Untangling the Thorns: Advances in the Neuroacantho-cytosis Syndromes

Ruth H. Walker[1,2]

[1]Department of Neurology, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA
[2]Department of Neurology, Mount Sinai School of Medicine, New York, NY, USA

ABSTRACT

There have been significant advances in neuroacanthocytosis (NA) syndromes in the past 20 years, however, confusion still exists regarding the precise nature of these disorders and the correct nomenclature. This article seeks to clarify these issues and to summarise the recent literature in the field. The four key NA syndromes are described here–chorea-acanthocytosis, McLeod syndrome, Huntington's disease-like 2, and pantothenate kinase-associated neurodegeneration. In the first two, acanthocytosis is a frequent, although not invariable, finding; in the second two, it occurs in approximately 10% of patients. Degeneration affecting the basal ganglia is the key neuropathologic finding, thus the clinical presentations can be remarkably similar. The characteristic phenotype comprises a variety of movement disorders, including chorea, dystonia, and parkinsonism, and also psychiatric and cognitive symptoms attributable to basal ganglia dysfunction. The age of onset, inheritance patterns, and ethnic background differ in each condition, providing diagnostic clues. Other investigations, including routine blood testing and neuroimaging can be informative. Genetic diagnosis, if available, provides a definitive diagnosis, and is important for genetic counseling, and hopefully molecular therapies in the future. In this article I provide a historical perspective on each NA syndrome. The first 3 disorders, chorea-acanthocytosis, McLeod syndrome, Huntington's disease-like 2, are discussed in detail, with a comprehensive review of the literature to date for each, while pantothenate kinase-associated neurodegeneration is presented in summary, as this disorder has recently been reviewed in this journal. Therapy for all of these diseases is, at present, purely symptomatic.

Key Words
Neuroacanthocytosis; Chorea; Chorea-acanthocytosis; McLeod syndrome; Acanthocytes; Huntington's disease-like 2.

INTRODUCTION

The term "neuroacanthocytosis" may be used generally to refer to disorders in which neurological abnormalities are accompanied by the presence of thorny red blood cells, known as acanthocytes (from the Greek *akanthos*, meaning "thorn") (Figure 1), on peripheral blood smear. Thus technically this term can refer to both those conditions in which there is degeneration of the basal ganglia and those in which there are inherited abnormalities of serum lipoproteins resulting in vitamin E malabsorption, spinal cord and peripheral nerve disorders. While subjects affected by these latter conditions may have impaired coordination, they do not have movement disorders, and will not be addressed here.

"Neuroacanthocytosis" should not be used as a final diagnosis, but rather to describe a particular clinical syndrome, pending protein-based or genetic confirmation. There are four core neuroacanthocytosis (NA) syndromes; two may be considered the prototypic disorders, chorea-acanthocytosis (ChAc) and McLeod (pronounced "McLoud") syndrome; the other two diseases are pantothenate kinase-associated neurodegeneration (PKAN), the primary neurodegeneration with brain iron accumulation (NBIA) disorder, and Huntington's disease-like 2 (HDL2). Acanthocytosis is seen in only about 10% of cases of PKAN and HDL2. Acanthocytosis can be seen occasionally in other movement disorder conditions, such as mitochondrial diseases, or in various metabolic disorders such as anorexia nervosa or hypothyroidism.

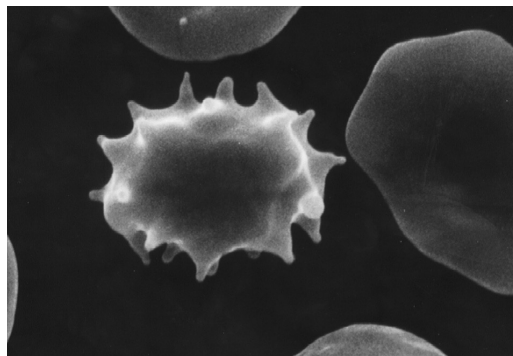Cases reported in the literature without definitive molecular or protein-based confirmation may only be presumptively classified as NA syndromes–as an example, Hardie's classic 1991 series of 19 NA cases[1] has recently been re-examined and determined to comprise cases of ChAc, McLeod syndrome, and PKAN.[2] However, as our experience with genetically-defined cases has expanded, clinical and inheritance features may permit a reasonable degree of accuracy in assigning a diagnosis in the absence of definitive testing (Table 1 and 2).

