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Choreoacanthocytosis

[*ChAc, Choreoacanthocytosis*]

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Summary

Disease characteristics. Choreoacanthocytosis (ChAc) is characterized by a progressive movement disorder, a myopathy that can be subclinical, cognitive and behavior changes, and acanthocytosis of the red blood cells. The movement disorder is mostly limb chorea, but some individuals present with a parkinsonian syndrome. Dystonia is common and affects the oral region and the tongue in particular, causing dysarthria and serious dysphagia with resultant

weight loss. Habitual tongue and lip biting are characteristic. Progressive cognitive and behavioral changes resemble those in a frontal lobe syndrome. Seizures are observed in almost half of affected individuals and can be the initial manifestation. Myopathy results in progressive distal muscle wasting and weakness. Mean age of onset in ChAc is about age 35 years, although ChAc can develop as early as the first decade or as late as the seventh decade. It runs a chronic progressive course and may lead to major disability within a few years. Life expectancy is reduced, with age of death ranging from 28 to 61 years.

Diagnosis/testing. The diagnosis of ChAc is based primarily on clinical findings, the presence of characteristic MRI findings, and evidence of muscle disease. CT and MRI reveal atrophy of the caudate nuclei with dilatation of the anterior horns of the lateral ventricles. MRI commonly shows T2-signal increase in the caudate and putamen. Acanthocytes are present in 5%-50% of the red cell population. In some cases, acanthocytosis may be absent or may appear only late in the course of the disease. Increased serum concentration of muscle creatine phosphokinase is observed in the majority of affected individuals. Muscle biopsy reveals central nuclei and atrophic fibers. *VPS13A,* encoding chorein, is the only gene currently known to be associated with ChAc. *VPS13A* molecular genetic testing and chorein detection are available on a research basis only.

Management. Treatment of ChAc may include: botulinum toxin for decreasing the oro-facio-bucco-lingual dystonia; feeding assistance; speech therapy; mechanical protective devices; splints for foot drop; phenytoin, clobazam, and valproate for seizure management; antidepressant or antipsychotic medications; dopamine antagonists such as atypical neuroleptics or tetrabenazine; and standard treatment for cardiomyopathy. Surveillance includes monitoring of nutritional status and adaptation of diet to assure adequate caloric intake, cardiac evaluations every five years, and EEG every third year.

Genetic counseling. ChAc is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Prenatal testing may be available through laboratories offering custom prenatal testing for families in which the disease-causing mutations have been identified in an affected family member.

Diagnosis

Clinical Diagnosis

Choreoacanthocytosis (ChAc) can be diagnosed with high certainty on clinical grounds alone; no formal criteria or obligatory findings have been established.

- The movement disorder is mostly chorea, but some individuals present with a parkinsonian syndrome. Dystonia is common and affects the oral region and the tongue in particular. Characteristic unintended tongue protrusion and habitual tongue and lip biting cause dysarthria and serious dysphagia with resultant weight loss. The movement disorder is progressive.
- Progressive cognitive and behavioral changes resemble a frontal lobe syndrome (i.e., loss of social inhibition and executive functions).
- Seizures, observed in almost half of affected individuals, can be the initial manifestation.
- The myopathy is progressive and characterized by distal muscle wasting and weakness, but may remain subclinical. Depression of deep tendon reflexes and vibration sense are common, resulting from an axonal neuropathy that contributes to

the observed amyotrophy. The pyramidal tracts are not involved and the plantar reflexes are flexor.

- Subtle eye movement abnormalities, e.g., impaired upgaze or slowed saccades, may be found. The retina is normal.

Neuroimaging. CT and MRI reveal atrophy of the caudate nuclei with dilatation of the anterior horns of the lateral ventricles [Okamoto et al 1997, Kutcher et al 1999, Sorrentino et al 1999, Gradstein et al 2005]. There may be slight generalized cerebral cortical atrophy. The extent of basal ganglia atrophy is best appreciated on sections in the frontal plane. MRI may show T2-signal increase in the caudate and putamen.

Muscle and liver enzymes. Increased serum concentration of muscle creatine phosphokinase is observed in the majority of individuals. Less commonly, the serum concentrations of LDH, AST, and ALT are increased.

Electrophysiologic tests demonstrate a sensory axonopathy with normal nerve conduction velocities and reduced sensory action potentials [Hardie et al 1991]. Electromyography commonly reveals neurogenic changes.

Testing

Acanthocytosis. Acanthocytes are found in the blood of individuals with ChAc in a highly variable proportion, usually 5%-50% of the red cell population. In some cases, acanthocytosis may be absent [Malandrini et al 1993] or may appear only late in the course of the disease [Sorrentino et al 1999]. The proportion of acanthocytes does not correlate with disease severity.

- Scanning electron microscopy of erythrocytes fixed with glutaraldehyde, probably the most reliable method of detecting acanthocytes, is not routinely available.
- A general standard for the determination of acanthocytosis has been proposed. Blood is diluted 1:1 with 0.9% saline and 10 U/mL heparin, and examined using phase-contrast microscopy after 30 minutes' incubation in a shaker. In normal samples, fewer than 6.3% of cells are spiculated [Storch et al 2005]. (Dry blood smears are often inadequate.)

Chorein detection. Western blot analysis revealed absence or marked reduction of chorein, the protein encoded by *VPS13A,* in cells from 14 individuals with ChAc. In contrast, normal levels of chorein were observed in samples from individuals with McLeod neuroacanthocytosis syndrome and Huntington disease, suggesting that loss of chorein expression is diagnostic of ChAc [Dobson-Stone et al 2004]. Such testing is available on a research basis only.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *VPS13A* is the only gene currently known to be associated with ChAc.

Molecular genetic testing: Research. Mutations are dispersed throughout the *VPS13A* gene and comprise missense, frameshift, nonsense, splice site and deletion mutations [Rampoldi et al 2001; Ueno et al 2001; Dobson-Stone et al 2002; Dobson-Stone et al 2004; Dobson-Stone et al 2005; Walker et al, in press]. The mutation detection rate is not known.

- A number of homozygous deletions spanning one or more *VPS13A* exons have been described; see Table 2 (pdf). It is conceivable that many individuals with ChAc could have heterozygous deletions [Dobson-Stone et al 2005] that are not detected using classic PCR-based DNA screening.
- Linkage-disequilibrium analysis demonstrated a founder effect in three Japanese probands with the same homozygous mutation [Ueno et al 2001] and a separate founder effect in five probands with French Canadian ancestry [Dobson-Stone et al 2005].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Choreocanthocytosis

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Direct DNA [1]	*VPS13A* mutations	Unknown	Research only

1. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with ChAc.

