

Neuroacanthocytosis

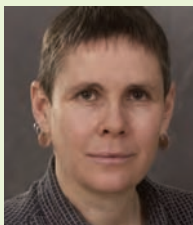


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Neuroacanthocytosis (NA) syndromes are a group of genetically defined disorders leading to progressive neurodegeneration of the basal ganglia. The core NA syndromes include autosomal recessive chorea-acanthocytosis and X-linked McLeod syndrome. These disorders have a Huntington disease-like phenotype of a choreatic movement disorder, psychiatric manifestations and cognitive decline, but may have additional multi-system features including myopathy and axonal neuropathy. In addition, patients with McLeod syndrome may develop a cardiomyopathy. Acanthocytes are found in a proportion of patients with Huntington's disease-like 2 and pantothenate kinase-associated neurodegeneration. The association of the erythrocyte membrane abnormality resulting in acanthocytosis and selective neurodegeneration of the basal ganglia suggests a common pathogenic pathway, however, this has not yet been fully elucidated.

NA refers to neurological disorders in which erythrocytes with a thorny appearance are present (Figure 1). The term was previously used for inherited disorders of lipoprotein synthesis, abetalipoproteinaemia and hypobetalipoproteinaemia, in which impaired vitamin E absorption results in posterior column degeneration

vocalisations, dysarthria and involuntary tongue- and lip-biting. The gait may have a "rubber man" appearance with truncal instability and near-falls, and sudden, violent trunk spasms. Most ChAc patients develop generalised chorea which may be indistinguishable from that of Huntington's disease (HD). A minority of ChAc patients have parkinsonism. In addition to orofaciolingual dystonia, limb dystonia is common. In at least one third of patients, seizures, typically generalized, are the first manifestation of disease. Impairment of memory and executive functions are frequently, although not invariably, observed. Psychiatric features are common and may manifest as schizophrenia-like psychosis or obsessive-compulsive disorder.

ChAc progresses slowly over 15-30 years, but sudden death, presumably caused by seizures, or possibly from autonomic involvement, is not uncommon. Neuroradiologically there is progressive striatal atrophy, especially affecting the head of caudate nucleus. Neuropathology demonstrates severe neuronal loss and gliosis primarily of the head of the caudate and to a lesser extent of the putamen, globus pallidus and substantia nigra.

Most ChAc patients have elevated levels of creatine phosphokinase (CK). Clinical neuromuscular manifestations include areflexia, sensory-motor

Neuroacanthocytosis syndromes are genetically defined neurodegenerative disorders with a Huntington-like phenotype

and cerebellar abnormalities. Currently, it should be reserved for disorders affecting the basal ganglia and resulting in various movement disorders.

In chorea-acanthocytosis (ChAc) and McLeod syndrome (MLS), acanthocytes are regularly seen, whereas in Huntington's disease-like 2 (HDL2) and pantothenate kinase-associated neurodegeneration (PKAN), they are only occasionally observed. Erythrocyte acanthocytosis can be variable, and the diagnosis of these syndromes does not require their demonstration on peripheral blood smears. All NA syndromes are very rare with cases numbering probably less than five thousand world-wide.

Chorea-acanthocytosis

Autosomal recessive chorea-acanthocytosis (ChAc) is a progressive neurodegenerative disorder with onset of neurological symptoms usually in the twenties.¹ Many patients develop a characteristic phenotype including feeding dystonia with tongue protrusion after contact with the food bolus, orofacial dyskinesias, involuntary

neuropathy, and variable weakness and atrophy. Muscle biopsy and electromyography commonly demonstrate neuropathic changes and, rarely, myopathic alterations.

ChAc is caused by various mutations of a 73 exon gene on chromosome 9, VPS13A, coding for chorein.² No obvious genotype-phenotype correlations have been observed. Chorein is implicated in intracellular protein sorting but its physiological functions are not yet known.