CHOREA-ACANTHOCYTOSIS

Historical perspective

ChAc was first clearly described by Critchley et al.[3,4] in 1967 in a large family in eastern Kentucky, and subsequently in a British patient,[5] all of whom had progressive neurologic disease with self-mutilating lip- and tongue-biting, dystonia, chorea, cognitive impairment, and acanthocytosis. A similar pedigree was published in 1967 by Levine and coworkers, although with a less clear phenotype and inheritance.[6,7] We have recently confirmed genetically that the disorder affecting Critchley's Kentucky family was indeed ChAc,[8] but have been unable to trace any descendants of Levine's New England family.

The name "Levine-Critchley syndrome" was proposed by Japanese authors,[9] who had long been aware of this disorder in their population.[10] However, this term has rarely been used in the published literature. Following the original descriptions, the first cases appearing in the English-language medical literature in 1978[11] and the early 1980s, used the names "chorea-acanthocytosis",[12,13] "choreoacanthocytosis",[14-16] "neuroacanthocytosis",[17] or merely a description of the clinical phenotype.[11,18-20]

The accuracy of the name "chorea-acanthocytosis" may be debated as chorea is not an invariable symptom,[21] however, I propose that it is preferable to "neuroacanthocytosis", especially once the genetic diagnosis has been confirmed. The latter term has also been used to refer to the other diseases discussed here, resulting in significant diagnostic confusion, and, as mentioned above, technically could refer also to the hypolipoproteinemic disorders.

Molecular features

ChAc is autosomal-recessively inherited. The causative gene, *VPS13A* (initially known as *CHAC*), located on chromosome 9q21, was identified simultaneously in two laboratories,[22,23] with the Japanese

Figure 1. Scanning electron micrograph of acanthocyte. Courtesy of Mitchell Brin, MD.

Table 1. Genetic and population features of neuroacanthocytosis syndromes

Disease	Mode of inheritance	Gene	Locus	Protein product	Age of onset	Genetic determinant of age of onset	Ethnic origin
Chorea-acanthocytosis	AR	VPS13A	9q21.2	Chorein	Early adulthood	N/A	Any
McLeod syndrome	X-linked recessive	XK	Xp21.1	XK	Middle age	N/A	Any
Huntington's disease-like 2	AD	JPH3	16q24.3	Junctophilin-3	Early-middle adulthood	Inversely related to size of trinucleotide repeat expansion	African
Pantothenate kinase-associated neurodegeneration	AR	PANK2	20p13	Pantothenate kinase 2	Childhood; sometimes later	Less severe mutations = atypical, late onset	Any

AD: autosomal dominant, AR: autosomal recessive, N/A: not applicable.

Table 2. Clinical, serological, and radiological features of neuroacanthocytosis syndromes

Disease	Movement disorders	Seizures	Peripheral neuropathy	Muscle involvement	Hepatic involvement	Cardiac involvement	Acantho-cytosis	Creatine kinase	Liver enzymes	Neuroimaging
Chorea-acanthocytosis	Dystonia, chorea, tics, parkinsonism	++	++	+	++	(+)	+++	+++	++	Atrophy of caudate nucleus
McLeod syndrome	Dystonia, chorea, tics, parkinsonism	++	++	++/+++	++	+++	+++	+++	++	Atrophy of caudate nucleus
Huntington's disease-like 2	Dystonia, chorea, parkinsonism	-	-	-	-	-	+	-	-	Atrophy of caudate nucleus and cortex
Pantothenate kinase-associated neurodegeneration	Dystonia, parkinsonism; (chorea rare)	-	-	-	-	-	+	-	-	Iron deposition in the GPi– "eye of the tiger"

GPi: globus pallidus, pars internus, -: absent, +: occasional/mildly abnormal, ++: often present/moderately abnormal, +++: frequent/markedly abnormal.

group naming the protein "chorein".[23]

Genetic testing is challenging due the large size of the gene, which comprises 73 exons. Two splicing variants are found in humans, 1A which contains exons 1–68 and 70–73 and 1B which contains exons 1–69.[24] Mutations can be found throughout the gene, with no specific hotspot. The absence of protein product chorein, in erythrocytes as determined by Western blot[24] confirms the diagnosis (Figure 2) and is available on a research basis (http://www.euro-hd. net/html/na/network/docs/chorein-wb-info.pdf).