Testing Strategy for a Proband

- When clinical findings suggest the diagnosis of ChAc, the next step is to evaluate a peripheral blood smear for acanthocytosis, serum concentration of creatine phosphokinase, and liver enzymes.
- If these tests support the diagnosis of ChAc, McLeod neuroacanthocytosis syndrome (see Differential Diagnosis) should be excluded by detailed characterization of Kell antigen expression on red blood cells.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *VPS13A*.

Clinical Description

Natural History

Mean age of onset in choreoacanthocytosis (ChAc) is aboutage 35 years, although ChAc can develop as early as the first decade or as late as the seventh decade. It runs a chronic progressive course and may lead to major disability within a few years. Some affected individuals are bedridden or wheelchair dependent by the third decade [Aasly et al 1999]. Life expectancy is reduced and several instances of sudden, unexplained death, or during epileptic seizures have been reported. Age at death ranges from age 28 to 61 years.

Movement disorder. Limb chorea is the most common movement disorder in individuals with ChAc. Flinging arm and leg movements, shoulder shrugs, and pelvic thrusts are common. An unsteadiness of stance and gait, often with falls, seems to have choreiform as well as dystonic components. Ambulation may be severely impaired. Violent trunk spasms may occur with sudden flexion or extension movements, the latter causing head banging with a risk of head and neck injury. Impaired postural reflexes may result in falls, sudden buckling of knees, and equinovarus foot deformity, the latter related to dystonia as well as atrophy of the peroneal muscles.

Most characteristic of ChAc are the involuntary movements that affect face, mouth, tongue, pharynx, and larynx. Involuntary vocalizations (vocal tics) are present in about two-thirds of affected individuals [Saiki et al 2004]. A variety of vocalizations have been described. These may consist of clicking, gasping, sighing, whistling, blowing, sucking, grunting noises,

perseveration of word elements or phrases, and continuous humming. There may be habitual teeth grinding (bruxism), spitting, or involuntary belching [Wihl et al 2001, Sibon et al 2004]. Continuous tongue and lip biting can lead to mutilation, which affected individuals typically try to avoid by keeping an object such as a handkerchief between the teeth.

Swallowing is often impaired, resulting in dysphagia with reduced caloric intake and potentially severe weight loss. Uncontrolled dystonic tongue protrusions tend to push food out of the mouth. Abnormal swallowing causes drooling.

Dysarthria is common; slurred speech may be a presenting symptom. In the course of ChAc, communication may become limited to grunting or whispering, and individuals may become mute and dependent on computer-based speech aids [Aasly et al 1999].

As the hyperkinetic orofacial state progresses to mutism, the choreiform and dystonic syndrome gradually evolves into parkinsonism in about one-third of affected individuals. Muscle tone, rest tremor, impaired postural reflexes, bradykinesia, facial masking, and micrographia may increase. Parkinsonism can, in some cases, be the initial symptom of ChAc [Bostantjopoulou et al 2000].

In a few cases, ocular motor abnormalities have been noted, with apraxic difficulties of lid opening, intermittent blepharospasm, frequent square wave jerks, slowing of saccades (mainly vertical) and reduced saccadic range [Gradstein et al 2005].

Behavior changes. Changes in personality and behavior along with psychopathologic abnormalities occur in about two-thirds of affected individuals [Danek et al 2004]. Apathy, depression, and bradyphrenia (slowness of thought) can be seen, but hyperactivity, irritability, distractability, and emotional instability can also be observed. Individuals may behave in an immature or uninhibited manner that includes sexual disinhibition. They may show obsessive-compulsive behavior including trichotillomania [Lossos et al 2005] and self-inflicted chronic excoriations on the head [Walker et al, in press]. Loss of insight, self-neglect, anxiety, paranoia, aggression against others, and autoaggression are observed. Suicidal ideation as well as suicidal actions are part of the disease spectrum [Kartsounis & Hardie 1996, Sorrentino et al 1999].

Cognitive changes. Cognitive deterioration is common. Memory and executive functions, such as the ability to sustain concentration over time and to plan and to change behavior to reach a specific goal, seem particularly affected. These findings resemble those in the frontal lobe syndrome observed in frontotemporal dementia [Kartsounis & Hardie 1996, Danek et al 2004].

Seizures. Epilepsy is observed in almost half of affected individuals and can be the initial manifestation [Al-Asmi et al 2005]. It is usually manifested as grand mal seizures and is probably secondarily generalized, for example, from temporal lobe foci.

Neuropathy and myopathy. Nerve and muscle involvement cause ankle areflexia in almost all individuals and cause muscle atrophy and weakness in at least half. Sensory loss is usually slight or may only be detected as reduced vibration sense.

Cardiomyopathy. Cardiomyopathy, for example, of the dilated type [Kageyama et al 2000], may occur but is uncommon, in clear contrast to McLeod neuroacanthocytosis syndrome (see Differential Diagnosis) [Mohiddin & Fananapazir 2004].

Phenotypic variability. Phenotypic variability is considerable. For example, a woman in her thirties who had initially shown orofacial dyskinesia and instability of stance and gait became

mute and wheelchair dependent, while her brother also in his thirties had seizures and showed only a minor movement disorder [Aasly et al 1999].

Molecular genetic testing has identified VPS13A mutations [Dobson-Stone et al 2002] in individuals with the characteristic clinical picture but no apparent acanthocytosis [Johnson et al 1998].

Other clinical findings. A presumed connection with hypothalamic and other endocrine abnormalities [Terao et al 1995] needs confirmation.

Splenomegaly is occasionally noted and may be caused by erythrocyte dysfunction and hemolysis as shown by the reduced levels of hemoglobin and haptoglobin. Hepatomegaly may be present, along with elevated liver enzymes; the clinical significance is as yet unclear.

Autonomic nervous system dysfunction was described in one individual [Kihara et al 2002].

In a few individuals, sleep disturbance was demonstrated by polysomnography [Dolenc-Groselj et al 2004].

ChAc seems to be slightly more common in males.

Other studies

- **MR spectroscopy** has revealed abnormal proton spectra from the basal ganglia in two individuals with ChAc [Molina et al 1998].
- **Tracer imaging studies** of the type presently available in most major medical centers may support a suspicion of ChAc. Regional cerebral glucose metabolism can be measured using 18F-fluorodeoxy-glucose positron emission tomography (FDG-PET) and regional cerebral perfusion can be depicted with single photon emission computed tomography (SPECT with e.g. HMPAO or ECD). They show reduced tracer accumulation in the caudate nucleus and putamen [Milanez et al 2001] and occasionally in the thalamus and frontal cortex [Brooks et al 1991, Delecluse et al 1991]. The metabolic changes may precede gross atrophy or MRI signal change [Dubinsky et al 1989].
- **Imaging of dopaminergic transmission** has revealed reduced presynaptic dopamine storage capacity in posterior putamen and loss of postsynaptic D2-receptor binding in the striatum [Brooks et al 1991].
- **CT scanning of leg muscles** reveals a selective pattern of fatty change that (in contrast to McLeod neuroacanthocytosis syndrome) tends to be symmetric [Ishikawa et al 2000].
- **CSF studies,** when reported, have been normal.
- **EEG** may show temporal spikes, both interictally and with seizure onset [Tiftikcioglu et al 2006].
- **Peripheral nerve biopsy** shows loss of myelinated fibers, particularly those of larger diameter. Unmyelinated fibers may also be affected. Signs of regeneration are observed [Hardie et al 1991, Malandrini et al 1993, Sorrentino et al 1999].
- **Muscle biopsy** reveals central nuclei and atrophic fibers. Most changes on biopsy, however, support the predominance of neurogenic atrophy, with variation in muscle fiber diameter and occurrence of small angulated fibers [Alonso et al 1989]. "Nemaline" rods in muscle have been reported, although their exact composition is unknown [Tamura et al 2005].

