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Phenotypic variability in chorea-acanthocytosis associated with novel *VPS13A* mutations

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Abstract

Objective

To perform a comprehensive characterization of a cohort of patients with chorea-acanthocytosis (ChAc) in Sweden.

Methods

Clinical assessments, targeted genetic studies, neuroimaging with MRI, [^{18}F]-fluorodeoxyglucose (FDG) PET, and dopamine transporter with ^{123}I FP-CIT (DaTscan) SPECT. One patient underwent magnetic resonance spectroscopy (MRS).

Results

Four patients living in Sweden but with different ethnical backgrounds were included. Their clinical features were variable. Biallelic *VPS13A* mutations were confirmed in all patients, including 3 novel mutations. All tested patients had either low or absent chorein levels. One patient had progressive caudate atrophy. Investigation using FDG-PET revealed severe bilateral striatal hypometabolism, and DaTscan SPECT displayed presynaptic dopaminergic deficiency in 3 patients. MRS demonstrated reduced N-acetylaspartate/creatine (Cr) ratio and mild elevation of both choline/Cr and combined glutamate and glutamine/Cr in the striatum in 1 case. One patient died during sleep, and another was treated with deep brain stimulation, which transiently attenuated feeding dystonia but not his gait disorder or chorea.

Conclusions

Larger longitudinal neuroimaging studies with different modalities, particularly MRS, are needed to determine their potential role as biomarkers for ChAc.

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Glossary

BG = basal ganglia; **CC/IT** = intercaudate distance to inner table width ratio; **ChAc** = chorea-acanthocytosis; **Cho** = choline; **Cr** = creatine; **DBS** = deep brain stimulation; **FDG** = fluorodeoxyglucose; **FH/CC** = frontal horn width to intercaudate distance ratio; **Glx** = glutamine; **HD** = Huntington disease; **MLS** = McLeod syndrome; **MRS** = magnetic resonance spectroscopy; **NAA** = N-acetylaspartate.

Chorea-acanthocytosis (ChAc) and McLeod syndrome (MLS) are the main forms of neuroacanthocytosis disorders, characterized by progressive and incurable hyperkinesias, neuromuscular abnormalities, and a reduced life span. However, epilepsy is common in ChAc, whereas dilated cardiomyopathy is a distinctive feature in 2/3 of patients with MLS.[1] Caudate atrophy is progressive in MLS but has not been described in ChAc[2] caused by biallelic mutations in the vacuolar protein sorting 13 homolog A (*VPS13A*) gene, encoding chorein.[1] Currently, almost 1,000 cases with ChAc have been reported in various populations. Here, we characterize 4 patients affected by ChAc and 3 new truncating mutations in *VPS13A*.

Methods

The patients (2 males and 2 females) were evaluated at 4 different centers in Sweden (table 1). Patients or their next-of-kin provided oral and written consent for this study, approved by the Regional Ethics Committee of Stockholm. Patients underwent clinical evaluation of motor features with Unified Huntington's Disease Rating Scale, cognitive screening with Montreal Cognitive Assessment, psychometric testing, laboratory tests, blood smears, and/or ancillary tests such as neurophysiologic tests and/or muscle biopsy. Analysis of the *VPS13A* gene was performed following exclusion of a trinucleotide expansion in the huntingtin (*HTT*) gene. The ClinVar database (ncbi.nlm.nih.gov/clinvar) was used to assess novelty of *VPS13A* mutations, and MutationTaster (mutationtaster.org) was used to predict the effects of mutations. Western blot for chorein in blood was performed in patients 1, 3, and 4 (Western blot analysis for chorein were performed with the financial support of the Advocacy for Neuroacanthocytosis Patients in the laboratories of Drs. Bettina Schmid (Biochemistry/DZNE) and Adrian Danek (Neurology) at Ludwig-Maximilians-Universität Munich, Germany). Neuroimaging included MRI, [^{18}F]-fluorodeoxyglucose (FDG)PET/CT, and assessment of presynaptic dopamine transporter with ^{123}I-labeled N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (FP-CIT) DaTscan SPECT. The parameters evaluated in Huntington disease (HD), frontal horn width to intercaudate distance ratio (FH/CC) and intercaudate distance to inner table width ratio (CC/IT), were measured. Magnetic resonance spectroscopy (MRS) was performed only in patient 1. Briefly, the concentrations of N-acetylaspartate (NAA), choline (Cho), combined glutamate and glutamine (Glx), creatine (Cr), and phosphocreatine were measured in the putamen and globus pallidus. These results were compared with normative data from 20 healthy controls (supplementary material, links.lww.com/NXG/A255).

