Untangling the Thorns: Advances in the Neuroacanthocytosis Syndromes

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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 has recently been re-examined and determined to comprise cases of ChAc, McLeod syndrome, and PKAN. 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. in 1967 in a large family in eastern Kentucky, and subsequently in a British patient, 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. We have recently confirmed genetically that the disorder affecting Critchley’s Kentucky family was indeed ChAc, but have been unable to trace any descendants of Levine’s New England family.

The name “Levine-Critchley syndrome” was proposed by Japanese authors, who had long been aware of this disorder in their population. 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 and the early 1980s, used the names “chorea-acanthocytosis”, “choreoacanthocytosis”, or merely a description of the clinical phenotype.

The accuracy of the name “chorea-acanthocytosis” may be debated as chorea is not an invariable symptom; 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, with the Japanese
group naming the protein “chorein.”

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. Mutations can be found throughout the gene, with no specific hotspot. The absence of protein product chorein, in erythrocytes as determined by Western blot 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, China, India, Iran, Israel, Japan, Mexico, Poland, Saudi Arabia, Slovenia, South Korea, Taiwan, Tunisia, and Turkey. The presence of a Japanese founder mutation accounts for the increased incidence in Japan.

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

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. Abnormalities of protein phosphorylation have been found, in addition to other abnormalities of red cell membrane proteins. Chorein is widely expressed, 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, 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. There are no specific regions indicating particular functions.

Mutations of VPS13B cause form of syndromic development delay known as Cohen’s syndrome.

Mutations of VPS13C are associated with a familial
form of frontotemporal dementia, 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. Tongue-protrusion dystonia with eating is very suggestive of the disorder, although may occasionally be seen in tardive dyskinesia, McLeod syndrome, and PKAN. However, the self-mutilation, with tongue- and lip-biting, 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.

Severe neck (“head drops”) and truncal flexion are also typical. Head-drops have been reported also in both McLeod syndrome and Huntington’s disease (HD). 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 balance is remarkably preserved with relatively few falls despite marked gait abnormalities.

Parkinsonism can be a presenting sign, 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.

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 and obsessive-compulsive symptoms are common. Vocal and motor tics and obsessive-compulsive symptoms and behaviors can be very functionally limiting. Self-injury, 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. These symptoms are likely related to degeneration of the head of the caudate nucleus.

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

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.
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.

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. This fact, and the logistical challenges to having this study performed in a standardized manner, 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. Occasionally other findings have been reported, such as iron deposition in the striatum and globus pallidus, or cerebellar atrophy. The significance of these observations is not clear.

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

Management

Treatment is purely symptomatic, employing the usual medications for dystonia and chorea. L-dopa has been reported to reduce dystonia, 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.

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.\textsuperscript{89,90} In some cases, despite the appearance of parkinsonism, the substantia nigra may be intact.\textsuperscript{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.\textsuperscript{92} The latter observation may account for the appearance of seizures.

Atrophy of the pyramidal tracts has been reported.\textsuperscript{93}

**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.\textsuperscript{94} The erythrocyte phenotype is defined as reduced Kell and absent Kx antigen expression on the cell surface.\textsuperscript{92,94} The association with acanthocytosis was first noted in 1977 in the propositus and subsequently in others.\textsuperscript{94} Elevated levels of creatine kinase were reported in 1981,\textsuperscript{95} and were associated with a myopathy which was initially thought to be benign.\textsuperscript{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.\textsuperscript{97-100} Hugh McLeod had an elevated creatine kinase,\textsuperscript{95} and in his 50’s was documented as having cardiac dysrhythmia, splenomegaly, areflexia, decreased peripheral sensation, and lower extremity weakness.\textsuperscript{100} 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.\textsuperscript{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.\textsuperscript{103} However, as refuted elsewhere,\textsuperscript{104} McLeod syndrome does not affect fertility, and is not transmitted to male children, thus would not cause death \textit{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.\textsuperscript{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,\textsuperscript{105} 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,\textsuperscript{106} primarily affecting the transportation of divalent cations.\textsuperscript{107} In addition to erythrocytes, XK is also present in muscle and in brain.\textsuperscript{108-110} In brain XK does not appear to be co-localized with Kell, as it is in other tissues.\textsuperscript{111}

There is no clear phenotype-genotype correlation, and symptoms can vary significantly within families.\textsuperscript{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.\textsuperscript{113,114} Symptomatic carrier females are occasionally reported, presumably due to X-chromosome inactivation.\textsuperscript{115,116}

McLeod syndrome has been reported in many ethnic groups, including patients from Japan,\textsuperscript{103,116} Chile,\textsuperscript{117,118} China,\textsuperscript{119} and Taiwan, although it is probably significantly rarer than ChAc.

The absence of Kell expression, as seen also in Kell null individuals,\textsuperscript{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, 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. Head-drops and orolingual dystonia with feeding, 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. 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, which is seen in approximately 2/3 of patients. Patients with McLeod syndrome may present with myopathy which can be severe and debilitating, and may occasionally lead to rhabdomyolysis.

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

**Neuropathology**

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

**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.

There is a risk of development of anti-Kell antibodies in patients who are transfused with Kell+ blood, with consequent transfusion reactions, 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.

