 5}
DYT1	<i>TOR1A</i>	Infantile-adolescence	Dystonia	Not reported	Yilmaz, et al. ^{eref 6} Xiao, et al. ^{eref 7} Calakos, et al. ^{eref 8}
DYT3	<i>TAF1</i>	Adulthood	Dystonia, P, T, chorea, myoclonus, myorhythmia, chorea-ballism, hyposmia	Not reported	Rosales, et al. ^{eref 9}
DYT5	<i>GCH1</i>	Childhood	Dystonia, P, T, diurnal fluctuation, Pyr, Psy, mental retardation, myoclonus, RLS	Not reported	Steinberger, et al. ^{eref 10}
DYT6	<i>THAP1</i>	Childhood-manhood	Dystonia	Not reported	LeDoux, et al. ^{eref 11} Dobri i , et al. ^{eref 12} Groen, et al. ^{eref 13} Houlden, et al. ^{eref 14}
DYT16	<i>PRKRA</i>	Childhood-adolescence	Dystonia, P, dysarthria, developmental delay, dysphagia, Pyr	Not reported	Camargos, et al. ^{eref 15}
DYT24	<i>ANO3</i>	Adolescence-Adulthood	Dystonia, T	Not reported	Charlesworth, et al. ^{eref 16}
DYT25	<i>GNAL</i>	Adolescence-Adulthood	Dystonia	Not reported	Fuchs, et al. ^{eref 17} Vemula, et al. ^{eref 18}
HPABH4A	<i>PTS</i>	Infantile	Mental retardation, hypotonia, Pyr, seizure, dysphagia, blond hair, microcephaly, eczema, short stature, hypotonia, CA, dystonia, P	Not reported	Hanihara, et al. ^{eref 19}
NBIA1	<i>PANK2</i>	Childhood	Dystonia, dysarthria, Pyr, CI, pigmentary retinopathy, dysphagia, chorea, Psy, CI, developmental delay, OMA, P	Basal ganglia	Wu et al. ^{eref 20} Sachin, et al. ^{eref 21} Angelini, et al. ^{eref 22}
NBIA4	<i>C19orf12</i>	Childhood	Dystonia, Pyr, CI, Psy, dysarthria, dysphagia, optic atrophy, P, peripheral neuropathy, Psy, urinary incontinence	Not reported	Hartig, et al. ^{eref 23} Devos, et al. ^{eref 24}
Kufor Rakeb disease	<i>ATP13A2</i>	Childhood	P, CI, Pyr, OMA, myoclonus, visual hallucinations, oculogyric dystonic spasms	Not reported	Krner, et al. ^{eref 25}

Disorders	Genes	Typical age at onset	Clinical characteristics	Brain calcification	References related to oromandibular dystonia
SCA1	<i>ATXN1</i>	Manhood	CA, dysarthria, Pyr, hyporeflexia, OMA, ataxia, CI, dysphagia, peripheral neuropathy, PN, dystonia, P	Not reported	Wu, et al. ^{eref 26}
SCA8	<i>ATXN8</i>	Adolescence-Adulthood	CA, dysarthria, CI, Pyr, peripheral neuropathy, dysphagia, Psy, T, dystonia, P	Not reported	Ushe, et al. ^{eref 27}
SCA36	<i>NOP56</i>	Adulthood	CA, hyporeflexia, LMN, OMA, hearing loss	Not reported	Miyashiro, et al. ^{eref 28}
Wilson disease	<i>ATP7B</i>	Childhood-manhood	Liver disease, Kayser-Fleischer rings, dysarthria, T, P, dystonia, CA, Pyr, bulbar signs, Psy, behavioral problem	Not reported	Teive, et al. ^{eref 29}
Present study	<i>SLC20A2 + THAP1</i>	Adolescence-Adulthood	Dystonia, P, T, CI, Psy, headache, seizure, CA, developmental delay, behavioral problem, dysarthria, dysphagia	Basal ganglia, thalamus, occipital lobe, cerebral WM, cerebellum	Baker, et al. ^{eref 30}

CA=cerebellar ataxia; CI=cognitive impairment; CLN=cereoid lipofuscinosis, neuronal; DYT=dystonia; HPABH4A=hyperphenylalaninemia, BH4-deficient; A; IBGC= idiopathic basal ganglia calcification; LMN=lower motor neuron signs; NBIA=neurodegeneration with brain iron accumulation; OMA=oculomotor abnormality; P=parkinsonism; Pyr=pyramidal signs; Psy=psychiatric symptoms; SCA=spinocerebellar ataxia; T=tremor; WM=white matter; references are available on supplemental references.