Choreoacanthocytosis in a Mexican Family

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**Background:** Choreoacanthocytosis (CHAC) (Online Mendelian Inheritance in Man accession No. 200150) is a hereditary neurodegenerative syndrome characterized by movement disorders, cognitive decline, myopathy, behavioral changes, and acanthocytosis and is caused by mutations in the VPS13A gene.

**Objective:** To describe the cases of 2 Mexican women with clinical and molecular characteristics compatible with CHAC.

**Design:** Case reports.

**Patients:** Choreoacanthocytosis was identified in 2 Mexican mestizo sisters with healthy consanguineous parents. Clinical manifestations began at different ages.

**Results:** The onset of signs and symptoms of CHAC in the proband was at age 32 years and was characterized by balancing problems followed by chorea, compulsive lip and tongue biting with buccolingual self-mutilation, dysarthria, dysphagia, and weight loss. The first clinical manifestations in the proband's sister occurred at age 45 years and included multiple motor and verbal tics, with coprolalia, followed by lip and tongue biting, self-mutilation, and chorea. The clinical findings in both sisters were remarkable for acanthocytosis that developed late, when neurologic changes were already evident. Mutation screening of the VPS13A gene revealed homozygosity for the frameshift mutation c.3556_3557dupAC in exon 33. Currently, the proband's sister, in whom neurologic defects developed 13 years after onset of CHAC in the proband, is the least affected.

**Conclusions:** The same mutation of the VPS13A gene can be expressed differently in the same family. This observation confirms the notion that there is considerable heterogeneity in the clinical manifestation of CHAC.

Arch Neurol. 2007;64(11):1661-1664

**CHOREOACANTHOCYTOSIS (CHAC)** is a type of neuroacanthocytosis, a heterogeneous group of hereditary syndromes characterized by the association of neurologic abnormalities with acanthocytic red blood cells.¹² Choreoacanthocytosis is mainly an autosomal recessive disorder caused by a variety of mutations in the VPS13A gene (Online Mendelian Inheritance in Man accession No. 200150; available at http://www.ncbi.nlm.nih.gov/omim/). The exact pathophyslogic mechanisms remain largely unknown, and no obvious genotype-phenotype correlation has been described to date.³ The clinical manifestation includes progressive movement disorders (primarily chorea but occasionally parkinsonism), clinical or subclinical myopathy, cognitive decline, compulsive behavior, and acanthocytosis of the red blood cells.³⁴ Dystonia is frequent, affecting the oral region and causing dysarthria and dysphagia with resultant weight loss. Seizures occur in almost 50% of patients.³ Clinical manifestations of CHAC overlap considerably with those seen in chorea with the McLeod phenotype (McLeod syndrome), an X-linked neuroacanthocytosis in which erythrocyte protein abnormalities have been much studied.⁴

A detailed description of neuropathologic findings in 2 Mexican patients affected with CHAC was published in 1989.³ Since then, to our knowledge, no further descriptions of Mexican patients with CHAC have been published in the scientific literature. The purpose of the present report is to report the cases of 2 sisters with the clinical phenotype of CHAC, with the mutation c.3556_3557dupAC in the VPS13A gene causing the disorder.

**REPORT OF CASES**

**CASE 1**

The proband, a 42-year-old woman with healthy parents in a consanguineous relationship (first-degree cousins) was 32 years old when the first clinical manifestations appeared. These included frequent falls and abrupt, undulant, asymmetric involuntary movements of the
trunk, neck, and upper limbs, associated with compulsive lip and tongue biting. At age 35 years, she began to experience episodes of anxiety and depression. Three years later, there was dysphagia to solid foods, dysarthria, and orofacial dyskinesia, with buccolingual self-mutilation (Figure 1) and consequent weight loss of 12 kg. At age 40 years, she could not walk because of hypotonia of the legs. The dysphagia worsened, and she was able to swallow only liquids and semisolid foods. Multiple pharmacologic approaches, including benzodiazepine, oral non-deposit form of haloperidol, biperiden hydrochloride, trihexyphenidyl hydrochloride, clonazepam, levodopa, fluoxetine hydrochloride, and vitamin B complex therapy, were sequentially initiated in an attempt to control symptoms, but with limited response. Two years later, at age 42 years, she became emaciated, anarthric, and reactive to the environment, performing only simple commands. The lower cranial nerves were patently affected, with lingual atrophy and paralysis. The arms and legs were flaccid, paretic, and hyporeflexic. Given the clinical suspicion of CHAC, several peripheral blood smear (PBS) preparations were analyzed, initially yielding nonsignificant results. However, as a consequence of the fortuitous finding of erythrocyte acanthocytosis in her sister several months later, a new PBS was analyzed, which revealed 40% acanthocytes (Figure 1). Other significant laboratory findings included elevated MB fraction of creatine kinase (395 U/L; reference range, 22-269 U/L) and heterozygous ε3/ε4 genotype of apolipoprotein E. There were no remarkable results for α-tocopherol, cobalamin, ceruloplasmin, and copper concentrations in plasma or for lipoprotein electrophoresis and iron kinetics. Assessment of peripheral nerve conduction velocity revealed a severe polynuropathic axonal sensorimotor defect. Brain imaging assessment included computed tomography and magnetic resonance imaging, which demonstrated global atrophy, especially of the caudate nuclei (Figure 1). Magnetic resonance spectroscopy of the brain showed no meaningful results.