ChAc has been reported from most ethnic groups from many countries, including Brazil,[25] China,[26-28] India,[29-31] Iran,[32] Israel,[33] Japan,[10] Mexico,[34,35] Poland,[36] Saudi Arabia,[37] Slovenia,[38] South Korea,[39] Taiwan,[40] Tunisia,[41] and Turkey.[42,43] The presence of a Japanese founder mutation accounts for the increased incidence in Japan.[44]

A Japanese family was reported to have apparent autosomal dominant ChAc,[45] however, this has been questioned,[46] and this mode of inheritance is not generally accepted. Other pedigrees have been described in which there was pseudo-dominant inheritance due to consanguinity.[47] Occasional heterozygous carriers have been reported to have acanthocytes, as in Critchley's original report,[4] however, these sub-

jects have not been systematically studied with a standard protocol to examine peripheral blood, and appear to be neurologically intact.

There is no clear genotype-phenotype correlation, and there can be striking variation between the presentations of affected members of one family.[32,33,35,37]

The affected protein chorein appears to be involved in polymerization of actin, thus its dysfunction may result in cell membrane disruption and the abnormalities of erythrocyte shape.[48,49] Abnormalities of protein phosphorylation have been found,[50] in addition to other abnormalities of red cell membrane proteins.[51,52] Chorein is widely expressed,[53] and clearly has functions throughout the body, although not all tissues are affected by the mutation.

In mammals the VPS13 protein family is made up VPS13A-D,[24] but the other family members do not compensate for the absence of VP13A in ChAc. Studies in *C. elegans*, Drosophila, yeast and other lower organisms indicate a role of homologous proteins in intracellular trafficking and vesicle functions.[54,55] There are no specific regions indicating particular functions.

Mutations of *VPS13B* cause form of syndromic development delay known as Cohen's syndrome.[56] Mutations of *VPS13C* are associated with a familial
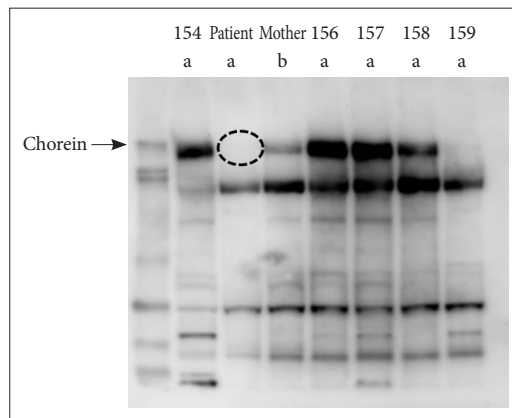
Figure 2. Western blot demonstrating absence of chorein (dashed oval) in sample from a patient with chorea-acanthocytosis. Courtesy of Benedikt Bader, MD, and Adrian Danek, MD.

form of frontotemporal dementia,[57] and may increase susceptibility to Parkinson's disease.

Clinical features

ChAc typically presents in early adulthood with hyperkinetic involuntary movements, specifically chorea and orolingual dystonia.[58] Tongue-protrusion dystonia with eating is very suggestive of the disorder, although may occasionally be seen in tardive dyskinesia, McLeod syndrome, and PKAN.[59] However, the self-mutilation, with tongue- and lip-biting,[60] which often accompanies this dystonia, is not reported in these other disorders. Patients often learn to use an intervention, such as a stick in the mouth, to reduce biting and tooth-grinding. This may function either as a mechanical block or a sensory trick (in the case of dystonia). Some patients will hold a piece of cloth in the mouth which also helps absorb saliva, as they often have sialorrhea. A characteristic, and alarming, maneuver to bypass the tongue protrusion is to extend the head and to push or throw food into the back of the throat, which increases the risk of aspiration.[61]

Severe neck ("head drops") and truncal flexion are also typical. Head-drops have been reported also in both McLeod syndrome[62] and Huntington's disease (HD).[63] The velocity of these movements suggests that they are choreic in nature, rather than being due to sudden losses in tone (negative myoclonus) or due to dystonia.