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.

**Molecular features**

HDL2 is caused by a CTG/CAG trinucleotide repeat expansion located within the *junctophilin-3* (*JPH3*) gene on chromosome 16q24.3. 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. 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, and only occurs...
in families of African ancestry.\textsuperscript{139,142-147} In some cases, for example in ethnically-mixed populations, such as those found in Brazil\textsuperscript{145,147} and Venezuela,\textsuperscript{146} the presence of African ancestry may be hidden by the family, and demonstrated only by haplotype studies.\textsuperscript{146}

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\textsuperscript{149,150} and to loss of the mutant protein.\textsuperscript{151} The CTG expansion does not result in abnormal amino acid tracts in brain tissue,\textsuperscript{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.\textsuperscript{141} Parkinsonism and dystonia are typically more prominent than in HD,\textsuperscript{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.\textsuperscript{147,152,153} For reasons which are not known, acanthocytosis is seen in 10% of patients.\textsuperscript{154}

Eye movements may be normal, or mildly hypometric, in contrast to HD.\textsuperscript{152}

Neuroimaging
As with the above conditions, imaging is similar to that observed in HD, although cortical atrophy may also be seen.\textsuperscript{155} Hyperintensity of the rim of the putamen is reported in 3 cases who underwent MRI scanning from one large family.\textsuperscript{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 throughout the cortex.\textsuperscript{139,155,156} As in HD, there is a gradient of neuronal loss from ventral to dorsal in the caudate nucleus and putamen.\textsuperscript{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.\textsuperscript{157} For many years their names were memorialized in the eponym used for this condition, however, with recognition of their association with Nazi atrocities\textsuperscript{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.\textsuperscript{158} As noted above, one of the series of NA cases reported by Hardie et al.\textsuperscript{1} was later identified as “HARP” – hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration.\textsuperscript{2,159} A few other cases were reported with this syndrome, which was subsequently found to be due to the identical genetic mutation which causes PKAN.\textsuperscript{159,160} The term “hypoprebetalipoproteinemia” is felt to be redundant.\textsuperscript{161}

Molecular features
PKAN is due to mutations in the gene PANK2 which encodes for pantothenate kinase 2.\textsuperscript{158,162} The age of onset and rate of disease progression appear to be related to the effect of the mutation upon the enzyme.\textsuperscript{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.\textsuperscript{162} Recent investigations have focused upon mitochondrial dysfunction, with deficiency of mitochondrial coenzyme A resulting in neurodegeneration.\textsuperscript{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 and thus are only summarized here. The clinical features of PKAN are typically quite distinct from those of the other neu- roacanthocytosis syndromes described above. Onset is usually in childhood, with progressive dystonia and parkinsonism, in addition to retinitis pigmentosa and cognitive impairment. Dystonia often affects the lower face resulting in grimacing and tongue protrusion. Atypical cases present later and tend not to have retinal problems. 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. However, this finding may be absent in genetically-confirmed cases, and is not entirely specific for this disorder. In late-onset disease this finding can appear following the appearance of clinical symptoms.

Management

Treatment of PKAN at this point remains purely symptomatic. DBS has been found to be useful both in patients with both severe and with less severe disease. 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. 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. The striking overlap in the phenotypes of ChAc and MLS suggests a potential final common pathway, however, this is not yet evident.

Conflicts of Interest

The author has no financial conflicts of interest.