CASE 2

The proband’s 54-year-old sister experienced the onset of signs of CHAC at age 45 years, characterized by multiple motor and verbal tics, both simple and complex; paranoid behavior; coprolalia; and lip and tongue biting with buccolingual self-mutilation. She refused to undergo neurologic evaluation and complied poorly with therapy. Given the awareness of the diagnosis of CHAC in her sister, no other diagnostic procedures were performed except for PBS and mutation screening of the VPS13A gene. She is walking at home but with frequent falls and dependence on her family.

MOLECULAR GENETIC ASSESSMENT

In patient 1, DNA was screened for VPS13A mutations by denaturing high-performance liquid chromatography followed by direct sequencing, as described elsewhere. We confirmed the presence of the mutation in patient 2 by direct sequencing. Both patients were homozygous for a frameshift mutation in exon 33 (c.3556_3557dupAC) (Figure 2), a genetic change first detected in a family from the United States (family CHAC4). Patients 1 and 2 have 2 sisters (one of them with compulsive alcoholism) and 2 brothers, all older than 30 years, who are otherwise healthy (Figure 3). Serial PBS preparations from the case patients’ siblings and nephews have been analyzed, yielding unremarkable results to date. Genetic counseling has been provided, but given the recessive inheritance of this syndrome, the family has refused genotyping unless another member with symptoms of CHAC is identified.

Figure 1. Patient with choreoacanthocytosis. A, Note self-mutilation of the lips owing to orofacial dyskinesia. B, Peripheral blood smear exhibits acanthocytes (Wright-Giemsa, original magnification, ×100). C, Coronal view of T1-weighted magnetic resonance image shows atrophy of the caudate nuclei.

Figure 2. Sequence chromatograms show the VPS13A c.3556_3557dupAC mutation found in patients 1 and 2. Asterisks indicate the inserted bases.
We present the case reports of 2 sisters with the rare CHAC syndrome. To our knowledge, this is the second report of this disorder in Mexicans.3,7 Although the same mutation of the VPS13A gene was responsible for the disease, the clinical expression differed between the 2 sisters for age at onset, appearance of neurologic findings, and severity of disease. These findings confirm that clinical heterogeneity seems to be the rule in CHAC.8,9 It is possible that gene environment or complex interactions among products of different genes are responsible for the variable expression of this syndrome. The exact determinants of the clinical spectrum of CHAC will be clarified when the function of the product encoded by the VPS13A gene is known.

The VPS13A gene (formerly CHAC gene) is located at chromosome locus 9q21, spanning a 250-kb region with at least 73 exons.10 This gene encodes the chorein protein, which is thought to have a role in the dynamic change of cellular structures.10 Choreoacanthocytosis occurs worldwide in individuals of different ethnic backgrounds, and various mutations in VPS13A cause the disorder.8 Inheritance is primarily autosomal recessive, but autosomal dominant inheritance has also been described.11 The clinical manifestations of CHAC develop between the third and fifth decades of life, primarily beginning with balancing problems and hyperkinetic choreic movements. Hypokinetic forms are infrequent and usually develop late in the course of the disease.3,12 In our patients, we documented the hyperkinetic form of CHAC. Cognitive changes occur in more than half of affected individuals and consist of depression, suicide ideation, obsessive-compulsive disorder, and symptoms of frontal lobe involvement. In the 2 cases described herein, the proband’s sister exhibited paranoid and schizophrenic behavior including isolation, coprolalia, and depression, as in Guilles de la Tourette syndrome.

The hematologic feature acanthocytosis in the context of neurologic abnormalities was first described by Estes et al13 in 1967. Acanthocytes can constitute from 5% to 50% of erythrocytes in a PBS from a patient with CHAC. This hematologic finding may appear late in the course of the disease, and the possibility of a positive result depends on the laboratory method used.14 Isotonically diluted blood can yield higher acanthocytes than standard dry blood smear preparations; thus, use of isotonically diluted erythrocytes combined with unfixed wet blood preparations would yield a normal level of less than 6.3% acanthocytes relative to total erythrocytes. This method is recommended in screening for serious acanthocytosis in movement disorders because it is inexpensive and easy to perform.14

Other nonspecific laboratory findings in CHAC include elevated plasma activity of creatine kinase and lactate dehydrogenase.3,15 Computed tomographic and magnetic resonance images can demonstrate atrophy of the caudate nuclei, and positron emission tomographic or single-photon emission computed tomographic images reveal hypoactivity of the basal ganglia and occasionally of the frontal cortex.16 The differential diagnosis of CHAC includes McLeod syndrome, abetalipoproteinemia, Hallervorden-Spatz syndrome, Wilson disease, Guilles de la Tourette syndrome, Huntington disease, Lesch-Nyhan syndrome, and dentatorubral and pallidolysian degeneration, among several other conditions.12 To date, there is no effective treatment of CHAC, and death usually occurs as a consequence of emaciation and prostration.

In conclusion, CHAC occurs worldwide, with variable clinical expression, even in individuals from the same family and, thus, sharing the same mutation of the VPS13A gene. Our observation suggests that complex gene-environment or gene-gene interactions may influence the phenotype of CHAC. Because PBS analysis is inexpensive and readily available, it can be performed serially in patients who are at risk of the disease; especially those with movement disorders and first-degree relatives having a confirmed diagnosis of CHAC.

Accepted for Publication: January 31, 2007.

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Financial Disclosure: None reported.

Additional Contributions: Lea A. Filippone, BA, assisted in mutation detection.

REFERENCES