The gait can appear quite bizarre with anterior flexion of the trunk at the hips and leg dystonia giving the appearance of a "rubbery" gait. Often bal-ance is remarkably preserved with relatively few falls despite marked gait abnormalities.

Parkinsonism can be a presenting sign,[64] although is more typical as a later symptom, suggesting, as in HD, a "burn-out" of the hyperkinetic movements. This may be due to progression of neuropathology involving the neurons of the direct pathway, subsequent to involvement of the indirect pathway, as has been suggested occurs in HD.[65,66]

ChAc often presents with psychiatric symptoms, which can lead to the prescription of anti-psychotic medications. The development of orofacial dyskinesia in these patients naturally suggests a tardive phenomenon, thus the treating psychiatrist should be alert to the appearance of new and atypical neurological signs or symptoms. Depression[30] and obsessive-compulsive symptoms are common. Vocal and motor tics[67] and obsessive-compulsive symptoms and behaviors can be very functionally limiting. Self-injury,[41,60] including tongue-, lip-, cheek- or finger-biting, or throwing the body to the floor, may be behavioral compulsions rather than purely due to a motor disorder.[68] These symptoms are likely related to degeneration of the head of the caudate nucleus.[69,70] The use of a mouth-guard to reduce lip-biting was reported to reduce other obsessive-compulsive behaviors and tics,[71] suggesting interactivity of the neuronal circuits involved in these behaviors.[70]

Features which distinguish ChAc (but also McLeod syndrome) from most of the other causes of chorea are seizures and peripheral neuropathy.[72,73] Patients may present with seizures, which are typically of temporal lobe origin,[43,74,75] and eventually appear in 40% of patients. Peripheral sensorimotor neuropathy with loss of deep tendon reflexes is common, and the presentation may even mimic motor neuron disease.[76] Involvement of the autonomic nervous system has been reported,[77] in addition to cardiac abnormalities,[78] and may account for reports of sudden death. Cardiomyopathy is not typical of ChAc, and is more consistent with McLeod syndrome, however, it has been reported in a couple of genetically-confirmed individuals without other cause for the condition (Barbara Karp, MD, personal communication).[78]

Studies of eye movements in ChAc found square-wave jerks, as in HD, and impaired saccades.[79] Impaired upward gaze has been noted (personal observations). These findings suggest of brainstem

involvement, in addition to the basal ganglia degeneration.

Swallowing and speech dysfunction are invariable features, due to progressive loss of motor control of the musculature required for these functions, and are very debilitating. While in the initial stages speech impairment is likely due to orolingual dystonia, as the disease progresses patients often become mute, suggesting a central origin of dysfunction.

Elevated serum creatine kinase is a useful indicator of the diagnosis. Muscle atrophy is common, and electromyography indicates neurogenic atrophy, however, biopsies have been reported to show inclusion bodies. Rhabdomyolysis may rarely occur.[80]

Hepatomegaly can also be observed, with elevation of liver enzymes, however, frank hepatic dysfunction has not been reported.

Despite being invoked in the name and definition of the disorder, acanthocytosis on peripheral blood smear is helpful, but is not a consistent finding, for reasons which are not known.[81] This fact, and the logistical challenges to having this study performed in a standardized manner,[82] mean that acanthocytosis should not be relied upon to make the diagnosis.

Neuroimaging

Neuroimaging appears generally similar to that of HD (Figure 3), and cannot be used to distinguish the conditions. Quantitative morphometry demonstrates atrophy of the head of the caudate nucleus.[69,70] Occasionally other findings have been reported, such as iron deposition in the striatum and globus pallidus,[31,39] or cerebellar atrophy.[29,83] The significance of these observations is not clear.