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REFERENCES

1. Hardie RJ, Pullon HW, Harding AE, Owen JS, Pires M, Daniels GL, et al. Neuroacanthocytosis. A clinical, haematological and pathological study of 19 cases. Brain 1991; 114(Pt 1A):13-49.
2. Gandhi S, Hardie RJ, Lees AJ. An update on the Hardie neuroacanthocytosis series. In: Walker RH, Salki S, Danek A, editors. Neuroacanthocytosis Syndromes II. 1st ed. Germany: Springer Berlin Heidelberg, 2008:43-51.
3. Critchley EM, Clark DB, Wilder A. An adult form of acanthocytosis. Trans Am Neurol Assoc 1967;92:132-137.
4. Critchley EM, Clark DB, Wilder A. Acanthocytosis and neurological disorder without betalipoproteinemia. Arch Neurol 1968;18:134-140.
5. Critchley E. Acanthocytosis associated with tics and involuntary movements. Z Neurol 1971;200:336-340.
6. Estes JW, Morley TJ, Levine IM, Emerson CP. A new hereditary acanthocytosis syndrome. Am J Med 1967;42: 868-881.
7. Levine IM, Estes JW, Looney JM. Hereditary neurological disease with acanthocytosis. A new syndrome. Arch Neurol 1968;19:403-409.
8. Velayos-Baeza A, Holinski-Feder E, Neitzel B, Bader B, Critchley EM, Monaco AP, et al. Chorea-acanthocytosis...
genotype in the original critchley kentucky neuroacanthocytosis kindred. Arch Neurol 2011;68:1330-1333.
9. Sakai T, Iwashita H, Kakugawa M. Neuroacanthocytosis syndrome and choreoacanthocytosis (Levine-Critchley syndrome). Neurology 1985;35:1679.
10. Hirose G. Neuroacanthocytosis in Japan-review of the literature and cases. In: Walker RH, Sakai S, Daniak A, editors. Neuroacanthocytosis Syndromes II, 1st ed. Germany: Springer Berlin Heidelberg; 2008:75-84.
11. Bird TD, Cederbaum S, Valev RW, Stahl WL. Familial degeneration of the basal ganglia with acanthocytosis: a clinical, neuropathological, and neurochemical study. Ann Neurol 1978;3:253-258.
12. Nagashima T, Iwashita H, Kuroiwa Y, Ohnishi S. [Chorea-acanthocytosis. A report of a family (author's transl)]. Rinsho Shinkeigaku 1979;19:609-615.
13. Ohnishi A, Sato T, Nagura H, Sakai T, Iwashita H, Kuroiwa Y, et al. Neurogenic muscular atrophy and low density of large myelinated fibres of sural nerve in chorea-acanthocytosis. J Neurol Neurosurg Psychiatry 1981;44:645-648.
14. Sakai T, Mawatari S, Iwashita H, Goto I, Kuroiwa Y. Chorea-acanthocytosis. Clues to clinical diagnosis. Arch Neurol 1981;38:335-338.
15. Serra S, Arena A, Xerra A, Gaglioietta AM, Galalitoto S. Amyotrophic choreoacanthocytosis: is it really a very rare disease? Ital J Neurol Sci 1986;7:521-524.
16. Kaplan PW, Erwin CW, Bowman MH, Massey EW. Evoked potentials in choreoacanthocytosis. Electroencephalogr Clin Neurophysiol 1986;63:349-352.
17. Yamamoto T, Hirose G, Shimazaki K, Takado S, Kosogawa H, Saei M. Movement disorders of familial neuroacanthocytosis syndrome. Arch Neurol 1982;39:298-301.
18. Kito S, Itoya E, Hiroshige Y, Matsumoto N, Miwa S. A pedigree of amyotrophic chorea with acanthocytosis. Arch Neurol 1980;37:514-517.
19. Gross KR, Skrivanek JA, Carlson KC, Kaufman DM. Familial amyotrophic chorea with acanthocytosis. New clinical and laboratory investigations. Arch Neurol 1985;42:753-756.
20. Spitz MC, Jankovic J, Killian JM. Familial tic disorder, parkinsonism, motor neuron disease, and acanthocytosis: a new syndrome. Neurology 1985;35:366-370.
21. Jankovic J, Killian JM, Spitz MC. Neuroacanthocytosis syndrome and choreoacanthocytosis (Levine-Critchley syndrome); reply. Neurology 1985;35:1679.
22. Rampoldi L, Dobson-Stone C, Rubio JR, Daniak A, Chalmers RM, Wood NW, et al. A conserved sorting-associated protein is mutant in chorea-acanthocytosis. Nat Genet 2001;28:119-120.
23. Ueno S, Maruki Y, Nakamura M, Tomemori Y, Kamae K, Tanabe H, et al. The gene encoding a newly discovered protein, chorein, is mutated in chorea-acanthocytosis. Nat Genet 2001;28:121-122.
24. Velayos-Baeza A, Vettori A, Copley RR, Dobson-Stone C, Monaco AP. Analysis of the human VPS13 gene family. Genomics 2004;84:536-549.
25. Rodrigues GR, Walker RH, Bader B, Danek A, Marques W Jr, Tumas V. Choreo-acanthocytosis: report of two Brazilian cases. Mov Disord 2008;23:2090-2093.
26. Org B, Devathasan G, Chong PN. Chorea-acanthocytosis in a Chinese patient—a case report. Singapore Med J 1989;30:506-508.
27. Li P, Huang R, Song W, Ji J, Burgunder JM, Wang X, et al. Deep brain stimulation of the globus pallidus internal improves symptoms of chorea-acanthocytosis. Neurol Sci 2012;33:269-274.
28. Liu J, Bader B, Danek A. Neuroacanthocytosis in china: a review of published reports. Tremor Other Hyperkinet Mov (N Y) 2014;4:248.
29. Sharma C, Nath K, Acharya M, Kumawat BL, Khandelwal D, Jain D. Cerebellar atrophy in neuroacanthocytosis. BMJ Case Rep 2014;2014. pii: bcr2014205232.
30. Balhara YM, Varghese ST, Kayal M. Neuroacanthocytosis: presenting with depression. J Neuropsychiatry Clin Neurosci 2006;18:426.
31. Kaul B, Goyal V, Shukla G, Srivastava A, Garg A, Bader B, et al. Mineral deposition on magnetic resonance imaging in chorea-acanthocytosis: a pathogenic link with pantothenate kinase-associated neurodegeneration? Neurol India 2013;61:169-170.
32. Karkheiran S, Bader B, Roohani M, Danek A, Shahidi GA. Chorea-acanthocytosis: report of three cases from Iran. Arch Iran Med 2012;15:790-782.
33. Lossos A, Dobson-Stone C, Monaco AP, Sofier D, Rahamim E, Newman JP, et al. Early clinical heterogeneity in choreoacanthocytosis. Arch Neurol 2005;62:611-614.
34. 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;16:426-431.
35. Ruiz-Sandoval JL, García-Navarro V, Chiquete E, Dobson-Stone C, Monaco AP, Alvarez-Palazuelos LE, et al. Choreoacanthocytosis in a Mexican family. Arch Neurol 2007;64:1661-1664.
36. Rafałowska J, Drac H, Jamrozik Z. Neuroacanthocytosis. Review of literature and case report. Folia Neuropathol 1996;34:178-183.
37. Bohsela S, Al-Jishi A, Dobson-Stone C, Rampoldi L, Saha P, Murad H, et al. Choreo-acanthocytosis: clinical and genetic findings in three families from the Arabian peninsula. Mov Disord 2003;18:403-407.
38. Kobal J, Dobson-Stone C, Danek A, Fedler V, Zvan B, Zalate M. Choreo-acanthocytosis presenting as dystonia. Acta Clin Croat 2014;53:107-112.
39. Lee JH, Lee SM, Bait SK. Demonstration of striatopallidal iron deposition in chorea-acanthocytosis by susceptibility-weighted imaging. J Neurol 2011;258:321-322.
40. Lin FC, Wei LJ, Shih PY. Effect of leviteracem on truncal tic in neuroacanthocytosis. Acta Neurol Taiwan 2006;15:38-42.
41. Samia Y, Yosra C, Fouad B, Mouna A, Olfa B, Jihed S, et al. Facial cellulitis revealing choreo-acanthocytosis: a case report. Pan Afr Med J 2014;17:322.
42. Ismailogullari S, Caglayan AO, Bader B, Danek A, Korkmaz S, Sharifov E, et al. Magnetic resonance spectroscopy in two siblings with chorea-acanthocytosis. Mov Disord 2010;25:2884-2897.
43. Tiftikcioğlu BI, Dericioglu N, Saygi S. Focal seizures originating from the left temporal lobe in a case with chorea-acanthocytosis. Clin EEG Neurosci 2006;37:46-49.
44. Ueno S, Kamae K, Yamashita Y, Maruki Y, Tomemori Y, Nakamura M, et al. Choreo-acanthocytosis with the rhino-deletion mutation. In: Danek A, editor. Neuroacanthocytosis Syndromes II. 1st ed. Germany: Springer Berlin Heidelberg; 2008:75-84.
45. Balhara YM, Varghese ST, Kayal M. Neuroacanthocytosis: presenting with depression. J Neuropsychiatry Clin Neurosci 2006;18:426.
46. Bader B, Velayos-Baeza A, Walker RH, Danek A. Domi-
nant transmission of chorea-acanthocytosis with VPS13A
mutations remains speculative. Acta Neuropathol 2009; 117:95-96; author reply 97-98.