Data availability

Data not provided in this article are available in a trusted repository (doi.org/10.5061/dryad.7h44j0zr9).

Results

Phenotype and genetics

The clinical features and mutations are summarized in table 1. Briefly, the mean age at onset was 34 (range 30–38) years, and the disease duration was 9.5 (range 2–17) years. All patients presented with cognitive decline of variable degree, and laboratory investigations revealed elevated creatine kinase levels and acanthocytes in blood smears. Feeding dystonia was prominent in patient 1 and therefore treated with botulinum injections in the tongue base[3] and later with bilateral deep brain stimulation (DBS) of the internal globus pallidus that resulted in a transient attenuation of feeding dystonia. Western blot analysis revealed absent chorein in patient 1 and low levels in patients 3 and 4. Chorea, dystonia, and vocalizations were initial features in patients 1 and 3, and their severe gait disorder was overcome when walking backward. Both patients were compound heterozygous for *VPS13A* mutations. In patient 2, seizures were the first symptom, followed by hyperkinesias and myopathy at later stages. Genetic investigation revealed homozygosity for a *VPS13A* mutation. The patient died during sleep at age 42 years despite good seizure control, and autopsy revealed incidental sarcoidosis affecting the heart. Patient 3 was diagnosed with tourettism during adolescence, followed by progressive hyperkinesias and a gait disorder that became evident at age 30 years. Symptoms progressed with generalized dystonia, predominantly of the torso, and marked blepharospasm. Genetic investigation revealed compound heterozygosity for *VPS13A* mutations. A younger sibling of patient 3, not investigated for *VPS13A* mutations, had seizures without motor abnormalities and died during sleep. Patient 4 had chorea and depression; her genetic investigation revealed homozygosity for a *VPS13A* mutation. Three of the 6 *VPS13A* mutations were new and pathogenic (table 1 and supplementary material, links.lww.com/NXG/A255). The course of disease for patient 1 is shown in video 1; patients 3 and 4 declined video recordings of their examination.

Neuroimaging

MRI displayed variable degrees of striatal atrophy in all patients that was progressive in patient 3. Patient 1 had FH/CC = 1.6 (normal range: 2.2–2.6) and CC/IT = 0.18 (normal range: 0.09–0.12) at age 37 years, with unchanged ratios 5

Table 1 Acanthocytes were present in all 3 patients, and chorein was absent in blood in patient 1

Features and genetics	Case no.	1	2	3	4
	Ethnicity	Latin American	Swedish	Swedish	Syrian
	Sex	M	F	M	F
Clinical course	Age at onset	33	36	30	37
	Current age or age at death[b]	46	42[b]	47[c]	40
	Symptom at onset	Personality change and chorea	Epilepsy	Gait disorder, facial chorea, and vocalizations	Chorea and fatigue
Motor features	Predominant motor symptoms	Chorea, dystonia, postural instability, and bradykinesia[a]	Chorea, postural instability, oral dystonia, and vocal tics	Generalized dystonia and severe blepharospasm	Chorea, including oral tics
	Chorea	+	+	+	+
	UHDRS (latest)	43	NA	55	25
	Feeding dystonia	+	–	(+)	–
Cognitive and behavioral function	Cognitive impairment	+	+	(+)	+
	MoCA	28	NA	NA	13
	Psychiatric symptoms	+ Frontal disinhibition	–	+ Tourettism	+ Depression
Neuromuscular assessment	Muscle weakness/atrophy	+	+	ND	–
	Reduced deep tendon reflexes	+	+	+	+
	Neuropathy (confirmed with ENeG)	–	NA	–	–
	Myopathy	+	+	NA	–
Other neurologic features	Epilepsy	–	+	–	–
Laboratory testing	CK (x upper reference value) (Ref. men 0.8–6.7 and women 0.6–3.5 μkat/L)	+ (15x)	+ (19x)	+ (4x)	+ (3x)
	Elevated AST or ALT	+	+	–	–
	Acanthocytes	+	+	+	+
	Chorein	Absent	NA	Low	Low
Imaging studies	MRI caudate atrophy	+	+	+ Progressive	+
	Reduced striatal uptake (DaTscan)	+	NA	+	+
	Striatal hypometabolism (FDG-PET)	+	NA	+	+
Genetics	Mutations in *VPS13A*	c.266dupT; exon 51–59 del (p.Ile90Tyrfs*; p?)	Homozygous c.4162_4166 delins C (p.Leu1388Glu-fsx6)	c.2428-2A>G; c.1595+4_1595+7delAGTA (p?; p?)	Homozygous c.7867C>T (p.Arg2623X)