Metabolic studies reveal decrease metabolism in the caudate nucleus and putamen,[84] as would be expected in a neurodegenerative condition. Dopamine- and serotonin-transporter binding were normal.[84] Magnetic resonance spectroscopy studies are consistent with neuronal loss and glial activation.[42]

Management

Treatment is purely symptomatic, employing the usual medications for dystonia and chorea. L-dopa has been reported to reduce dystonia,[38] although it is not typically helpful. Botulinum toxin may be helpful for focal dystonia. Deep brain stimulation (DBS) may reduce the hyperkinetic movements in selected patients.[85]

Treatment of psychiatric symptoms is often the most important issue in terms of improving quality of life, can be challenging. Use of medications directed at obsessive-compulsive behaviours, such as citalopram,[86] may be helpful, but quetiapine has also been reported to be very effective.[87]

Seizures typically respond well to conventional anti-convulsant agents, but are occasionally refractory to multiple drugs. Levetiracetam has also been reported to reduce truncal tics.[40]

Alternative means of nutrition, such as a feeding tube, should be considered early in light of the significant risk of aspiration and the marked weight loss which is characteristic. Communication devices, such as computer-assisted speech, can also be valuable interventions.

Dramatic and painful joint destruction has been reported due to hypotonia and involuntary movements. The presence of a progressive neurodegenerative condition should not preclude orthopedic intervention.[88]

Neuropathology

On neuropathologic examination the basal ganglia are primarily affected with neuronal loss and gliosis in the caudate nucleus, and to a lesser extent
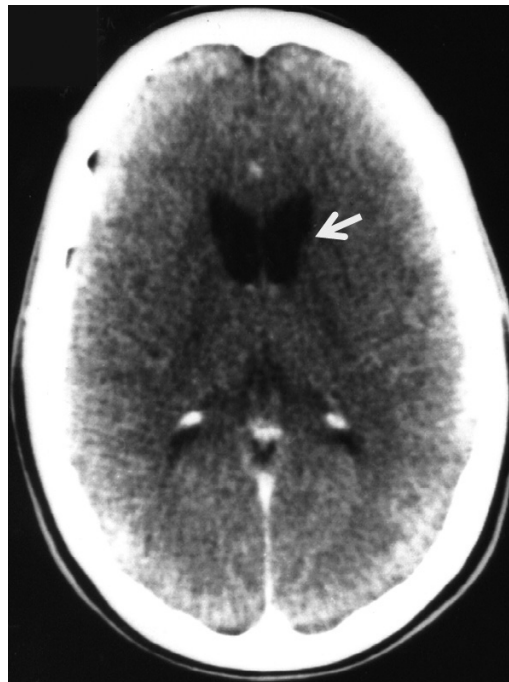

Figure 3. Non-contrast CT of brain of patient with chorea-acanthocytosis, showing marked atrophy of the caudate nucleus (arrow). Courtesy of Mitchell Brin, MD.

the putamen, globus pallidus and substantia nigra.[89,90] In some cases, despite the appearance of parkinsonism, the substantia nigra may be intact.[91] There is no evidence of any inclusion bodies or other proteinaceous aggregates despite examination utilizing a variety of different antibodies.

Studies in two subjects who were parkinsonian at death demonstrated preferential loss of striatal substance P-containing projection neurons and of parvalbumen-containing interneurons in both striatum and cortex.[91] The latter observation may account for the appearance of seizures.

Atrophy of the pyramidal tracts has been reported.[90]

MCLEOD SYNDROME

Historical perspective

The X-linked "McLeod phenotype" was first identified in 1961 in a dental student at Harvard, Hugh McLeod, during a search for novel erythrocyte antigens which involved the routine (unconsented) screening of incoming students' blood.[92] The erythrocyte phenotype is defined as reduced Kell and absent Kx antigen expression on the cell surface.[92,93] The association with acanthocytosis was first noted in 1977 in the propositus[93] and subsequently in others.[94] Elevated levels of creatine kinase were reported in 1981,[95] and were associated with a myopathy which was initially thought to be benign.[96] The connection with a neurodegenerative condition was not made until a number of years later when it was reported that subjects with this phenotype developed a movement disorder and other symptoms.[97-101] Hugh McLeod had an elevated creatine kinase,[95] and in his 50's was documented as having cardiac dysrhythmia, splenomegaly, areflexia, decreased peripheral sensation, and lower extremity weakness.[102] Cognitively he remained intact and continued working as a dentist, and developed only mild shoulder shrugging (likely either chorea or tics) at age 64. His body underwent neuropathologic examination and his tissues are included in a recent report of muscle pathology.[102]