Neuropathology. On autopsy, the cerebral cortex appears unaffected [Hardie et al 1991]. There is macroscopic bilateral atrophy of the caudate nucleus, the putamen, and the globus pallidus, corresponding to histologic loss of neurons and gliosis, which is particularly severe in the caudate and less so in the putamen and the external and internal pallidum [Vital et al 2002]. Pronounced neuronal loss in the substantia nigra is the likely correlate of parkinsonism. Gliosis and extraneuronal pigment, but no Lewy bodies, are observed in the substantia nigra. The locus coeruleus, inferior olives, and cerebellum appear unaffected. Loss of spinal cord anterior horn cells, a correlate of neurogenic muscle atrophy, is only seen in some of the autopsies of individuals with ChAc. Gliosis may also occur in the thalamus.

Glutamic acid decarboxylase (GAD) and choline acetyltransferase levels were reported to be normal in caudate nucleus and putamen; GAD was increased in substantia nigra in the absence of neuronal loss. Substance P and dopamine metabolites were reduced in the brains of individuals with ChAc [De Yebenes et al 1988, Galatioto et al 1993].

Genotype-Phenotype Correlations

Presently available data are inconclusive with regard to genotype-phenotype correlation in ChAc.

Nomenclature

The term "neuroacanthocytosis" is nonspecific and may refer to any disorder with neurologic abnormalities and acanthocytosis, including McLeod neuroacanthocytosis syndrome, abetalipoproteinemia (Bassen-Kornzweig syndrome), or hypobetalipoproteinemia.

The term "Levine-Critchley syndrome" should no longer be used since no recent evaluations have been performed in the two kindreds initially reported by Critchley et al (1967) and Levine et al (1968). The family reported by Levine et al (1968) in particular had atypical features.

Other outdated terms include 'chorea-amyotrophy-acanthocytosis syndrome' and 'familial amyotrophic chorea with acanthocytosis'.

Prevalence

The number of individuals with ChAc known worldwide is estimated at 500-1000. Reports have come from practically all ethnic backgrounds.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Because of the protean manifestations of cnoreoacanthocytosis (ChAc), a wide range of disorders needs to be considered in the differential diagnosis, including the general categories of parkinsonian syndromes, choreiform and other movement disorders, seizure disorders, and neuromuscular disorders [Danek et al 2005]

McLeod neuroacanthocytosis syndrome (MLS) is a multisystem disorder with central nervous system (CNS), neuromuscular, and hematologic manifestations in males that overlap considerably with those seen in ChAc [Danek et al 2001]. CNS manifestations are a neurodegenerative basal ganglia disease including 1) movement disorder, 2) cognitive impairment, and 3) psychiatric symptoms. Neuromuscular manifestations include a mostly subclinical sensorimotor axonopathy, muscle weakness, and atrophy. The hematologic manifestations are red blood cell acanthocytosis, compensated hemolysis, and the McLeod blood group phenotype resulting from absent expression of the Kx erythrocyte antigen and

reduced expression of the Kell blood group antigens. This latter finding distinguishes MLS from ChAc, in which Kell blood group antigen expression is normal. Heterozygous females have mosaicism for the Kell blood group antigens and RBC acanthocytosis but only rarely have CNS and neuromuscular manifestations. Mutations in the *XK* gene are causative. Inheritance is X-linked.

Abetalipoproteinemia (ABL) and hypobetalipoproteinemia (HBL) share acanthocytosis with ChAc and McLeod neuroacanthocytosis syndrome, as well as the presence of dysarthria, neuropathy, and areflexia, but differ in their hallmark findings of pigmentary retinopathy, vitamin E deficiency, steatorrhea, and lack of basal ganglia movement disorder. ABL and HBL are caused by mutations in the genes encoding the microsomal triglyceride transfer protein and apolipoprotein B, respectively. ABL is inherited in an autosomal recessive manner. HBL has clinical manifestations in both the homozygous and heterozygous states. The neurologic findings include the following [Kane & Havel 1995]:

- A progressive spinocerebellar degeneration
- A demyelinating sensorimotor and axonal peripheral neuropathy with hyporeflexia, diminished vibration and position sense, ataxia of gait, dysmetria, and dysarthria
- Rarely, pyramidal tract signs
- Rarely, cranial nerve involvement

Pantothenate kinase-associated neurodegeneration (PKAN) (formerly Hallervorden-Spatz syndrome) is characterized by progressive dystonia and basal ganglia iron deposition with onset usually before age ten years. Commonly associated features include dysarthria, rigidity, and pigmentary retinopathy. About 25% of individuals have an "atypical" presentation with onset after age ten years, prominent speech defects, psychiatric disturbances, and more gradual progression of disease. Acanthocytes are often seen in PKAN [Hayflick et al 2003, Pellecchia et al 2005]. "**HARP syndrome**" (**h**ypoprebetalipoproteinemia, **a**canthocytosis, **r**etinitis pigmentosa, and **p**allidal degeneration) is allelic with PKAN [Ching et al 2002, Houlden et al 2003].

The 'eye of the tiger' is a characteristic MRI finding identified on transverse images of the globus pallidus as a central region of hyperintensity surrounded by a rim of hypointensity. In greater than 98% of individuals with neurodegeneration with brain iron accumulation and the 'eye of the tiger' sign on MRI at least on *PANK2* mutation is identified. Inheritance is autosomal recessive manner.

Tourette syndrome is often diagnosed during initial stages of ChAc [Saiki et al 2004]. Its picture of motor and vocal tics, obsessive-compulsive behavior, and impaired impulse control can be similar to part of the ChAc spectrum.

Lesch-Nyhan syndrome, an X-linked recessive disorder caused by decreased activity of the enzyme hypoxanthine guanine phosphoribosyl transferase (HPRT), is characterized by neurologic dysfunction, cognitive and behavioral disturbances, and uric acid overproduction (hyperuricemia). The most common presenting features are hypotonia and developmental delay, which are evident by age three to six months. Affected individuals are delayed in sitting; most never walk. Within the first few years, extrapyramidal involvement (e.g., dystonia, choreoathetosis, opisthotonus) and pyramidal involvement (e.g., spasticity, hyperreflexia, and extensor plantar reflexes) become evident. Persistent self-injurious behavior (biting the fingers, hands, lips, and cheeks; banging the head or limbs) is a hallmark of the disease.