47. Andermann E, Badhwar A, Al-Asmi A, Shustik C, Mercho S, Dubeau F, et al. Chorea-acanthocytosis in a large French-Canadian kindred with dominant or pseudo-dominant inheritance. Neurology 2004;69:A248.

48. Föller M, Herrmann A, Gu S, Alesutan I, Qadri SM, Borst O, et al. Chorein-sensitive polymerization of cortical actin and suicidal cell death in chorea-acanthocytosis. FASEB J 2012;26:1526-1534.

49. Shikawa N, Nakamura S, Sameshima M, Deguchi A, Hayashi T, Sasaki N, et al. Chorein, the protein responsible for chorea-acanthocytosis, interacts with β-adducin and β-actin. Biochem Biophys Res Commun 2013;441:96-101.

50. De Franceschi L, Scardoni G, Tomelleri C, Danek A, Walker RH, Jung HH, et al. Computational identification of phospho-tyrosine sub-networks related to acanthocyte generation in neuroacanthocytosis. PLoS One 2012;7:e31015.

51. De Franceschi L, Tomelleri C, Matte A, Brunati AM, Bo-vee-Geurts PH, Bertoldt M, et al. Erythrocyte membrane changes of chorea-acanthocytosis are the result of altered Lyn kinase activity. Blood 2011;118:5652-5663.

52. Siegl C, Hamminger P, Jank H, Ahting U, Bader B, Danek A, et al. Alterations of red cell membrane properties in neuroacanthocytosis. PLoS One 2013;8:e27615.

53. Kurano Y, Nakamura M, Ichiha M, Matsuda M, Mizuno E, Kato M, et al. In vivo distribution and localization of chorein. Biochem Biophys Res Commun 2007;353:431-435.

54. Samaranayake HS, Cowan AE, Klobutcher LA. Vacuolar protein sorting protein 13A, TtVPS13A, localizes to the tetrahymena thermophila phagosome membrane and is required for efficient phagocytosis. Eukaryot Cell 2011;10:1207-1218.

55. Park JS, Neiman AM. VPS13 regulates membrane morphogenesis during sporulation in Saccharomyces cerevisiae. J Cell Sci 2012;125(Pt 12):3004-3011.

56. Kolehmainen J, Wilkinson R, Lehesjoki AE, Chandler K, Kivite-Kallio HS, Clayton-Smith J, et al. Delineation of Coinge syndrome following a large-scale genotype-phenotype screen. Am J Hum Genet 2004;75:122-127.

