CHOREA-ACANTHOCYTOSIS PRESENTING AS DYSTONIA

Jan Kobal[1], Carol Dobson-Stone[2], Adrian Danek[3], Valentin Fidler[4], Bojana Zvan[1] and Marjan Zaletel[1]

[1]Division of Vascular Neurology, University Medical Center Ljubljana, Ljubljana, Slovenia; [2]Neuroscience Research Australia and University of New South Wales, Sydney, Australia; [3]Neurologische Klinik, Ludwig-Maximilians Universität, Munich, Germany; [4]Xlab Research, University Technology Park, Ljubljana, Slovenia

SUMMARY – The aim of this article is to present two Slovenian chorea-acanthocytosis (ChAc) siblings with an unusual predominantly dystonic ChAc phenotype. For diagnostic purposes, the genomic DNA was screened for VPS13A mutations. Movement disorder was evaluated and scored according to the Dystonia Movement and Disability Scale (DMDS) in order to evaluate the effects of L-dopa on dystonia. Brain imaging was performed with the use of magnetic resonance imaging scan and 99m Tc-ethyl cysteinate dimmer single photon emission computed tomography (Tc-ECD SPECT). Clinical neurological examination disclosed gait dystonia. Marked swallowing difficulty due to tongue and feeding dystonia was observed. Both siblings were found to be heterozygous for a substitution in exon 22 (c.2191C>T) and for a deletion in exon 35 (c.3995_3996delinsA) leading to mutation in VPS13A. After being administered L-dopa for three months, both subjects showed significant symptomatic improvement documented by reduced DMDS scores. It is concluded that VPS13A mutation testing may improve diagnosis of dystonia and recognition of atypical ChAc phenotypes. It seems that L-dopa could be effective in the treatment of dystonia due to VPS13A mutations.

Key words: *Neuroacanthocytosis; Dystonia; Chorea; VPS13A testing; Levodopa*

Introduction

Chorea-acanthocytosis (ChAc) is a rare, hereditary, neurodegenerative disease marked by phenotypic heterogeneity. It manifests as a mixed movement disorder, including chorea and parkinsonism. Dystonia is an unusual clinical presentation of the disease. Other features include seizures, neuropathy, myopathy, autonomic features, dementia and psychiatric symptoms[1]. The main neuropathologic feature of ChAc is degeneration of the striatum[2]. VPS13A is the only currently known gene to be associated with ChAc[2]. Thus, testing for VPS13A mutation may be helpful in diagnostic evaluation of various movement disorders such as dystonia.

Dystonia which is characterized by involuntary, sustained muscle contractions affecting one or more sites of the body, frequently causing twisting and repetitive movements or abnormal postures is an uncommon clinical form of ChAc. In the early stages of ChAc, the phenotype often comprises dysphagia and tongue dystonia and appears quite indicative of the disease[3]. Eating can also be impaired as tongue and throat twitches can interfere with chewing and swallowing of the food. People with ChAc may uncontrollably bite their tongue, lips, and inside of the mouth.

In this article, we present two Slovenian VPS13A mutation confirmed ChAc siblings, in whom an unusual, predominantly dystonic ChAc phenotype with mild frontal type dementia and elements of parkinsonism was observed. In addition, we noticed allevia-

Correspondence to: *Marjan Zaletel, MD, PhD* and *Jan Kobal MD, PhD*, Division of Neurology, University Medical Center, Zaloška 2, SI-1525 Ljubljana, Slovenia
E-mails: marjan.zaletel@kclj.si, jan.kobal@gmail.com

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tion of dystonia after L-dihydroxyphenylalanine (L-dopa) administration.