It has been postulated that Henry VIII of England suffered from McLeod syndrome, as an explanation for the apparent change in his personality in adulthood, in addition to his inability to father a son.[103] However, as refuted elsewhere,[104] McLeod syndrome does not affect fertility, and is not transmitted to male children, thus would not cause death *in utero* nor of male infants.

Molecular features

McLeod syndrome is caused by mutations of the *XK* gene located on the X chromosome, resulting in absent or dysfunctional XK protein.[105] The protein XK is localized on the surface of the erythrocyte membrane and is linked to the Kell protein via a disulphide bond. When XK is abnormal, there is reduced expression of the 23 antigens normally expressed by Kell,[106] which comprises the third most important erythrocyte antigen system after ABO and rhesus. McLeod phenotype can be detected on blood typing, for example, if an individual donates blood or requires a blood transfusion, prior to manifestation of the neurologic symptoms. The diagnosis requires the use of a panel of anti-Kx and anti-Kell antibodies (a report of "Kell negative" or "Kell positive" is not adequate), and can be confirmed by genetic testing.

Preliminary evidence suggests that XK is a membrane transport protein,[105] primarily affecting the transportation of divalent cations.[107] In addition to erythrocytes, XK is also present in muscle and in brain.[108-110] In brain XK does not appear to be colocalized with Kell, as it is in other tissues.[111]

There is no clear phenotype-genotype correlation, and symptoms can vary significantly within families.[112] Some missense mutations appear to have a lesser effect upon the protein, and may solely affect the position of the protein in the erythrocyte membrane, but not other functions, such as in neuronal tissue, resulting in a minimal phenotype.[113,114] Symptomatic carrier females are occasionally reported, presumably due to X-chromosome inactivation.[115,116]

McLeod syndrome has been reported in many ethnic groups, including patients from Japan,[101,116] Chile,[117,118] China,[119] and Taiwan, although it is probably significantly rarer than ChAc.

The absence of Kell expression, as seen also in Kell null individuals,[120] does not appear to have clinical consequences other than for blood transfusion.

Clinical features

The clinical features of McLeod syndrome overlap significantly with those of ChAc, and patients can look strikingly similar, however, a major differ-

ence is that there can be a much wider range of phenotypic variability and severity in McLeod syndrome. The neurologic or psychiatric features typically develop in men in mid-life. Patients may be identified prior to the appearance of these features either when blood-typing is performed, or when routine medical screening reveals an elevated creatine kinase or liver enzymes.

The initial presentation may be with psychiatric or cognitive issues,[121] however, unlike the other neurodegenerative choreas, these symptoms are not invariable. A range of movement disorders can be seen, including chorea, dystonia, and parkinsonism. Patients with chorea may eventually progress to parkinsonism.[118] Head-drops[62] and orolingual dystonia with feeding,[122] otherwise suggestive of ChAc, are occasionally seen, although not the self-mutilating lip-biting. Peripheral sensorimotor neuropathy and areflexia are typical, and are often early or predominant features.[123] Similar to ChAc, 50% of subjects have seizures, which usually respond well to standard anticonvulsant medications.

Hepatic dysfunction is manifested by enlargement of the liver and elevated liver enzymes. While usually benign, catastrophic liver failure has been rarely reported. The spleen is also often enlarged.

An important distinction between McLeod syndrome and the other choreas, including those described here, is the presence of cardiomyopathy,[124,125] which is seen in approximately 2/3 of patients.