57. Kihara M, Nakashima H, Taki M, Takahashi M, Kawamura K, et al. Alterations of red cell membrane properties in chorea-acanthocytosis: a mouth guard as a therapeutic approach. J Am J Psychiatry 2004;161:1716.

58. Velayos Baeza A, Dobson-Stone C, Rampoldi L, Bader R, Walker RH, Danek A, et al. Chorea-Acanthocytosis. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, 1993-2015.

59. Schneider SA, Aggarwal A, Bhatt M, Dupont E, Tisch S, Limouzin P, et al. Severe tongue protrusion dystonia: clinical syndromes and possible treatment. Neurology 2006;67:940-943.

60. Goonaratne IK, Weeratunga PN, Gamage R. Teaching video neuroimagess: orofacial dyskinesia and oral ulceration due to involuntary biting in neuroacanthocytosis. Neurology 2014;82:70.

61. Bader B, Walker RH, Vogel M, Prosielgel M, McIntosh J, Danek A. Tongue protrusion and feeding dystonia: a hallmark of chorea-acanthocytosis. Mov Disord 2010;25:127-129.

62. Chauveu M, Damon-Perriere N, Lataghe C, Spaminato U, Jung H, Burbaud P, et al. Head drops are also observed in McLeod syndrome. Mov Disord 2011;26:1562-1563.

63. Spaminato U, Debruxelles S, Rouanet M, Lafoucrière D, Bader B, Danek A, et al. Head drops are also observed in advanced Huntington disease. Parkinsonism Relat Disord 2013;19:569-570.

64. Bontjanpoupolou S, Katsarou Z, Kazis A, Vadikolia C. Neuroacanthocytosis presenting as parkinsonism. Mov Disord 2000;15:1271-1273.

65. Albin RL, Reiner A, Anderson KD, Dure L, Handelin B, Balfour R, et al. Preferential loss of striato-external pallidal projection neurons in presymptomatic Huntington's disease. Ann Neurol 1992;31:425-430.

66. Starr PA, Kang GA, Heath S, Shimamoto S, Turner RS. Pallidal neuronal discharge in Huntington's disease: support for selective loss of striatal cells originating the indirect pathway. Exp Neurol 2008;211:227-233.

67. Saiki S, Hirose G, Sakai K, Matsunami I, Higashi K, Saiki M, et al. Chorea-acanthocytosis associated with Tourettism. Mov Disord 2004;19:833-836.

68. Walker RH, Liu Q, Ichiha M, Muroya S, Nakamura M, Sano A, et al. Self-mutilation in chorea-acanthocytosis: manifestation of movement disorder or psychopathology? Mov Disord 2006;21:2268-2269.

69. Henkel K, Danek A, Grafman J, Butman J, Kassubek J. Head of the caudate nucleus is most vulnerable in chorea-acanthocytosis: a voxel-based morphometry study. Mov Disord 2006;21:1728-1731.

70. Walterfang M, Looi JC, Stynen M, Walker RH, Danek A, Niethammer M, et al. Shape alterations in the striatum in chorea-acanthocytosis. Psychiatry Res 2011;192:29-36.

71. Fontenelle LE, Leite MA. Treatment-resistant self-mutilation, tics, and obsessive-compulsive disorder in neuroacanthocytosis: a mouth guard as a therapeutic approach. J Clin Psychiatry 2008;69:1186-1187.

72. Rampoldi L, Danek A, Monaco AP. Clinical features and molecular bases of neuroacanthocytosis. J Mol Med (Berl) 2002;80:475-491.

73. Scheid R, Bader B, Ott DV, Merkenschlager A, Danek A. Development of mesial temporal lobe epilepsy in chorea-acanthocytosis. Neurology 2009;73:1419-1422.

74. Bader B, Vollmar C, Ackl N, Ebert A, la Fougère C, Noachtar S, et al. Bilateral temporal lobe epilepsy confirmed with intracranial EEG in chorea-acanthocytosis. Seizure 2011;20:340-342.

75. Al-Asmi A, Jansen AC, Badhwar A, Dubeau F, Tampieri D, Shustik C, et al. Familial temporal lobe epilepsy as a presenting feature of choreoa-acanthocytosis. Epilepsia 2005;46:1256-1263.

76. Neutel D, Miltenberger-Miltényi G, Silva I, de Carvalho M. Chorea-acanthocytosis presenting as motor neuron disease. Muscle Nerve 2012;45:293-295.

77. Kihara M, Nakashima H, Taki M, Takahashi M, Kawamur- ra Y. A case of chorea-acanthocytosis with dysautonomia; quantitative autonomic deficits using CASS. Auton Neurosci 2002;97:42-44.

78. Kageyama Y, Kodama Y, Tadano M, Yamamoto S, Ichikawa K. [A case of chorea-acanthocytosis with dilated cardiomyopathy and myopathy]. Rinsho Shinkeigaku 2000;40:816-820.

79. Gradstein L, Danek A, Grafman J, Fitzgibbon EJ. Eye movements in chorea-acanthocytosis. Invest Ophthalmol Vis Sci 2005;46:1979-1987.