Case Report

The patients were first examined at 44 and 43 years of age, due to gait instability and involuntary movements that had started in their late thirties. Detailed clinical neurological examination was performed, followed by physical examination and laboratory tests to exclude somatic pathology that could lead to the formation of acanthocytes. Movement disorder was evaluated and scored according to the Dystonia Movement and Disability Scale (DMDS)[4]. Clinical neurological examination disclosed gait dystonia, which consisted of neck retroflexion with hyperlordosis, as well as inversion of the foot of the advancing leg and flexion of the opposite knee and foot when walking. Due to gait instability, the patients could barely walk a few steps. The female patient in particular presented with marked swallowing difficulties due to tongue and feeding dystonia. Also, she developed an interesting feeding technique by pushing parts of solid food into her throat with the use of her fingers. Generalized dystonia affected her face, trunk, extremities and allowed her only scarce moments of independence. When in distress, choreatic truncal movements were observed in the male patient. The female patient had developed movement disorder about two years earlier than her brother and was first seen by a neurologist at about one and a half year later. Therefore, she presented with consistently worse DMDS scores (Fig. 1A). In addition, signs of parkinsonism were observed in her, including mask like face, stooped posture and bradykinesia. Cognitive deficits suggestive of frontal lobe dementia with psychomotor slowing were revealed by cognitive clinical examination. Worsening of clinical features and the lack of chorea led us to the question of whether the dystonia observed in the siblings might respond to L-dopa treatment. Following daily administration of L-dopa/benserazide 100/25 t.i.d. for 3 months, both subjects showed significant symptomatic improvement documented by reduced DMDS scores (Fig. 1A). Improved ambulation was the most striking effect of L-dopa treatment. The patients were able to walk unaided for approximately 600 meters and were able to go shopping in the nearby grocery store.

After 18 months of successful L-dopa treatment, dystonia in the female worsened and she gradually deteriorated to her pretreatment status. As a result, L-dopa administration was discontinued (Fig. 1A). In contrast, her brother showed stable improvement over 3 years of therapy. Further clinical course in the female was relentlessly progressive with development of further dyskinesia. She died in a nursing home, most likely due to terminal pneumonia about 4 years after the first examination. The male patient remained free of dyskinesia and independent for about eight and half years after the first examination. However, parkin-

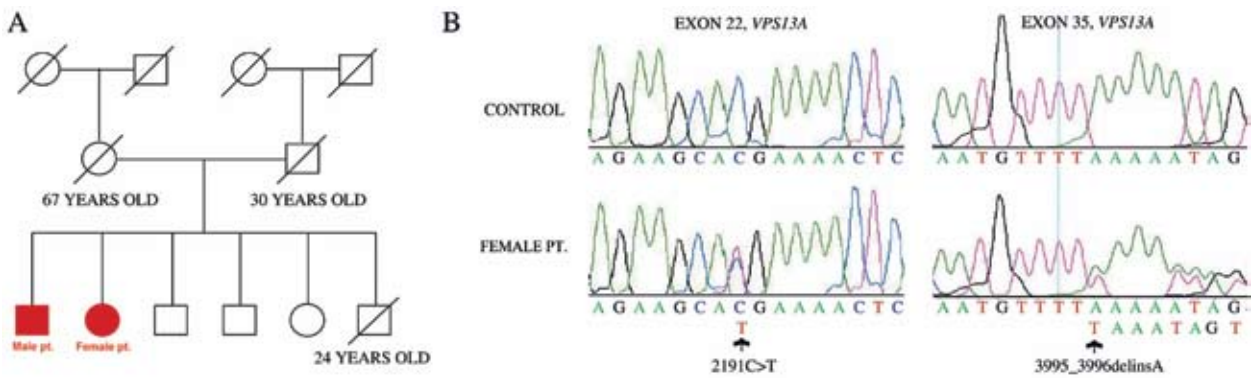

Fig. 1. Effects of L-dopa treatment on the dystonia-parkinsonism phenotype of chorea-acanthocytosis: graphs depict dystonia movement and dystonia disability scores before and up to 24 months after initiation of L-dopa treatment (A); representative 99mTc-ECD SPECT brain images showing symmetrically decreased radiolabeling in the frontal and temporal lobes and in the basal ganglia in the male and female in comparison with an age-matched healthy control, before and after 18-month L-dopa treatment (B).

sonian features and dysphagia were progressive. He was eventually admitted to a nursing home, where he suffered from food aspiration, was resuscitated, and consequentially spent the last months of his life in a vegetative state.

A written informed consent for publication of the data was obtained from the patients' closest relatives (two brothers and a sister).