Abbreviations: + = present; – = absent; (+) = mild feature; ALT = alanine transaminase; AST = aspartate aminotransferase; CK = creatine kinase; FDG = fluorodeoxyglucose; MoCA = Montreal Cognitive Assessment; NA = no assessed; ND = no determined; UHDRS = Unified Huntington's Disease Rating Scale. All patients also had areflexia and hyperCKemia. Mutations for patients 2 and 3 are new.
[a] Treated with bilateral deep brain stimulation of the internal globus pallidus.
[b] Sudden unexpected death in epilepsy (SUDEP). Age at death was 42.
[c] A younger brother to patient 3 had epilepsy at age 24 years and died during sleep at age 28 years; however, he did not show obvious movement abnormalities.

years later. MRS for patient 1 demonstrated a mild reduction of NAA/Cr ratio and mild elevation of Cho/Cr and Glx/Cr in the striatum (table e-1 and figure e-1, links.lww.com/NXG/A255). Patient 3 had FH/CC = 1.5 and CC/IT = 0.20 at age 39 years. Six years later, the FH/CC was 1.2 and CC/IT 0.26, indicating progressive caudate atrophy (figure e-4). Patients 2 and 4 had iron deposition in the globus pallidus. In patients 1, 3, and 4, we observed profound reduction of glucose metabolism in the dorsal striatum (caudate nucleus and putamen) and reduced dopamine transporter binding (figure 1 and supplementary document). Patients 1 and 3 also had an increased glucose metabolism in the thalamus, whereas patient 4 had a normal thalamic metabolism. An extended description on the clinical course and neuroimaging findings are found in the supplementary files (figures e-1 to e-5).

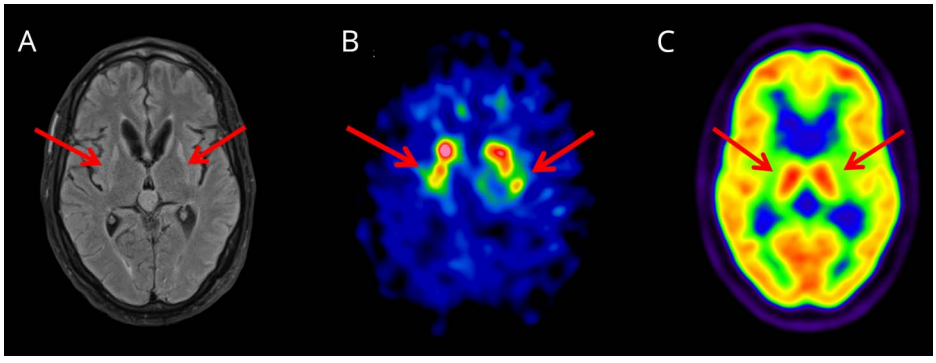
Discussion

Here, we add to the number of *VPS13A* mutations associated with variable phenotypic expression in 4 cases of ChAc. Similar to HD, structural neuroimaging for ChAc demonstrated both caudate atrophy with dilatation of the anterior horns and variable cortical atrophy.[1,4] Other MRI findings include increased T2-weighted signal in the caudate and putamen and hippocampal sclerosis and atrophy,[1] in contrast to some patients with ChAc with normal findings in the basal ganglia (BG).[5] In addition, iron accumulation in the BG in patient 2 is in line with previous findings in ChAc[1]. Caudate atrophy is progressive in MLS,[2] but this is, to our knowledge, the first report on progressive caudate atrophy in ChAc.