Patients with McLeod syndrome may present with myopathy[126] which can be severe and debilitating,[102,127] and may occasionally lead to rhabdomyolysis.[128]

Acanthocytosis can be helpful in the diagnosis, but may be absent.[129]

Neuroimaging

Similar to ChAc and the other neurodegenerative choreas, the main observation on brain imaging is atrophy of the caudate nucleus and putamen.[130] White matter changes have been reported.[131]

Metabolic studies indicate decreased metabolism of the basal ganglia, but also in extra-striatal regions.[115,132,133] This latter finding is postulated to be secondary to basal ganglia dysfunction as the cortex is generally spared on neuropathologic examination. Magnetic resonance spectroscopy in a small number of individuals demonstrated mixed findings.[132]

Neuropathology

On neuropathologic evaluation, there is neuronal loss and reactive gliosis in the caudate nucleus, putamen and globus pallidus, with no specific immunohistochemical markers.[134]

Management

Most symptoms of McLeod syndrome are managed as they occur, however, annual echocardiography is recommended for early detection and treatment of cardiac issues such as a potentially treatable cardiomyopathy or arrhythmias.[100,125]

There is a risk of development of anti-Kell antibodies in patients who are transfused with Kell+ blood, with consequent transfusion reactions,[136] therefore it is suggested that people with MLS bank their own blood in case of future need by themselves or others. This is particular important, for example, with disease progression and an increased risk of falls.

HUNTINGTON'S DISEASE-LIKE 2

Historical perspective

Since identification of the mutation responsible for HD in 1994 it has become apparent that there are a significant number of families in which an HD-like syndrome was inherited in an autosomal dominant manner.[137,138] In 2001 one of these disorders was found to be due to a novel trinucleotide repeat expansion, and was named Huntington's disease-like 2.[139]

Molecular features

HDL2 is caused by a CTG/CAG trinucleotide repeat expansion located within the *junctophilin-3* (*JPH3*) gene on chromosome 16q24.3.[140] The normal repeat size is 6 to 27 CTG/CAG triplets. Expansions greater than 41 repeats cause disease. The largest size expansion reported to date is 58 triplets.[141] The age of onset is inversely related to the size of the trinucleotide repeat, as seen in HD and many other trinucleotide repeats disorders. Anticipation with subsequent generations has not yet been demonstrated, possibly due to the paucity of studies of multi-generation families.

HDL2 appears to be due to either a rare African ancestral mutation or a tendency for longer alleles prone to expansion in Africans,[142] and only occurs

in families of African ancestry.[139,142-147] In some cases, for example in ethnically-mixed populations, such as those found in Brazil[145,147] and Venezuela,[146] the presence of African ancestry may be hidden by the family, and demonstrated only by haplotype studies.[148]

Junctophilin-3 is involved in calcium regulation, and appears to play a role in junctional membrane structures. HDL2 pathogenesis is proposed to be multifactorial, related both to the formation of toxic mRNA inclusions in the cytoplasm[149,150] and to loss of the mutant protein.[151] The CTG expansion does not result in abnormal amino acid tracts in brain tissue,[151] thus the immediate cause of pathogenesis is unclear.

Clinical features

HDL2 typically manifests in the 3rd or 4th decade with cognitive deficits, chorea, dystonia, myoclonus, or parkinsonism.[139] Parkinsonism and dystonia are typically more prominent than in HD,[141,152] and do not appear to correlate with particularly large trinucleotide repeat expansions. As in HD and the other basal ganglia neurodegenerative disorders described here, the early features may be behavioral or psychiatric.[147,152,153] For reasons which are not known, acanthocytosis is seen in 10% of patients.[154]

Eye movements may be normal, or mildly hypometric, in contrast to HD.[152]

Neuroimaging

As with the above conditions, imaging is similar to that observed in HD, although cortical atrophy may also be seen.[155] Hyperintensity of the rim of the putamen is reported in 3 cases who underwent MRI scanning from one large family.[152]

Management

Treatment is purely symptomatic for these patients. Hyperkinetic movements can be treated with dopamine-depleting or -blocking agents. Parkinsonism may respond to L-dopa. Psychiatric symptoms should be addressed using standard medications.