HPRT enzyme activity that is less than 1.5% normal in cells from any tissue (e.g., blood, cultured fibroblasts, or lymphoblasts) establishes the diagnosis of Lesch-Nyhan syndrome. Clinical testing of the *HPRT1* gene is available.

Wilson disease. Individuals who present with neuropsychiatric disease and elevated liver enzymes should be evaluated for Wilson disease, in addition to neuroacanthocytosis syndromes. Wilson disease is a disorder of copper metabolism that can present from age three years to over 50 years. The liver disease includes recurrent jaundice, simple acute self-limited hepatitis-like illness, autoimmune-type hepatitis, fulminant hepatic failure, and chronic liver disease. Neurologic presentations include movement disorders (tremors, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar involvement). Psychiatric disturbance includes depression, neurotic behaviors, disorganization of personality and, occasionally, intellectual deterioration. Treatment with copper chelating agents or zinc can prevent the development of hepatic, neurologic, and psychiatric findings in asymptomatic affected individuals and can reduce findings in many symptomatic individuals.

Diagnosis depends upon the detection of low serum copper and ceruloplasmin concentrations and increased urinary copper excretion. Molecular genetic testing of the *ATP7B* gene is clinically available. Inheritance is autosomal recessive [Gow et al 2000].

Huntington disease (HD) is a progressive disorder of motor, cognitive, and psychiatric disturbances. In addition to the almost identical choreiform movement disorder and imaging findings of HD and ChAc, the changes in personality and behavior are similar [Kutcher et al 1999]. Seizures are much more common in ChAc than in HD. Increased serum concentrations of CK [Sakai et al 1981] or liver enzymes are usually not seen in HD. The mean age of onset of HD is age 35 to 44 years; the median survival time is 15 to 18 years after onset. Neuropathology in HD is more widespread and (in contrast to ChAc) also involves the cerebral cortex [Vonsattel & DiFiglia 1998]. The diagnosis of HD rests on the detection of an expansion of a CAG/polyglutamine tract in the *HD* gene. HD shows autosomal dominant inheritance and anticipation, i.e., earlier disease onset in subsequent generations.

Huntington disease-like 2 (HDL2) typically presents in midlife with a picture similar to ChAc and HD, with a relentlessly progressive triad of movement, emotional, and cognitive abnormalities progressing to death over ten to 20 years [Margolis et al 2004]. *JPH3* is the only gene known to be associated with HDL2 [Holmes et al 2001]. In the presence of a clinical syndrome consistent with HDL2, 41 or more CTG trinucleotide repeats in *JPH3* is considered diagnostic of HDL2. HDL2 is inherited in an autosomal dominant manner; to date, it has only been reported in individuals of African ancestry. Acanthocytosis is found in a few individuals with HDL2 [Walker et al 2003].

Other disorders. Several other rare genetic movement disorders may be confused with ChAc. These include dentatorubral-pallidoluysian atrophy (DRPLA), benign hereditary chorea, and other disorders that may mimic HD [Ross et al 1997, Xiang et al 1998, Kambouris et al 2000, Curtis et al 2001, Fernandez et al 2001, Richfield et al 2002, Xu et al 2004].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- **Swallowing assessment**
- **Cardiac evaluation** for possible cardiomyopathy

- **Electroencephalography** to allow for early detection of signs indicating an increased risk for epileptic seizures and consideration of use of antiepileptic drugs
- **Neuropsychologic assessment** to identify and address possible psychosocial complications
- **Electromyography and nerve conduction testing** to document the extent of neuromuscular disease
- **Physical therapy evaluation** to identify and address areas of possible benefit

Treatment of Manifestations

Botulinum toxin may be helpful in increasing the oro-facio-bucco-lingual dystonia that interferes with eating.

Assistance with feeding is often necessary to prevent aspiration [Aasly et al 1999].

With progression to mutism, evaluation for computer-assisted speech systems is appropriate [Aasly et al 1999].

Mechanical protective devices may be needed for complications such as teeth grinding, head banging, and repeated falls.

Splints can be tried for foot drop. Since the equinovarus deformity has a dystonic component, local injections of botulinum toxin have been used.

Phenytoin, clobazam, and valproate are reported to be effective for seizure control management.

Psychiatric medications such as antidepressant or antipsychotic medications are based on conventional approaches.

The pharmacologic approach with dopamine antagonists such as atypical neuroleptics or tetrabenazine as used for chorea or Tourette syndrome should also be offered, although affected individuals should be carefully monitored for side effects of parkinsonism and depression [Borchardt et al 2000].

Treatment of cardiomyopathy is standard.

Prevention of Secondary Complications

- Fall prevention
- Keeping an object such as a handkerchief in the mouth to diminish damage to lips and tongue from involuntary biting

Surveillance

- Monitoring of nutritional status and adaptation of diet to assure adequate caloric intake
- Cardiac evaluation approximately every fifth year
- EEG approximately every third year

Agents/Circumstances to Avoid

- Seizure-provoking circumstances (e.g., sleep deprivation, alcohol intake)

- Anticonvulsants that may worsen involuntary movements (e.g., carbamazepine, lamotrigine)

Therapies Under Investigation

Neurosurgical approaches have been reported in single anecdotal cases:

- **Ablative procedures.** Staged bilateral posteroventral pallidotomy supposedly improved feeding in one affected individual [Fujimoto et al 1997]. The outcome was not reported for unilateral ventral lateral thalamic coagulation and alternative ablative procedures [Cavalli et al 1995].
- **Deep brain stimulation.** Stimulation of the internal globus pallidus was judged ineffective [Wihl et al 2001] whereas bilateral thalamic stimulation successfully reduced incapacitating trunk spasms, re-established ambulation, and improved feeding in one affected individual [Burbaud et al 2002].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

The atypical dopamine antagonist clozapine was at least temporarily effective in a single observation [Wihl et al 2001].

The antiepileptic drug levetiracetam was effective in eliminating trunk jerks, blinking, and head nodding in a single case [Lin et al 2006].

Dopamine decreased dystonia in one individual but was ineffective in his sister [Kobal, personal communication].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Choreoacanthocytosis (ChAc) is inherited in an autosomal recessive manner.

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- The unaffected parents are obligate carriers (heterozygotes) and have an alteration in one copy of the *VPS13A* gene.
- Consanguinity of affected individuals' parents has been noted in a number of reports [Sorrentino et al 1999, Bohlega et al 2003, Al-Asmi et al 2005].
- Current knowledge indicates that carriers are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- The offspring of an individual with ChAc are obligate heterozygotes (carriers) for a disease-causing mutation in the *VPS13A* gene.
- The risk that a child will inherit a second disease-causing *VPS13A* allele depends upon the other parent's carrier status.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing using molecular genetic techniques is not offered because it is not clinically available.