Methods

Electromyography (EMG) was performed to confirm the peripheral neuropathic disorder. Brain imaging was performed with the use of magnetic resonance imaging scan (MRI, GE Signa MR tomograph, TR 3000 ms, TE 24 ms, slice thickness 5 mm) and 99m Tc-ethyl cysteinate dimmer single photon emission computed tomography (99m Tc-ECD SPECT, Multispect 2, Siemens, 180 projections, 1 frame/2 degrees, 128x128 matrix, slice thickness 7.2 mm). The patients' parents and siblings were free from any neurological disorders. Genomic DNA was screened for *VPS13A* mutations using techniques described previously[5].

Results

Magnetic resonance imaging (MRI) diagnostic work-up disclosed symmetric atrophy of the heads of the caudate nuclei. On 99m Tc-ECD SPECT, symmetrically decreased radiolabeling indicating a decrease in the cerebral blood flow and metabolism in the frontal, temporal lobes, and basal ganglia (Fig. 1B, without L-dopa) was observed. Control 99m Tc-ECD SPECT performed 18 months after treatment initiation showed a 30% decrease in radiolabeling of the basal ganglia compared to the pretreatment values in the female, but showed virtually no change in the male (Fig. 1B, 18 months of L-dopa).

Abnormally high percentages of acanthocytes in peripheral blood were detected, comprising 63% and 75% of total red blood cells in the female and male, respectively. This led us to further screening for *VPS13A* gene mutations. Both siblings were found to be heterozygous for a substitution in exon 22 (c.2191C>T), leading to a nonsense mutation (p.R731X), and for a deletion in exon 35 (c.3995_3996delinsA), leading to a frameshift mutation (p.F1332X), in *VPS13A* (Fig. 2), as previously reported[5,6] (Fig. 2B). A predominantly sensory axonal neuropathy was also found on EMG.

Discussion

Chorea-acanthocytosis is an autosomal recessive disorder (Fig. 2A) caused by mutations in the vacuolar protein sorting 13 homolog A (VPS13A) gene[1]. The mutations have been shown to abrogate or severely reduce expression of the VPS13A protein product, chorein. Chorein is assumed to be involved in intracellular

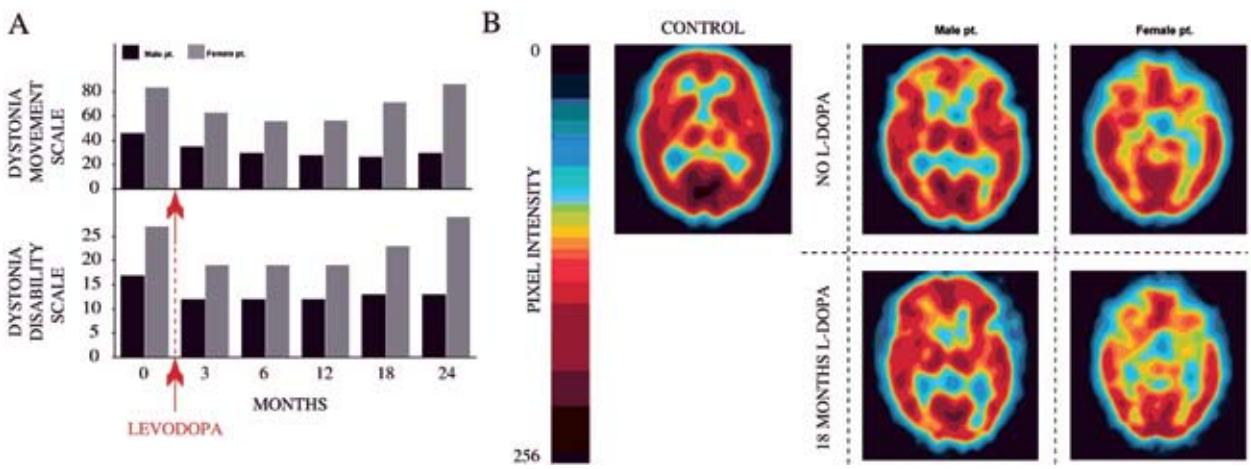

Fig. 2. Pedigree of the Slovenian kindred exhibiting autosomal recessive inheritance of chorea-acanthocytosis: the affected siblings are shown in red (A); identification of VPS13A mutations. Sequence chromatograms from the female and control DNA are displayed. Location of 2191C>T and 3995_3996delinsA mutations are marked by arrows. These mutations were also detected in the male patient; for exon 35, the reverse (antisense) strand DNA sequence is displayed (B).