McLeod syndrome

The so-called McLeod blood group phenotype is defined by absent Kx red blood cell antigen and weak expression of Kell antigens, and is often incidentally detected on routine screening.^{3,4} Most carriers of the McLeod blood group phenotype have erythrocyte acanthocytosis and elevated CK levels, and develop the McLeod syndrome (MLS).^{4,6} Onset of neurological symptoms ranges from 25-60 years and disease duration ranges between 10-30 and even more years.^{4,5} About 30% of patients present with chorea resembling HD,^{4,5}

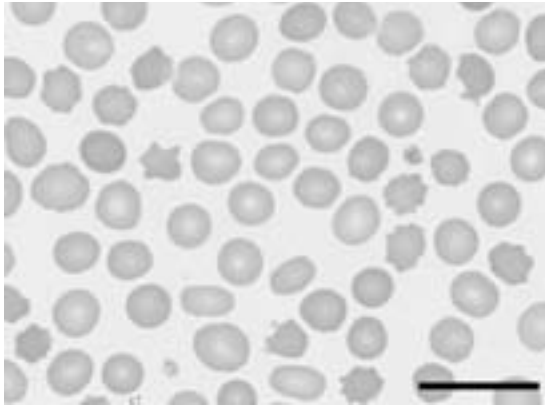


Figure 1: Acanthocytes
Peripheral blood smear showing significant acanthocytosis in a patient with McLeod syndrome manifesting with schizophrenia and later developing generalized chorea, myopathy and cardiomyopathy (May Grunewald-Giemsa; x100; scale bar = 25 µm).

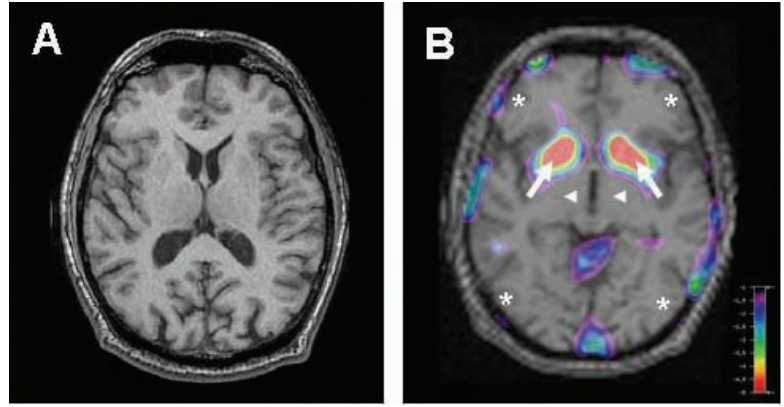


Figure 2: MRI and FDG-PET
(A) T1-weighted cerebral MRI demonstrating only subtle atrophy of the head of the caudate nucleus. (B) Quantitative FDG-PET of the same patient demonstrating severe impairment of the FDG-uptake of the striatum (arrow). FDG-uptake in the thalamus (arrowhead) and the cerebral cortex (stars) appears to be normal.

| Table 1: Neuroacanthocytosis syndromes |
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| <p>Core neuroacanthocytosis syndromes</p> <ul style="list-style-type: none"> Chorea-acanthocytosis (ChAc) McLeod syndrome (MLS) Huntington's disease-like 2 (HDL2) Pantothenate kinase associated neurodegeneration (PKAN; including HARP subtype) |
| <p>Neuroacanthocytosis with lipoprotein disorders</p> <ul style="list-style-type: none"> Abetalipoproteinemia (Bassen-Kornzweig syndrome) Familial hypobetalipoproteinaemia Anderson disease Atypical Wolman disease |
| <p>Acanthocytosis in systemic diseases where neurological findings may also be present</p> <ul style="list-style-type: none"> Severe malnutrition (e.g. anorexia nervosa) Cancers, sarcoma Thyroid disorders, myxoedema Splenectomy Liver cirrhosis, hepatic encephalopathy Psoriasis Eales' disease (angiopathia retinae juvenilis) MELAS |
| <p>HARP, hypobetalipoproteinaemia, acanthocytosis, retinitis pigmentosa, pallidal degeneration; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.</p> |

and most patients will develop this sign during the course of the disease. Involuntary movements may also include facial dyskinesias and vocalisations. In contrast to ChAc, only exceptional McLeod patients have lip- or tongue-biting, dysphagia, dystonia, or parkinsonism.⁴ Psychiatric manifestations including depression, schizophrenia-like psychosis and obsessive-compulsive disorder are frequent and

may appear prior to the movement disorders.⁶ A subset of MLS patients develops cognitive deficits, particularly in later disease stages. Generalised seizures occur in about half of the patients.