Related Genetic Counseling Issues

Possible autosomal dominant ChAc. Some families with a clinical syndrome compatible with ChAc and apparent autosomal dominant transmission have been reported. It is not known if these disorders are linked to the *VPS13A* locus [Levine et al 1968, Marson et al 2003].

- Saiki et al (2003) identified a novel mutation in the last nucleotide of exon 57 of the *VPS13A* gene in affected sibs in a family with apparent autosomal dominant ChAc. However, definite conclusions about mode of inheritance could not be made, as DNA was not available from the presumptively affected father.
- Pseudodominant inheritance of ChAc was observed in a family in which the affected mother was homozygous for a *VPS13A* mutation [Bohlega et al 2003 (family 1)].

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and disease will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See DNA banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of choreoacanthocytosis are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Note: It is the policy of *GeneReviews* to include information on prenatal testing and preimplantation genetic diagnosis available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of their use by the author(s), editor(s), or reviewer(s).

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Choreoacanthocytosis

Gene Symbol	Chromosomal Locus	Protein Name
VPS13A	9q21	Vacuolar protein sorting 13A

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Choreoacanthocytosis

200150	CHOREOACANTHOCYTOSIS; CHAC
605978	VACUOLAR PROTEIN SORTING 13, YEAST, HOMOLOG OF, A; VPS13A

Table C. Genomic Databases for Choreoacanthocytosis

Gene Symbol	Entrez Gene	HGMD
VPS13A	23230 (MIM No. 605978)	VPS13A

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

The original gene symbol, *CHAC*, was changed to *VPS13A* to acknowledge its similarity with *VPS13/SOI1* in yeast. Three other human genes belong to the same family: *VPS13B*, *VPS13C*, and *VPS13D*, on chromosomes 8q22, 15q21, and 1p36 respectively [Velayos-Baeza et al 2004]. *VPS13B* (*COH1)* is altered in individuals with Cohen syndrome (OMIM 216550), a rare autosomal recessive disorder characterized by non-progressive psychomotor retardation and microcephaly, retinal dystrophy, and characteristic facial features [Kolehmainen et al 2003]; no human disorders have yet been associated with the *VPS13C* or *VPS13D* genes. All four human *VPS13* genes have multiple splicing variants.

Little is known about the function of chorein. Amino acid sequence analysis failed to identify conserved domains, motifs, or identifiable structural features [Rampoldi et al 2001]. Vps13, chorein's yeast homologue, is required for proper intracellular trafficking of certain trans-Golgi network (TGN) proteins [Brickner & Fuller et al 1997]. It is reasonable to hypothesize a role

for chorein similar to that of its yeast counterpart. Indeed, chorein may control one or more steps in the cycling of proteins through the TGN to early and late endosomes, lysosomes, and the plasma membrane. Functional experiments are required to assess chorein's biologic function in mammalian systems.

A mouse model of choreoacanthocytosis (ChAc) has been developed. Mice with a deletion of *VPS13A* exons 60 and 61 show acanthocytosis and late-onset motor disturbance (gait disturbance and early fall from the rotarod, but no involuntary movements). This contrasts with humans, who typically present with chorea as the major motor symptom. Brain pathology indicated apoptotic cells in the striatum. Levels of homovanillic acid, a dopamine metabolite, were reduced in the midbrain [Tomemori et al 2005].

Normal allelic variants: The *VPS13A* gene is organized in 74 exons over a chromosomal region of about 240 kb. Several splicing variants are known, variant A (exons 1-68, 70-73) being the main expressed form. Alteration/absence of variant A-encoded chorein is sufficient to cause ChAc [Dobson-Stone et al 2002]. At least two other 3'-end alternative splicing forms are expressed: variant B (exons 1-68, 69) and variant D (1-68, 68b); the approximate sizes of these three mRNA forms are 11.2 (variant A), 10 (B) and 9.6 (D) kb. Other splicing variants, probably minor forms, have also been detected [Velayos-Baeza et al 2004].

Pathologic allelic variants: Table 2 (pdf) shows the mutations in *VPS13A*.

Normal gene product: Variant A encodes a 3174-amino acid protein. Variants B and D would encode 3095- and 3069-amino acid proteins, respectively.

Abnormal gene product: Most mutations in ChAc are predicted to lead to absence of chorein. The basic defect of the acanthocytic membrane has not yet been determined [Terada et al 1999]. Melone et al (2002) found increased levels of tissue transglutaminase, a cross-linking enzyme involved in assembly of macromolecular structures in two individuals with clinically diagnosed ChAc. The authors suggested that increased cross-linking activity could cause cellular membrane distortions. Such distortions in muscle cells and erythrocytes could lead, respectively, to the increase in serum creatine kinase and the acanthocytosis observed in ChAc.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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Email: glenn@naadvocacy.org
www.naadvocacy.org

Huntington's Disease Society of America (HDSA)
HDSA has material on their site to assist in caretaking issues for adult onset progressive neurologic diseases
www.hdsa.org

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org
www.wemove.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Aasly J, Skandsen T, Ro M. Neuroacanthocytosis--the variability of presenting symptoms in two siblings. Acta Neurol Scand. 1999;100:322–5. [PubMed: 10536920]

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. [PubMed: 16060937]

Alonso ME, Teixeira F, Jimenez G, Escobar A. Chorea-acanthocytosis: report of a family and neuropathological study of two cases. Can J Neurol Sci. 1989;16:426–31. [PubMed: 2804805]

Bohlega S, Al-Jishi A, Dobson-Stone C, Rampoldi L, Saha P, Murad H, Kareem A, Roberts G, Monaco AP. Chorea-acanthocytosis: clinical and genetic findings in three families from the Arabian peninsula. Mov Disord. 2003;18:403–7. [PubMed: 12671946]

Borchardt CM, Jensen C, Dean CE, Tori J. Case study: childhood-onset tardive dyskinesia versus choreoacanthocytosis. J Am Acad Child Adolesc Psychiatry. 2000;39:1055–8. [PubMed: 10939235]

Bostantjopoulou S, Katsarou Z, Kazis A, Vadikolia C. Neuroacanthocytosis presenting as parkinsonism. Mov Disord. 2000;15:1271–3. [PubMed: 11104222]

Brickner JH, Fuller RS. SOI1 encodes a novel, conserved protein that promotes TGN-endosomal cycling of Kex2p and other membrane proteins by modulating the function of two TGN localization signals. J Cell Biol. 1997;139:23–36. [PubMed: 9314526]