Neuropathology

The findings on neuropathological examination are strikingly similar to those seen in HD. Intranuclear inclusions immunoreactive for ubiquitin and expanded polyglutamine repeats are found through-

out the cortex.[139,155,156] As in HD, there is a gradient of neuronal loss from ventral to dorsal in the caudate nucleus and putamen.[156]

PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION

Historical perspective

Iron deposition in the globus pallidus in subjects with neurological illness was first described by Hallervorden and Spatz, following their neuropathological examination of the brains of those with intellectual or physical disabilities who were "euthanized" by the Nazis.[157] For many years their names were memorialized in the eponym used for this condition, however, with recognition of their association with Nazi atrocities[157] new nomenclature has been adopted, reflecting the affected proteins.

PKAN is the most common NBIA disorder, and the only one to date in which acanthocytes have been reported, albeit in only about 10% of cases.[158] As noted above, one of the series of NA cases reported by Hardie et al.[1] was later identified as "HARP"–hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration.[2,159] A few other cases were reported with this syndrome, which was subsequently been found to be due to the identical genetic mutation which causes PKAN.[159,160] The term "hypoprebetalipoproteinemia" is felt to be redundant.[161]

Molecular features

PKAN is due to mutations in the gene *PANK2* which encodes for pantothenate kinase 2.[158,162] The age of onset and rate of disease progression appear to be related to the effect of the mutation upon the enzyme.[163] Pantothenate kinase 2 is critical for the synthesis of coenzyme A, a major component of many biochemical pathways. This enzyme is found throughout the body, and in particular in the infantile basal ganglia and the retina.[162] Recent investigations have focused upon mitochondrial dysfunction, with deficiency of mitochondrial coenzyme A resulting in neurodegeneration.[164,165] It is not known whether iron deposition is a critical feature or an epiphenomenon, however, the latter appears more likely at present.

Clinical features

The features of this disorder have recently been reviewed in detail in this journal[166] and thus are only summarized here. The clinical features of PKAN are typically quite distinct from those of the other neuroacanthocytosis syndromes described above. Onset is usually in childhood, with progressive dystonia and parkinsonism, in addition to retinitis pigmentosa and cognitive impairment.[158,163,167] Dystonia often affects the lower face resulting in grimacing and tongue protrusion. Atypical cases present later and tend not to have retinal problems.[158,163] Chorea is rarely seen.

The cause of acanthocytes in a small percentage of patients has not been investigated, but may be related to defective lipid synthesis due to coenzyme A deficiency, resulting in abnormal structural properties of erythrocyte membranes.

Neuroimaging

The classical MRI finding is the "eye-of-the-tiger" in the globus pallidus, with central edema surrounded by iron deposition.[158,163] However, this finding may be absent in genetically-confirmed cases,[168] and is not entirely specific for this disorder.[169,170] In late-onset disease this finding can appear following the appearance of clinical symptoms.

Management

Treatment of PKAN at this point remains purely symptomatic.[166] DBS has been found to be useful both in patients with both severe and with less severe disease.[171-173]

Genetic confirmation of PKAN, and distinction from other NBIA disorders, is important as targeted biochemical therapies are currently being investigated. A small, uncontrolled study of the iron chelator deferiprone suggested that there is a reduction in pallidal iron, and clinical stabilization in some patients.[174] A large clinical trial is currently underway. Other promising agents which bypass the affected biochemical pathway are currently being developed and tested in animal models.

CONCLUSION

I have described here the four neurological conditions in which movement disorders, due to degeneration of the basal ganglia, can be accompanied by acanthocytosis. Prior to the molecular era, the potential for significant overlap in the clinical presentations resulted in diagnostic confusion, which is reflected in the literature. However, there are typical features for each condition, for example the self-mutilating lip- and tongue-biting in ChAc, the age of onset and gender in McLeod syndrome, and the ethnic background and inheritance pattern in HDL2, which help distinguish each disease. Laboratory testing demonstrating elevated creatine kinase and liver enzymes helps identify ChAc and McLeod syndrome. The "eye-of-the-tiger" seen on MRI supports the diagnosis of PKAN.

The relationship of red cell membrane abnormalities to basal ganglia neurodegeneration in each disease remains unclear, but may be due to common vulnerabilities affecting membrane structure.[175] The striking overlap in the phenotypes of ChAc and MLS suggests a potential final common pathway, however, this is not yet evident.

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