trafficking of a number of transmembrane proteins. However, its function remains largely unknown[7,8]. VPS13A mutations result in a movement disorder, which usually takes the form of choreatic dyskinesias, typically found in conjunction with acanthocytic red blood cells (RBC)[9]. The clinical manifestations of VPS13A mutations are variable and include progressive movement abnormalities ranging from chorea to parkinsonism[10], with dystonia observed infrequently[9,10]. Muscular weakness due to myopathy/polyneuropathy is typically associated, as we diagnosed in our patients. Cognitive impairment, personality changes and epilepsy may accompany and/or precede movement abnormalities[11,12]. A variety of psychiatric symptoms may also occur[10,13]. ChAc phenotypes are therefore remarkably heterogeneous and their pathogenesis is obscure. As a result, current therapeutic approaches are restricted to the treatment of symptoms. The mutant VPS13A genotype in the patients described here resulted in a predominantly dystonic phenotype of ChAc with elements of parkinsonism. This particular phenotype, in conjunction with the significant heterogeneity of clinical phenotypes produced by other VPS13A mutations[10], suggests that VPS13A mutations not infrequently manifest with phenotypes where chorea develops years to decades after the onset of the disease[11-13]. As shown in this article, patients may even develop movement disorder that never progresses to obvious chorea. Patients with late onset or absent chorea may not undergo chorein or VPS13A mutation testing until late in the disease course. Current understanding of early ChAc phenotypes may therefore be biased towards phenotypes exhibiting obvious chorea in the early stage of the disease. The diagnosis of ChAc may, however, be confirmed by measuring chorein levels in RBC membranes of ChAc patients and/or by demonstrating VPS13A mutations[7].

Several forms of dystonia beyond L-dopa responsive dystonias in the strict sense have been reported to benefit from L-dopa, which is probably due to the metabolic defect in dopamine synthesis[14,15]. However, this strategy was not useful in the treatment of idiopathic dystonia[16]. The dystonia of both our ChAc patients responded favorably to L-dopa treatment. In the female patient, however, the effect was short-term, with eventual reappearance of dystonic dyskinesias.

Studies in Parkinson's disease patients have suggested that L-dopa might be beneficial and even slow down the progression of Parkinson's disease, but it may also encourage early motor complications, such as dystonic dyskinesias. The mechanism of these effects, however, remains obscure[17]. It seems that L-dopa in addition to increasing dopamine synthesis might have an impact on intracellular trafficking of transmembrane proteins, which consequently alter their modifying role of striatal G-protein coupled receptors and therefore might favor the expression of dyskinesia[18,19]. The symptoms that present in ChAc patients sharing the same mutation may be heterogeneous[12] and may resemble parkinsonism, 'peak dose', as well as 'off period' dyskinesia in Parkinson's disease patients. According to experimental data, it might be due to alteration in the processes of intracellular trafficking of different, unrelated transmembrane proteins influenced by chorein[7]. We speculate that in the female patient, the 'off period' dyskinesia developed again after initial improvement with L-dopa therapy, due to the longer disease course and consequently more developed striatal pathology, whereas in the male with less developed striatal pathology, the effect of increased dopamine synthesis was beneficial for a prolonged period of time. Parkinsonism, which in ChAc patients is not reactive to L-dopa[20], took its further progressive course.

Our propositions are in line with the reports revealing dopaminergic dysfunction by neuroimaging and neuropathologic analysis of brains obtained from ChAc patients and showing striatal as well as nigral atrophy[10,21]. In addition, depletion of dopamine and its metabolites was found in most brain areas, most notably in the striatum of ChAc patients[22]. The clinical course in our patients was paralleled by 99m Tc-ECD SPECT neuroimaging that revealed almost unchanged regional cerebral perfusion over 18-month L-dopa treatment in patient K.A. Interestingly, clinical deterioration in patient R.M. after 18-month L-dopa treatment was accompanied by a 30% decrease in regional cerebral perfusion.

In conclusion, our study suggests that the use of VPS13A mutation testing may improve diagnosis of dystonia and recognition of atypical ChAc phenotypes. L-dopa may be beneficial in the symptomatic treatment of dystonia due to VPS13A mutations.