80. Robinson D, Smith M, Reddy R. Neuroacanthocytosis. Am J Psychiatry 2004;161:1716.
Late appearance of acanthocytes during the course of chorea-acanthocytosis. J Neurol Sci 1999;163:175-178.

2. Storch A, Kornhaus M, Schwarz J. Testing for acanthocytosis. A prospective reader-blinded study in movement disorder patients. J Neurol 2005;252:84-90.

3. Katsube T, Shimono T, Ashikaga R, Hosono M, Kitagaki H, Murakami T. Demonstration of cerebellar atrophy in neuroacanthocytosis of 2 siblings. AJNR Am J Neuroradiol 2009;30:386-388.

4. Müller-Vahl KR, Berding G, Emrich HM, Peschel T. Chorea-acanthocytosis in monozygotic twins: clinical findings and neuropathological changes as detected by diffusion tensor imaging, FDG-PET and (123)I-beta-CIT-SPECT. J Neurol 2007;254:1081-1088.

5. Miquel M, Spampinato U, Lattaque C, Aviles-Olmos I, Bader B, Bertram K, et al. Short and long term outcome of bilateral pallidal stimulation in chorea-acanthocytosis. PLoS One 2013;8:e79241.

6. Habermeyer B, Fuhr P, Hiss B, Alber C, Müller-Spahn F. Obsessive-compulsive disorder due to neuroacanthocytosis treated with cilaplatinum. A case report. Pharmacopsychiatry 2006;39:193-194.

7. Åk S, Gürsel SC, Baş DF, Yağcıoğlu AE. Quetiapine treatment for self-mutilation in chorea-acanthocytosis: a case report. J Clin Psychopharmacol 2015;35:208-209.

8. Stafford GH, Howard RS, Lavelle J. The management of osteoarthritis in movement disorders: a case discussion. Temor Other Hyperkint Mov (N Y) 2013;3: pii: tre-03-153-3642-4.

9. Rinne JO, Daniel SE, Scaravilli F, Pires M, Harding AE, Marsden CD. The neuropathological features of neuroacanthocytosis. Mov Disord 1994;9:297-304.

10. Miki Y, Nishie M, Ichiba M, Nakamura M, Mori F, Ogawa M, et al. Chorea-acanthocytosis with upper motor neuron degeneration and 3419_3420 delCA and 3970_3973 delAGTC VPS13A mutations. Acta Neuropathol 2010;119:271-273.

11. Connolly BS, Hatzri LN, Lang AE. Neuropathological findings in chorea-acanthocytosis: new insights into mechanisms underlying parkinsonism and seizures. Acta Neuropathol 2014;127:613-615.

12. Allen FH Jr, Krabbe SM, Corcoran PA. A new phenotype (McLeod) in the Kell blood-group system. Vox Sang 1961;6:555-560.

13. Wimer BM, Marsh WL, Taswell HF, Galey WR. Haematoocytosis syndrome. Mov Disord 1983;1:203-210.

14. Marsh WL, Marsh NJ, Moore A, Symmans WA, Johnson CL, Redman CM. Elevated serum creatine phosphokinase in subjects with McLeod syndrome. Vox Sang 1981;40:403-411.

15. Swash M, Schwartz MS, Carter ND, Heath R, Leak M, Rogers KL. Benign X-linked myopathy with acanthocytes (McLeod syndrome). Its relationship to X-linked muscular dystrophy. Brain 1983;106(III):717-733.

16. Witt TN, Danek A, Reiter M, Heim MU, Dirschinger J, Olsen EG. McLeod syndrome: a distinct form of neuroacanthocytosis. Report of two cases and literature review with emphasis on neuromuscular manifestations. J Neurol 1992;239:302-306.

17. Malandrini A, Fabrizi GM, Truschi F, Di Pietro G, Moschini F, Bartalucci P, et al. Atypical McLeod syndrome manifested as X-linked chorea-acanthocytosis, neuromyopathy and dilated cardiomyopathy: report of a family. J Neurol Sci 1994;124:89-94.

18. Danek A, Utter I, Vogl T, Tatsch K, Witt TN. Cerebral involvement in McLeod syndrome. Neurology 1994;44:117-120.

19. Danek A, Rubio JP, Rampoldi L, Ho M, Dobson-Stone C, Tison F, et al. McLeod neuroacanthocytosis: genotype and phenotype. Ann Neurol 2001;50:755-764.

20. Takashima H, Sakai T, Iwashita H, Matsuda Y, Tanaka K, Oda K, et al. A family of McLeod syndrome, masquerading as chorea-acanthocytosis. J Neurol Sci 1994;124:56-60.

21. Hewer E, Danek A, Schosser BG, Miranda M, Reichard R, Castiglioni C, et al. McLeod myopathy revisited: more neurogenic and less benign. Brain 2007;130 (Pt 12):3285-3296.

22. Whitley CB, Kramer K. A New Explanation for the Reproductive. Woes and Midlife Decline of Henry VIII. Hist J 2010;53:827-848.

23.Stride P, Lopes Floro K. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

24. Ho M, Chelly J, Carter N, Danek A, Crocker P, Monaco AP. Isolation of the gene for McLeod syndrome that encodes a novel membrane transport protein. Cell 1994;77:869-884.