Brooks DJ, Ibanez V, Playford ED, Sawle GV, Leigh PN, Kocen RS, Harding AE, Marsden CD. Presynaptic and postsynaptic striatal dopaminergic function in neuroacanthocytosis: a positron emission tomographic study. Ann Neurol. 1991;30:166–71. [PubMed: 1897909]

Burbaud P, Rougier A, Ferrer X, Guehl D, Cuny E, Arne P, Gross Ch, Bioulac B. Improvement of severe trunk spasms by bilateral high-frequency stimulation of the motor thalamus in a patient with chorea-acanthocytosis. Mov Disord. 2002;17:204–7. [PubMed: 11835468]

Cavalli G, de Gregorio C, Nicosia S, Melluso C, Serra S. [Cardiac involvement in familial amytrophic chorea with acantocytosis: description of two new clinical cases] Ann Ital Med Int. 1995;10:249–52. [PubMed: 8718661]

Ching KH, Westaway SK, Gitschier J, Higgins JJ, Hayflick SJ. HARP syndrome is allelic with pantothenate kinase-associated neurodegeneration. Neurology. 2002;58:1673–4. [PubMed: 12058097]

Critchley EM, Clark DB, Wikler A. An adult form of acanthocytosis. Trans Am Neurol Assoc. 1967;92:132–7. [PubMed: 4255726]

Curtis AR, Fey C, Morris CM, Bindoff LA, Ince PG, Chinnery PF, Coulthard A, Jackson MJ, Jackson AP, McHale DP, Hay D, Barker WA, Markham AF, Bates D, Curtis A, Burn J. Mutation in the gene encoding ferritin light polypeptide causes dominant adult-onset basal ganglia disease. Nat Genet. 2001;28:350–4. [PubMed: 11438811]

Danek A, Jung HH, Melone MA, Rampoldi L, Broccoli V, Walker RH. Neuroacanthocytosis: new developments in a neglected group of dementing disorders. J Neurol Sci. 2005;229-230:171–86. [PubMed: 15760637]

Danek A, Rubio JP, Rampoldi L, Ho M, Dobson-Stone C, Tison F, Symmans WA, Oechsner M, Kalckreuth W, Watt JM, Corbett AJ, Hamdalla HH, Marshall AG, Sutton I, Dotti MT, Malandrini A, Walker RH, Daniels G, Monaco AP. McLeod neuroacanthocytosis: genotype and phenotype. Ann Neurol. 2001;50:755–64. [PubMed: 11761473]

Danek A, Sheesley L, Tierney M, Uttner I, Grafman J. Cognitive and neuropsychiatric findings in McLeod syndrome and in chorea-acanthocytosis. In: Danek A (ed) Neuroacanthocytosis Syndromes. Springer, Dordrecht, The Netherlands, pp 95-115. 2004

de Yebenes JG, Brin MF, Mena MA, De Felipe C, del Rio RM, Bazan E, Martinez A, Fahn S, Del Rio J, Vazquez A, et al. Neurochemical findings in neuroacanthocytosis. Mov Disord. 1988;3:300–12. [PubMed: 2905427]

Delecluse F, Deleval J, Gerard JM, Michotte A, Zegers de Beyl D. Frontal impairment and hypoperfusion in neuroacanthocytosis. Arch Neurol. 1991;48:232–4. [PubMed: 1993017]

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, Dupre N, Rouleau GA, Volkmann J, Arpa J, Lees A, Geraud G, Chouinard S, Nemeth A, Monaco AP. Mutational spectrum of the CHAC gene in patients with chorea-acanthocytosis. Eur J Hum Genet. 2002;10:773–81. [PubMed: 12404112]

Dobson-Stone C, Velayos-Baeza A, Filippone LA, Westbury S, Storch A, Erdmann T, Wroe SJ, Leenders KL, Lang AE, Dotti MT, Federico A, Mohiddin SA, Fananapazir L, Daniels G, Danek A, Monaco AP. Chorein detection for the diagnosis of chorea-acanthocytosis. Ann Neurol. 2004;56:299–302. [PubMed: 15293285]

Dobson-Stone C, Velayos-Baeza A, Jansen A, Andermann F, Dubeau F, Robert F, Summers A, Lang AE, Chouinard S, Danek A, Andermann E, Monaco AP. Identification of a VPS13A founder mutation in French Canadian families with chorea-acanthocytosis. Neurogenetics. 2005;6:151–8. [PubMed: 15918062]

Dolenc-Groselj L, Jazbec J, Kobal J. Sleep features in chorea-acanthocytosis. In: Danek A (ed) Neuroacanthocytosis Syndromes. Springer, Dordrecht, The Netherlands, pp 123-5. 2004

Dubinsky RM, Hallett M, Levey R, Di Chiro G. Regional brain glucose metabolism in neuroacanthocytosis. Neurology. 1989;39:1253–5. [PubMed: 2788833]

Fernandez M, Raskind W, Matsushita M, Wolff J, Lipe H, Bird T. Hereditary benign chorea: clinical and genetic features of a distinct disease. Neurology. 2001;57:106–10. [PubMed: 11445636]

Fujimoto Y, Isozaki E, Yokochi F, Yamakawa K, Takahashi H, Hirai S. A case of chorea-acanthocytosis successfully treated with posteroventral pallidotomy. Rinsho Shinkeigaku. 1997;37:891–4. [PubMed: 9490899]

Galatioto S, Serra S, Batolo D, Marafioti T. Amyotrophic choreo-acanthocytosis: a neuropathological and immunocytochemical study. Ital J Neurol Sci. 1993;14:49–54. [PubMed: 8473152]

Gow PJ, Smallwood RA, Angus PW, Smith AL, Wall AJ, Sewell RB. Diagnosis of Wilson's disease: an experience over three decades. Gut. 2000;46:415–9. [PubMed: 10673307]

Gradstein L, Danek A, Grafman J, Fitzgibbon EJ. Eye movements in chorea-acanthocytosis. Invest Ophthalmol Vis Sci. 2005;46:1979–87. [PubMed: 15914612]

Hardie RJ, Pullon HW, Harding AE, Owen JS, Pires M, Daniels GL, Imai Y, Misra VP, King RH, Jacobs JM, et al. Neuroacanthocytosis. A clinical, haematological and pathological study of 19 cases. Brain 114 (Pt. 1991;1A):13–49. [PubMed: 1998879]

Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, Gitschier J. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. N Engl J Med. 2003;348:33–40. [PubMed: 12510040]

Holmes SE, O'Hearn E, Rosenblatt A, Callahan C, Hwang HS, Ingersoll-Ashworth RG, Fleisher A, Stevanin G, Brice A, Potter NT, Ross CA, Margolis RL. A repeat expansion in the gene encoding

junctophilin-3 is associated with Huntington disease-like 2. Nat Genet. 2001;29:377–8. [PubMed: 11694876]