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References

1. SOKOLOV E, SCHNEIDER SA, BAIN PG. Chorea-acanthocytosis. Pract Neurol 2012;12:40-3.
2. WALKER RH, JUNG HH, DOBSON-STONE C, RAMPOLDI L, SANO A, TISON F, DANEK A. Neurologic phenotypes associated with acanthocytosis. Neurology 2007;68:92-8.
3. BADER B, WALKER RH, VOGEL M, PROSIEGEL M, McINTOSH J, DANEK A. Tongue protrusion and feeding dystonia: a hallmark of chorea-acanthocytosis. Mov Disord 2010;25:127-9.
4. BURKE RE, FAHN S, MARSDEN CD, BRESSMAN SB, MOSKOWITZ C, FRIEDMAN J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology 1985;35:73-7.
5. DOBSON-STONE C, DANEK A, RAMPOLDI L, HARDIE RJ, CHALMERS RM, WOOD NW, BOHLEGA S, DOTTI MT, FEDERICO A, SHIZUKA M, TANAKA M, WATANABE M, IKEDA Y, BRIN M, GOLDFARB LG, KARP BI, MOHIDDIN S, FANANAPAZIR L, STORCH A, FRYER AE, MADDISON P, SIBON I, TREVISOL-BITTENCOURT PC, SINGER C, CABALLERO IR, AASLY JO, SCHMIERER K, DENGLER R, HIERSEMENZEL LP, ZEVIANI M, MEINER V, LOSSOS A, JOHNSON S, MERCADO FC, SORRENTINO G, DUPRÉ N, ROULEAU GA, VOLKMANN J, ARPA J, LEES A, GERAUD G, CHOUINARD S, NÉMETH A, MONACO AP. Mutational spectrum of the CHAC gene in patients with chorea-acanthocytosis. Eur J Hum Genet 2002;10:773-81.
6. TOMIYASU A, NAKAMURA M, ICHIBA M, UENO S, SAIKI S, MORIMOTO M, KOBAL J, KAGEYAMA Y, INUI T, WAKABAYASHI K, YAMADA T, KANEMORI Y, JUNG HH, TANAKA H, ORIMO S, AFAWI Z, BLATT I, AASLY J, UJIKE H, BABOVIC-VUKSANOVIC D, JOSEPHS KA, TOHGE R, RODRIGUES GR, DUPRÉ N, YAMADA H, YOKOCHI F, KOTSCHET K, TAKEI T, RUDZIŃSKA M, SZCZUDLIK A, PENCO S, FUJIWARA M, TOJO K, SANO A. Novel pathogenic mutations and copy number variations in the VPS13A gene in patients with chorea-acanthocytosis. Am J Med Genet B Neuropsychiatr Genet 2011;156:620-31.
7. DOBSON-STONE C, VELAYOS-BAEZA A, FILIPPONE LA, WESTBURY S, STORCH A, ERDMANN T, *et al*. Chorein detection for the diagnosis of chorea-acanthocytosis. Ann Neurol 2004;56:299-302.
8. VELAYOS-BAEZA A, LEVECQUE C, DOBSON-STONE C, MONACO AP. The function of chorein. In: WALKER RH, SAIKI S, DANEK A, editors. Neuro-acanthocytosis syndromes II. Berlin: Springer, 2008;87-105.
9. WALKER RH, JUNG HH, DOBSON-STONE C, RAMPOLDI L, SANO A, TISON F, DANEK A. Neurologic phenotypes associated with acanthocytosis. Neurology 2007;68:92-8.
10. HARDIE RJ, PULLON HW, HARDING AE, OWEN JS, PIRES M, DANIELS GL, IMAI Y, MISRA VP, KING RH, JACOBS JM. Neuroacanthocytosis. A clinical, haematological and pathological study of 19 cases. Brain 1991;114(Pt 1A):13-49.
11. Al-ASMI A, JANSEN AC, BADHWAR A, DUBEAU F, TAMPIERI D, SHUSTIK C, MERCHO S, SAVARD G, DOBSON-STONE C, MONACO AP, ANDERMANN F, ANDERMANN E. Familial temporal lobe epilepsy as a presenting feature of choreoacanthocytosis. Epilepsia 2005;46:1256-63.
12. SAIKI S, HIROSE G, SAKAI K, MATSUNARI I, HIGASHI K, SAIKI M, KATAOKA S, HORI A, SHIMAZAKI K. Chorea-acanthocytosis associated with tourettism. Mov Disord 2004;19:833-6.
13. MULLER-VAHL KR, BERDING G, EMRICH HM, PESCHEL T. Chorea-acanthocytosis in monozygotic twins: clinical findings and neuropathological changes as detected by diffusion tensor imaging, FDG-PET and (123)I-beta-CIT-SPECT. J Neurol 2007;254:1081-8.
14. SCHNEIDER SA, MOHIRE MD, TRENDER-GERHARD I, ASMUS F, SWEENEY M, DAVIS M, GASSER T, WOOD NW, BHATIA KP. Familial dopa-responsive cervical dystonia. Neurology 2006;66:599-601.
15. WU LJ, JANKOVIC J. Runner's dystonia. J Neurol Sci 2006;251:73-6.
16. JANKOVIC J. Treatment of dystonia. In: WATTS RL, KOLLER WC, editors. Movement disorders. New York: McGraw Hill, 2004;527-39.
17. FAHN S, OAKES D, SHOULSON I, KIEBURTZ K, RUDOLPH A, LANG A, OLANOW CW, TANNER C, MAREK K; Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351:2498-508.
18. FEYDER M, BONITO-OLIVA A, FISONE G. L-dopa induced dyskinesia and abnormal signaling in striatal medium spiny neurons: focus on dopamine D1 receptor-mediated transmission. Front Behav Neurosci 2011;5:71.
19. LEE J, GOMEZ-RAMIREZ J, JOHNSTON TH, VISANJI N, BROTCHIE J M. Receptor-activity modifying protein