25. Russo D, Redman C, Lee S. Association of XK and Kell blood group proteins. J Biol Chem 1998;273:13950-13956.

26. Rivera A, Kam SY, Ho M, Romero JR, Lee S. Ablation of the Kell/Xk complex alters erythrocyte dislocation caused by somatostasis. Blood Cells Mol Dis 2013;50:80-85.

27. Redman CM, Russo D, Lee S, Kell, X- and McLeod syndrome. Baillieres Best Pract Res Clin Haematol 1999;12:621-635.

28. Russo D, Wu X, Redman CM, Lee S. Expression of Kell blood group protein in nonerythroid tissues. Blood 2000;96:340-346.

29. Jung HH, Hergersberg M, Vogt M, Pahnke J, Treyer V, Röthlisberger B, et al. McLeod phenotype associated with and Jacquetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

30. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

31. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

32. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

33. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

34. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

35. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

36. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.

37. Henry VIII, McLeod syndrome and Jacobetta's curse. J R Coll Physicians Edinb 2013;43:353-360.
131-135.
132. Miranda M, Castiglioni C, Frey BM, Hergersberg M, Danek A, Jung HH. Phenotypic variability of a distinct deletion in McLeod syndrome. Mov Disord 2007;22:1358-1361.
133. Miranda M, Jung HH, Danek A, Walker RH. The chorea of McLeod syndrome: progression to hypokinesia. Mov Disord 2012;27:1701-1702.
134. Man BL, Yuen YP, Fu YP. The first report of a Chinese family with McLeod syndrome. BMJ Case Rep 2014;2014. pii: bcr2013202785.
135. Lee S, Russo DC, Reiner AP, Lee JH, Sy MY, Telen MJ, et al. Molecular defects underlying the Kell null phenotype. J Biol Chem 2001;276:27281-27289.
136. Jung HH, Danek A, Walker RH, Frey BM, Gassner C. McLeod Neuroacanthocytosis Syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews(R) [Internet]. Seattle (WA): University of Washington, 1993-2015.
137. Gantenbein AR, Damon-Perrière N, Bohlender JE, Chauveau M, Lataxque C, Miranda M, et al. Feeding dystonia in McLeod syndrome. Mov Disord 2011;26:2123-2126.
138. Wada M, Kimura M, Daimon M, Kurita K, Kato T, Johmura Y, et al. An unusual phenotype of McLeod syndrome with late onset axonal neuropathy. J Neuropathol Exp Neurol 2009;68:1216-1222.
139. Starling A, Schlesinger D, Kok F, Passos-Bueno MR, Vainzof M, Zatz M. A family with McLeod syndrome and calpainopathy with clinically overlapping diseases. Neurology 2005;65:1832-1833.
140. Kawamura T, Takayama Y, Sakoe K, Ogawa T, Yoshioka T, Ishizawa M, et al. A case of McLeod syndrome with unusually severe myopathy. J Neurol Sci 1999;166:36-39.
141. Jung HH, Brandner S. Malignant McLeod myopathy. Muscle Nerve 2002;26:424-427.
142. Klempir J, Roth J, Zárubová K, Písacka M, Spacková N, Tilley L. The McLeod syndrome without acanthocytes. Parkinsonism Relat Disord 2008;14:364-366.
143. Valkó PO, Hänggi J, Meyer M, Jung HH. Evolution of striatal degeneration in McLeod syndrome. Eur J Neurol 2010;17:612-618.
144. Nicholl DJ, Sutton I, Dotti MT, Supple SG, Danek A, Lawden M. White matter abnormalities on MRI in neuroacanthocytosis. J Neurol Neurosurg Psychiatry 2004;75:1201-1205.
145. Dyda U, Mueller S, Sándor PS, Meier D, Boesiger P, Jung HH. Cerebral metabolic alterations in McLeod syndrome. Eur Neurol 2006;56:17-23.
146. Oechsner M, Buchert R, Beyer W, Danek A. Reduction of striatal glucose metabolism in McLeod chooreacanthocytosis. J Neurol Neurosurg Psychiatry 2001;70:517-520.
147. Geser F, Tolnay M, Jung HH. The Neuropathology of McLeod Syndrome. In: Walker RH, Saiki S, Danek A, editors. Neuroacanthocytosis Syndromes II. Germany: Springer Berlin Heidelberg, 2008;197-203.
148. Finsterer J, Stößberger C. Atrial fibrillation/flutter in myopathies. Int J Cardiol 2008;128:304-310.
149. Bansal I, Jeon HR, Hui SR, Calhoun BW, Manning DW, Kelly TJ, et al. Transfusion support for a patient with McLeod phenotype without chronic granulomatus disease and with antibodies to Ks and Km. Vox Sang 2008;94:216-220.
150. Andrew SE, Goldberg YP, Kremer B, Squitieri F, Theilmann J, Zeiser J, et al. Huntington disease without CAG expansion: phenocopies or errors in assignment? Am J Hum Genet 1994;54:852-863.
151. Wild EL, Mudanolohwe EE, Sweeney MG, Schneider SA, Beck J, Bhatia KP, et al. Huntington’s disease phenocopies are clinically and genetically heterogeneous. Mov Disord 2008;23:716-720.
152. Margolis RL, O’Hearn E, Rosenblatt A, Willour V, Holmes SE, Franz ML, et al. A disorder similar to Huntington’s disease is associated with a novel CAG repeat expansion. Ann Neurol 2001;50:373-380.
153. Holmes SE, O’Hearn E, Rosenblatt A, Callahan C, Hwang HS, Ingersoll-Ashworth RG, et al. A repeat expansion in the gene encoding junctophilin-3 is associated with Huntington disease-like 2. Nat Genet 2001;29:377-378.
154. Walker RH, Jankovic J, O’Hearn E, Margolis RL. Phenotypic features of Huntington’s disease-like 2. Mov Disord 2003;18:1527-1530.
155. Barden S, Abrahams F, Soodyall H, van der Merwe L, Greenberg J, Brink T, et al. A South African mixed ancestry family with Huntington disease-like 2: clinical and genetic features. Mov Disord 2007;22:2083-2089.
156. Magazi DS, Krause A, Bonev V, Moagi M, Iqbal Z, Dhudla M, et al. Huntington’s disease: genetic heterogeneity in black African patients. S Afr Med J 2008;98:200-203.
157. Stevanin G, Fujigasaki H, Lebre AS, Camuzat A, Jeannequin C, Dode C, et al. Huntington’s disease-like phenotype due to trinucleotide repeat expansions in the TBP and JPH3 genes. Brain 2003;126(Pt 7):1599-1603.
158. Rodrigues GG, Walker RH, Brice A, Cazeneuve C, Russell-Owen O, Teive HA, et al. Huntington’s disease-like 2 in Brazil—report of 4 patients. Mov Disord 2006;21:2244-2247.
159. Paradisi I, Ikonomu V, Arias S. Huntington disease-like 2 (HDL2) in Venezuela: frequency and ethnic origin. J Hum Genet 2013;58:3-6.
160. Castilhos RM, Souza AF, Furtado GV, Gheno TC, Silva AL, Vargas FR, et al. Huntington disease and Huntington disease-like in a case series from Brazil. Clin Genet 2014;86:373-377.
161. Santos C, Wanderley H, Vedolin L, Pena SD, Jardim L, Sequeiros J. Huntington disease-like 2: the first patient with apparent European ancestry. Clin Genet 2008;73:480-485.
162. Rudnicki DD, Holmes SE, Lin MW, Thornton CA, Ross CA, Margolis RL. Huntington disease-like 2 is associated with CUG repeat-containing RNA foci. Ann Neurol 2007;61:272-282.
163. Rudnicki DD, Pletnikova O, Vonsattel JP, Ross CA, Margolis RL. A comparison of Huntington disease and Huntington disease-like 2 neuropathology. J Neuropathol Exp Neurol 2008;67:366-374.
164. Seixas AI, Holmes SE, Santus C, Takekawa H, Pavlovich A, Sachs N, Pruitl JL, et al. Loss of junctophilin-3 contributes to Huntington disease-like 2 pathogenesis. Ann Neurol 2012;71:245-257.
165. Schneider SA, Marshall KE, Xiao J, LéDoux MS. JPH3 repeat expansions cause a progressive akinetic-rigid syndrome with severe dementia and putaminal rim in a five-generation African-American family. Neurogenetics 2012;
Fischer CA, Licht EA, Mendez MF. The neuropsychiatric manifestations of Huntington’s disease-like 2. J Neuropsychiatry Clin Neurosci 2012;24:489-492.