Houlden H, Lincoln S, Farrer M, Cleland PG, Hardy J, Orrell RW. Compound heterozygous PANK2 mutations confirm HARP and Hallervorden-Spatz syndromes are allelic. Neurology. 2003;61:1423–6. [PubMed: 14638969]

Ishikawa S, Tachibana N, Tabata KI, Fujimori N, Hayashi RI, Takahashi J, Ikeda SI, Hanyu N. Muscle CT scan findings in McLeod syndrome and chorea-acanthocytosis. Muscle Nerve. 2000;23:1113–6. [PubMed: 10883007]

Johnson SE, Dahl A, Sjaastad O. Progressive pseudobulbar paresis, early choreiform movements, and later rigidity: appearance in two sets of dizygotic twins in the same family. Mov Disord. 1998;13:556–62. [PubMed: 9613754]

Kageyama Y, Kodama Y, Tadano M, Yamamoto S, Ichikawa K. A case of chorea-acanthocytosis with dilated cardiomyopathy and myopathy. Rinsho Shinkeigaku. 2000;40:816–20. [PubMed: 11218703]

Kambouris M, Bohlega S, Al-Tahan A, Meyer BF. Localization of the gene for a novel autosomal recessive neurodegenerative Huntington-like disorder to 4p15.3. Am J Hum Genet. 2000;66:445–52. [PubMed: 10677304]

Kane J, Havel RJ. Disorder of the biogenesis and secretion of lipoprotein containing the B apolipoproteins. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The Metabolic and Molecular Bases of Inherited Disease, Vol. 2. McGraw-Hill, New York, pp 1853-85. 1995

Kartsounis LD, Hardie RJ. The pattern of cognitive impairments in neuroacanthocytosis. A frontosubcortical dementia. Arch Neurol. 1996;53:77–80. [PubMed: 8599563]

Kihara M, Nakashima H, Taki M, Takahashi M, Kawamura Y. A case of chorea-acanthocytosis with dysautonomia; quantitative autonomic deficits using CASS. Auton Neurosci. 2002;97:42–4. [PubMed: 12036185]

Kolehmainen J, Black GC, Saarinen A, Chandler K, Clayton-Smith J, Traskelin AL, Perveen R, Kivitie-Kallio S, Norio R, Warburg M, Fryns JP, de la Chapelle A, Lehesjoki AE. Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport. Am J Hum Genet. 2003;72:1359–69. [PubMed: 12730828]

Kutcher JS, Kahn MJ, Andersson HC, Foundas AL. Neuroacanthocytosis masquerading as Huntington's disease: CT/MRI findings. J Neuroimaging. 1999;9:187–9. [PubMed: 10436764]

Levine IM, Estes JW, Looney JM. Hereditary neurological disease with acanthocytosis. A new syndrome. Arch Neurol. 1968;19:403–9. [PubMed: 5677189]

Lin FC, Wei LJ, Shih PY. Effect of levetiracetam on truncal tic in neuroacanthocytosis. Acta Neurol Taiwan. 2006;15:38–42. [PubMed: 16599284]

Lossos A, Dobson-Stone C, Monaco AP, Soffer D, Rahamim E, Newman JP, Mohiddin S, Fananapazir L, Lerer I, Linetsky E, Reches A, Argov Z, Abramsky O, Gadoth N, Sadeh M, Gomori JM, Boher M, Meiner V. Early clinical heterogeneity in choreoacanthocytosis. Arch Neurol. 2005;62:611–4. [PubMed: 15824261]

Malandrini A, Fabrizi GM, Palmeri S, Ciacci G, Salvadori C, Berti G, Bucalossi A, Federico A, Guazzi GC. Choreo-acanthocytosis like phenotype without acanthocytes: clinicopathological case report. A contribution to the knowledge of the functional pathology of the caudate nucleus. Acta Neuropathol (Berl). 1993;86:651–8. [PubMed: 8310821]

Margolis RL, Holmes SE, Rosenblatt A, Gourley L, O'Hearn E, Ross CA, Seltzer WK, Walker RH, Ashizawa T, Rasmussen A, Hayden M, Almqvist EW, Harris J, Fahn S, MacDonald ME, Mysore J, Shimohata T, Tsuji S, Potter N, Nakaso K, Adachi Y, Nakashima K, Bird T, Krause A, Greenstein P. Huntington's Disease-like 2 (HDL2) in North America and Japan. Ann Neurol. 2004;56:670–4. [PubMed: 15468075]

Marson AM, Bucciantini E, Gentile E, Geda C. Neuroacanthocytosis: clinical, radiological, and neurophysiological findings in an Italian family. Neurol Sci. 2003;24:188–9. [PubMed: 14598080]

Melone MA, Di Fede G, Peluso G, Lus G, Di Iorio G, Sampaolo S, Capasso A, Gentile V, Cotrufo R. Abnormal accumulation of tTGase products in muscle and erythrocytes of chorea-acanthocytosis patients. J Neuropathol Exp Neurol. 2002;61:841–8. [PubMed: 12387450]

Milanez T, Kobal J, Grmek M, Fettich J. 99mTc HMPAO brain perfusion in family with chorea-acanthocytosis. Eur J Nuc Med. 2001;28:1242.

Mohiddin SA, Fananapazir L. Cardiac involvement in the neuroacanthocytosis syndromes. In: Danek A (ed) Neuroacanthocytosis Syndromes. Springer, Dordrecht, The Netherlands, pp 139-52. 2004

Molina JA, Garcia-Segura JM, Benito-Leon J, et al. In vivo proton magnetic resonance spectroscopy in patients with neuroacanthocytosis. Parkinsonism and Related Disorders. 1998;4:11–15.

Okamoto K, Ito J, Furusawa T, Sakai K, Tokiguchi S, Homma A, Koike R, Tsuji S. CT and MR findings of neuroacanthocytosis. J Comput Assist Tomogr. 1997;21:221–2. [PubMed: 9071289]

Pellecchia MT, Valente EM, Cif L, Salvi S, Albanese A, Scarano V, Bonuccelli U, Bentivoglio AR, D'Amico A, Marelli C, Di Giorgio A, Coubes P, Barone P, Dallapiccola B. The diverse phenotype and genotype of pantothenate kinase-associated neurodegeneration. Neurology. 2005;64:1810–2. [PubMed: 15911822]

Rampoldi L, Dobson-Stone C, Rubio JP, Danek A, Chalmers RM, Wood NW, Verellen C, Ferrer X, Malandrini A, Fabrizi GM, Brown R, Vance J, Pericak-Vance M, Rudolf G, Carre S, Alonso E, Manfredi M, Nemeth AH, Monaco AP. A conserved sorting-associated protein is mutant in chorea-acanthocytosis. Nat Genet. 2001;28:119–20. [PubMed: 11381253]

Richfield EK, Vonsattel JP, MacDonald ME, Sun Z, Deng YP, Reiner A. Selective loss of striatal preprotachykinin neurons in a phenocopy of Huntington's disease. Mov Disord. 2002;17:327–32. [PubMed: 11921119]