Consistent with previous studies on ChAc, we identified severe hypometabolism in the BG, loss of dopaminergic nigrostriatal projections, and dopamine transporter binding sites in all assessed patients.[6–9] Importantly, hypometabolism in the BG is not specific for ChAc, as it occurs also in MLS and HD. Furthermore, patients 1 and 3 had increased metabolism in the thalamus. Whereas thalamic hypermetabolism has been reported in patients with blepharospasm,[10] we noted that only patient 3 has generalized dystonia and blepharospasm. The only previous MRS study in genetically confirmed ChAc demonstrated decreased NAA/Cr ratio in the atrophic striatum of 2 brothers.[8] This abnormality reflects neuronal loss and gliosis. In contrast, the myo-inositol/Cr ratio was increased in this part of the BG. MRS abnormalities have previously been described in cortical areas of 5 patients with MLS, but abnormalities in the striatum were not determined.[11] In HD, MRS abnormalities are widespread and depend on disease stage. Our results showing reduced NAA, reflecting neuronal loss and gliosis, are in line with previous observations. The elevations of Cho, reflecting increased cellular membrane turnover and glutamate/Glx, suggest a possible role of glutamate excitotoxicity in ChA as a potential biomarker in the pathophysiology of ChAc.

A common clinical feature is the progression into bradykinesia, observed in 2 of 4 patients. The low binding of DaTscan to dopamine transporter in the striatum is a reasonable correlate to parkinsonism in patients 1 and 3; neuronal loss has been described in patients with ChAc with parkinsonism.[1] On the other hand, reduced binding in patient 4 is likely a premonitory sign of hypokinesia and no a side effect of neuroleptic since DaTscan is a presynaptic tracer. To date, there are only 5 reports on genetically confirmed ChAc in Scandinavia.[3,e2,e3,e8,e9] All 6 mutations reported herein are truncating, and 3 of them are novel. This is consistent with previously reported *VSP13A* gene mutations, of which the majority predict a complete or partial loss of protein function.[e3] Low or absent chorein levels in 3 of our patients strengthen the notion that the *VPS13A* variants are indeed pathogenic. The reasons for the wide clinical variability in ChAc remain elusive.[1] Patient 3 presented with tourettism during adolescence and was diagnosed with ChAc at age 30 years, followed by a disease course spanning 17 years. This is remarkable considering that the mean disease duration in ChAc is 11 years.[e4] Furthermore, sudden unexpected death in epilepsy (SUDEP) appears to be common in ChAc and was recently reported in 6 of 52 patients.[e4] Patient 2 died during sleep at age 42 years, raising the

Figure 1. Neuroimaging findings in chorea-achantocytosis



Axial T2-weighted FLAIR MRI of patient 3 (at age 46 years) shows a pronounced atrophy of the caudate nuclei and putamina and increased signal intensity from the putamina (arrows) (A) DaTscan SPECT and fluorodeoxyglucose PET in the same patient at age 43 years demonstrate very low DAT density in both putamen (B, arrows) respectively severe hypometabolism in the striata (C, arrows). DAT = dopamine transporter; FLAIR = fluid-attenuated inversion recovery.

suspicion of SUDEP. However, it cannot be excluded that the presence of sarcoidosis in her heart could have predisposed to a lethal arrhythmia.

Although our report brings additional information to the genetic and clinical variability in ChAc, the retrospective nature of our study precluded volumetric MRI analyses. Finally, our study calls for further longitudinal neuroimaging studies using different modalities to assess their potential role as biomarkers in ChAc.

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Disclosure

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Jan Weinberg, MD, PhD	Karolinska University Hospital	Drafting and revising the manuscript; patient care; and analysis and interpretation of data
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Martin Paucar, MD, PhD	Karolinska University Hospital and Karolinska Institutet	Revising the manuscript; study concept and design; analysis and interpretation of data; and study supervision and coordination

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