1 expression is increased in the striatum following repeated L-dopa administration in a 6-hydroxydopamine lesioned rat model of Parkinson's disease. Synapse 2008;62:310-3.

20. SPITZ MC, JANKOVIC J, KILLIAN JM. Familial tic disorder, parkinsonism, motor neuron disease and acanthocytosis: a new syndrome. Neurology 1985;35:366-70.
21. RINNE JO, DANIEL SE, SCARAVILLI F, HARDING AE, MARSDEN CD. The neuropathological features of neuroacanthocytosis. Mov Dis 1994;9:297-304.
22. De YEBENES JG, BRIN MF, MENA MA, De FELIPE C, Del RIO RM, BAZAN E, MARTINEZ A, FAHN S, Del RIO J, VAZQUEZ A. Neurochemical findings in neuroacanthocytosis. Mov Disord 1988;3:300-12.

Sažetak

DISTONIJA KAO MANIFESTACIJA KOREA-AKANTOCITOZE

J. Kobal, C. Dobson-Stone, A. Danek, V. Fidler, B. Zvan i *M. Zaletel*

Prikazuje se dvoje slovenskih bolesnika, brat i sestra, s koreom-akantocitozom, s neuobičajenim pretežito distoničnim fenotipom korea-akantocitoze. Proveden je dijagnostički probir genomske DNA na mutacije VPS13A. Poremećaj kretanja procijenjen je i ocijenjen prema *Dystonia Movement and Disability Scale* (DMDS) kako bi se procijenili učinci L-dopa na distoniju. Slikovni prikazi mozga napravljeni su pomoću magnetske rezonance i Tc-ECD SPECT (*99m Tc-ethyl cysteinate dimmer single photon emission computed tomography*). Klinički neurološki pregled otkrio je distoniju hoda. Zapažene su znatne teškoće pri gutanju zbog distonije jezika i distonija hranjenja. I brat i sestra bili su heterozigotni za supstituciju u eksonu 22 (c.2191C>T) i za deleciju u eksonu 35 (c.3995_3996delinsA), koje uzrokuju mutaciju u VPS13A. Nakon davanja L-dopa kroz tri mjeseca oboje je pokazalo značajno poboljšanje simptoma, što je dokumentirano sniženim zbirom na DMDS. Zaključuje se da testiranje na mutaciju VPS13A može pomoći u dijagnosticiranju distonije i prepoznavanju atipičnih fenotipova korea-akantocitoze. Čini se da bi L-dopa mogla biti učinkovita u liječenju distonije uzrokovane mutacijama VPS13A.

Ključne riječi: *Neuroakantocitoza; Distonija; Korea; VPS13A testiranje; Levodopa*