CHOREA-ACANTHOCYTOSIS PRESENTING AS DYSTONIA

Jan Kobal1, Carol Dobson-Stone2, Adrian Danek3, Valentin Fidler4, Bojana Zvan1 and Marjan Zaletel1

1Division of Vascular Neurology, University Medical Center Ljubljana, Ljubljana, Slovenia; 2Neuroscience Research Australia and University of New South Wales, Sydney, Australia; 3Neurologische Klinik, Ludwig-Maximilians Universität, Munich, Germany; 4Xlab 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 dimer 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 symptoms1. The main neuropathologic feature of ChAc is degeneration of the striatum2. VPS13A is the only currently known gene to be associated with ChAc2. 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 disease3. 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-
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-
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.

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. 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. 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\textsuperscript{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)\textsuperscript{9}. The clinical manifestations of VPS13A mutations are variable and include progressive movement abnormalities ranging from chorea to parkinsonism\textsuperscript{10}, with dystonia observed infrequently\textsuperscript{7,10}. 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\textsuperscript{11,12}. A variety of psychiatric symptoms may also occur\textsuperscript{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\textsuperscript{10}, suggests that VPS13A mutations not infrequently manifest with phenotypes where chorea develops years to decades after the onset of the disease\textsuperscript{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\textsuperscript{2}.

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\textsuperscript{14,15}. However, this strategy was not useful in the treatment of idiopathic dystonia\textsuperscript{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\textsuperscript{7}. 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\textsuperscript{18,19}. The symptoms that present in ChAc patients sharing the same mutation may be heterogeneous\textsuperscript{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. 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\textsuperscript{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\textsuperscript{20,21}. In addition, depletion of dopamine and its metabolites was found in most brain areas, most notably in the striatum of ChAc patients\textsuperscript{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.
Acknowledgments

We thank Anthony P. Monaco for his guidance and supervision of C.D.-S. in this study. This study was supported by grant P3-0019 from the Slovenian Research Agency (D.S.). C.D.-S. was supported by Wellcome Trust prize studentship 060886/Z/00/Z during this study and is now supported by Project Grant 630428 from the National Health and Medical Research Council of Australia.

References


Dystonia in ChAc

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.


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 neobičajenim 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 dijagnostiranju 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