Neuroimaging reveals selective atrophy of the striatum and impaired striatal glucose metabolism.^{4,6} Neuropathological findings consist of non-specific neuronal loss and gliosis predominantly of the caudate nucleus and to a lesser extent of the putamen and the pallidum.⁷

Elevated CK levels are almost always found. Neuromuscular manifestations include myopathy and sensory-motor axonal neuropathy.^{8,9} Although about 50% of the MLS patients develop muscle weakness and atrophy during the disease course, severe gait difficulties are rare.⁹ Neuromuscular pathology shows sensory-motor axonal neuropathy, neurogenic muscle changes and variable signs of myopathy.⁹

About 60% of MLS patients develop a cardiomyopathy with atrial fibrillation, malignant arrhythmias or dilated cardiomyopathy. Cardiac complications are a frequent cause of death, thus MLS patients and asymptomatic carriers of the McLeod blood group phenotype should have a cardiologic evaluation.^{4,9,10}

Some female heterozygotes have been reported to develop CNS manifestations related to MLS with corresponding neuropathological changes. Reduction of striatal glucose uptake was demonstrated in asymptomatic female heterozygotes.⁶ In addition, MLS may be part of a "contiguous gene syndrome" on the X chromosome including chronic granulomatous disease, Duchenne muscular dystrophy and/or X-linked retinitis pigmentosa.

MLS is caused by mutations of the XK gene encoding the XK protein, which carries the Kx RBC antigen.¹¹ Most pathogenic mutations are nonsense mutations or deletions predicting an absent or shortened XK protein lacking the Kell protein binding site. The exact function of the human XK protein is not elucidated but the data from a *C. elegans* analogue of the XK gene suggest a possible role in apoptosis regulation.¹²

Huntington's disease-like 2

Huntington's disease-like 2 (HDL2) is an autosomal dominant neurodegenerative disorder.¹³ All affected families identified to date have been of African ancestry, however, this may be occult and revealed only by haplotype studies. Age at disease onset is variable and disease duration is usually 10-20 years. Initial presentation often includes personality change or other psychiatric symptoms, progressing to a movement disorder, usually chorea, but also parkinsonism and dystonia.¹⁴ Unlike ChAc and MLS, deep tendon reflexes are usually brisk; there are no peripheral nerve or muscle abnormalities, and seizures have not been reported. Acanthocytosis is found in about 10% of patients and CK levels are normal. Neuroimaging reveals bilateral striatal atrophy, in particular of the caudate nucleus. In contrast to ChAc and MLS, generalized cortical atrophy may develop during the disease course. Neuropathologically, ubiquitin-immunoreactive intranuclear neuronal inclusions, similar to those seen in HD, are found.¹³

HDL2 is caused by expanded trinucleotide repeats of the juncophilin 3 gene (JPH3). As in HD, there is anticipation and the age of onset is inversely related to the size of the trinucleotide repeat expansion. Affected individuals have CTG/CAG repeat expansions of 41-59 triplets (normal population: 6-27). JPH3 plays a role in junctional membrane structures, and may be involved in the regulation of calcium.

Pantothenate kinase-associated neurodegeneration

Pantothenate kinase-associated neurodegeneration (PKAN) is an autosomal recessive condition belonging to the group of disorders known as neurodegeneration with brain iron accumulation (NBIA). So far, PKAN is the only NBIA in which acanthocytosis has been reported. PKAN typically presents in childhood with rapid progression over 10 years.¹⁵ Initial manifestations may include orofacial and limb dystonia, choreoathetosis and spas-