Ross CA, Margolis RL, Rosenblatt A, Ranen NG, Becher MW, Aylward E. Huntington disease and the related disorder, dentatorubral-pallidoluysian atrophy (DRPLA). Medicine (Baltimore). 1997;76:305–38. [PubMed: 9352736]

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. [PubMed: 15254946]

Saiki S, Sakai K, Kitagawa Y, Saiki M, Kataoka S, Hirose G. Mutation in the CHAC gene in a family of autosomal dominant chorea-acanthocytosis. Neurology. 2003;61:1614–6. [PubMed: 14663054]

Sakai T, Mawatari S, Iwashita H, Goto I, Kuroiwa Y. Choreoacanthocytosis. Clues to clinical diagnosis. Arch Neurol. 1981;38:335–8. [PubMed: 6453575]

Sibon I, Ghorayeb I, Arne P, Tison F. Distressing belching and neuroacanthocytosis. Mov Disord. 2004;19:856–9. [PubMed: 15254955]

Sorrentino G, De Renzo A, Miniello S, Nori O, Bonavita V. Late appearance of acanthocytes during the course of chorea-acanthocytosis. J Neurol Sci. 1999;163:175–8. [PubMed: 10371080]

Storch A, Kornhass M, Schwarz J. Testing for acanthocytosis A prospective reader-blinded study in movement disorder patients. J Neurol. 2005;252:84–90. [PubMed: 15654559]

Tamura Y, Matsui K, Yaguchi H, Hashimoto M, Inoue K. Nemaline rods in chorea-acanthocytosis. Muscle Nerve. 2005;31:516–9. [PubMed: 15660376]

Terada N, Fujii Y, Ueda H, Kato Y, Baba T, Hayashi R, Ohno S. Ultrastructural changes of erythrocyte membrane skeletons in chorea- acanthocytosis and McLeod syndrome revealed by the quick-freezing and deep-etching method. Acta Haematol. 1999;101:25–31. [PubMed: 10085435]

Terao S, Sobue G, Takahashi M, Miura N, Mitsuma T, Takeda A, Sakakibara T. Disturbance of hypothalamic-pituitary hormone secretion in familial chorea-acanthocytosis. No To Shinkei. 1995;47:57–61. [PubMed: 7669403]

Tiftikcioglu BI, Dericioglu N, Saygi S. Focal seizures originating from the left temporal lobe in a case with chorea-acanthocytosis. Clin EEG Neurosci. 2006;37:46–9. [PubMed: 16475485]

Tomemori Y, Ichiba M, Kusumoto A, Mizuno E, Sato D, Muroya S, Nakamura M, Kawaguchi H, Yoshida H, Ueno S, Nakao K, Nakamura K, Aiba A, Katsuki M, Sano A. A gene-targeted mouse model for chorea-acanthocytosis. J Neurochem. 2005;92:759–66. [PubMed: 15686477]

Ueno S, Maruki Y, Nakamura M, Tomemori Y, Kamae K, Tanabe H, Yamashita Y, Matsuda S, Kaneko S, Sano A. The gene encoding a newly discovered protein, chorein, is mutated in chorea-acanthocytosis. Nat Genet. 2001;28:121–2. [PubMed: 11381254]

Velayos-Baeza A, Vettori A, Copley RR, Dobson-Stone C, Monaco AP. Analysis of the human VPS13 gene family. Genomics. 2004;84:536–49. [PubMed: 15498460]

Vital A, Bouillot S, Burbaud P, Ferrer X, Vital C. Chorea-acanthocytosis: neuropathology of brain and peripheral nerve. Clin Neuropathol. 2002;21:77–81. [PubMed: 12005256]

Vonsattel JP, DiFiglia M. Huntington disease. J Neuropathol Exp Neurol. 1998;57:369–84. [PubMed: 9596408]

Walker RH, Liu Q, Ichiba M, Muroya S, Nakamura M, Sano A, Kennedy CA, Sclar G. Self-mutilation in chorea-acanthocytosis - manifestation of movement disorder or psychopathology? Mov Disord . in press

Walker RH, Rasmussen A, Rudnicki D, Holmes SE, Alonso E, Matsuura T, Ashizawa T, Davidoff-Feldman B, Margolis RL. Huntington's disease--like 2 can present as chorea-acanthocytosis. Neurology. 2003;61:1002–4. [PubMed: 14557581]

Wihl G, Volkmann J, Allert N, Lehrke R, Sturm V, Freund HJ. Deep brain stimulation of the internal pallidum did not improve chorea in a patient with neuro-acanthocytosis. Mov Disord. 2001;16:572–5. [PubMed: 11391763]

Xiang F, Almqvist EW, Huq M, Lundin A, Hayden MR, Edstrom L, Anvret M, Zhang Z. A Huntington disease-like neurodegenerative disorder maps to chromosome 20p. Am J Hum Genet. 1998;63:1431–8. [PubMed: 9792871]

Xu X, Pin S, Gathinji M, Fuchs R, Harris ZL. Aceruloplasminemia: an inherited neurodegenerative disease with impairment of iron homeostasis. Ann N Y Acad Sci. 2004;1012:299–305. [PubMed: 15105274]

Suggested Readings

Andermann E, Danek A, Irvine G, Jung HH, Rampoldi L, Tison F, Walker RH. Second International Neuroacanthocytosis Symposium: Expanding the Spectrum of Choreatic Syndromes: Montreal Neurological Hospital and Institute, April 17-19 2005. Mov Disord. 2005;20:1673–84.

Danek A. (2004) Neuroacanthocytosis Syndromes. Springer, Dordrecht, The Netherlands. ed

Danek A, Walker RH. Neuroacanthocytosis. Curr Opin Neurol. 2005;18:386–92. [PubMed: 16003113]

Walker RH, Danek A, Dobson-Stone C, Guerrini R, Jung HH, Lafontaine AL, Rampoldi L, Tison F, Andermann E. Developments in neuroacanthocytosis: expanding the spectrum of choreatic syndromes. Mov Disord [Epub ahead of print]. 2006 [PubMed: 16958034]

Walker RH, Dobson-Stone C, Rampoldi L, Sano A, Tison F, Danek A. Neurologic phenotypes associated with acanthocytosis. Neurology . in press

Chapter Notes

Author Notes

A Danek offers chorein testing on a research basis only. Please email danek@lmu.de or download instructions for sample preparation from www.nefo.med.uni-muenchen.de/~adanek/Chorein_Blot.pdf

Revision History

- 13 October 2006 (me) Comprehensive update posted to live Web site
- 10 January 2005 (ad) Revision: Differential Diagnosis; Testing
- 16 July 2004 (me) Comprehensive update posted to live Web site
- 14 June 2002 (me) Review posted to live Web site
- 7 March 2002 (lr) Original submission