Table 2: Predictive Accuracy of MCI from Cache County

| Disorder | ChAc | MLS | HDL2 | PKAN |
|------------------------------|--|--|-------------------------------|------------------------------------|
| Gene | VPS13A | XK | JPH3 | PANK2 |
| Protein | Chorein | XK | Junctophilin-3 | Panthothenate kinase 2 |
| Inheritance | AR | X-linked | AD | AR |
| Acanthocytes | +++ | +++ | + / - | + / - |
| Serum CK (U/L) | 300 - 3000 | 300 - 3000 | Normal | Normal |
| Neuroimaging | Striatal atrophy | Striatal atrophy | Striatal and cortical atrophy | "Eye of the tiger" sign |
| Usual onset | 20 - 30 | 30 - 60 | 20 - 40 | Childhood |
| Chorea | +++ | +++ | +++ | +++ |
| Other movement disorders | Feeding and gait dystonia, tongue and lip biting, Parkinsonism | Vocalizations | Dystonia, Parkinsonism | Dystonia, Parkinsonism, spasticity |
| Seizures | Generalized, partial-complex | Generalized | None | None |
| Neuromuscular manifestations | Areflexia, weakness, atrophy | Areflexia, weakness, atrophy | None | None |
| Cardiac manifestations | None | Atrial fibrillation, malignant arrhythmias, dilated cardiomyopathy | None | None |

ticity. Most patients develop pigmentary retinopathy and one third cognitive impairment. About 8% of PKAN patients have acanthocytosis, possibly due to abnormalities of lipid synthesis.¹⁵ MRI demonstrates the typical "eye-of-the-tiger" pattern of iron deposition in the globus pallidus.

PKAN is caused by mutations of the panthothenate kinase 2 gene (PANK2) (chromosome 20p13). Truncating mutations are responsible for the majority of cases. PKAN catalyses the rate-limiting step in the synthesis of coenzyme A from vitamin B5 (pantothenate). The residual enzymatic activity correlates with the disease phenotype, as typical patients have no active enzyme but atypical patients with adult onset usually harbour PANK2 missense mutations.¹⁵

Diagnostic considerations

The determination of acanthocytosis in peripheral blood smears is difficult in a standard setting and is not even necessary for the diagnosis of a NA syndrome. Automated blood counts usually show an elevated number of hyperchrome erythrocytes. Although routine blood films may demonstrate acanthocytes, the detection rate is variable and standard values are lacking. A standardised method using a 1:1 dilution with physiological saline and phase contrast microscopy is more sensitive and specific.¹⁶ Serum CK is elevated in most cases with ChAc and MLS. ChAc patients have absent chorein expression in erythrocytes on Western blot. MLS is detected by determination of absent Kx antigen and reduced Kell antigens on the erythrocytes in males and flu-

orescence absorbent cell sorting with Kell antigens in female heterozygotes. Genetic analysis of the VPS13A and XK genes is confirmatory but may be difficult to accomplish in VPS13 due to the large dimension of the gene. Cerebral MRI is diagnostic only in PKAN, and the diagnosis is confirmed by analysis of the PANK2 gene. Analysis of the JPH3 gene CTG expansion is useful in patients of African ancestry with suspected HDL2.

Therapy

There are no curative or disease-modifying treatments available at present. Recognition of treatable complications such as seizures, aspiration and cardiac problems is essential. Psychiatric problems should be treated according to their clinical presentation. Dopamine antagonists or depleters such as tiapride, clozapine or tetrabenazine may ameliorate the chorea. Non-medical therapies with a multidisciplinary approach are often helpful. Dystonia of the lower face and tongue can result in severe tongue and lip self-mutilation in ChAc and may be ameliorated by a bite plate. Weight loss can be a prominent early feature, and evaluation of swallowing is very important. Placement of a feeding tube may be necessary to avoid nutritional compromise and to reduce the risk of aspiration. Speech therapy and the evaluation of communication devices may be necessary. Gait abnormalities and falls are frequent and physiotherapy may improve gait and balance. Most importantly, extended and continuous multidisciplinary psychosocial support should be provided for the patients and their families.

Conclusions

NA syndromes must be included in the differential diagnosis of HD. Their consideration is mandatory if HD genetic testing is negative. Clinical and paraclinical findings typical for NA include epilepsy, peripheral neuropathy, cardiomyopathy (MLS) and orofacial dyskinesia, and feeding dystonia (ChAc). ♦

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NOTE

The Advocacy for Neuroacanthocytosis Patients - www.naadvocacy.org - supports the collaboration of the authors and makes the diagnostic chorein expression test (http://www.nefo.med.uni-muenchen.de/~adanek/Chorein_Blot.pdf) freely available. It currently solicits NA research grant proposals: <http://tinyurl.com/p3j5so>