Walker RH, Rasmussen A, Rudnicki D, Holmes SE, Alonso E, Matsuura T, et al. Huntington’s disease—like 2 can present as chorea-akanthocytosis. Neurology 2003;61:1002-1004.

Walker RH, Morgello S, Davidoff-Feldman B, Melnick A, Walsh MJ, Shashidharan P, et al. Autosomal dominant chorea-akanthocytosis with polyglutamine-containing neuronal inclusions. Neurology 2002;58:1031-1037.

Greenstein PE, Vonsattel JP, Margolis RL, Joseph JT. Huntington’s disease like-2 neuropathology. Mov Disord 2007;22:1416-1423.

Shevell M. Hallervorden and history. N Engl J Med 2003;348:3-4.

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

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;61:1423-1426.

Ching KH, Westaway SK, Gitschier J, Higgins JJ, Hayflick SJ. HARP syndrome is allelic with pantothenate kinase-associated neurodegeneration. Neurology 2002;58:1673-1674.

Hegele RA. Neuroacanthocytosis and dyslipoproteinemia. Mov Disord 2005;20:1674-1675.

Zhou B, Westaway SK, Levinson B, Zhou B, Johnson MA, Gitschier J, Hayflick SJ. A novel pantothenate kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. Nat Genet 2001;28:345-349.

Hartig MB, Hört Engel K, Garavaglia B, Zorzi G, Kmiec T, Klöppstock T, et al. Genotypic and phenotypic spectrum of PANK2 mutations in patients with neurodegeneration with brain iron accumulation. Ann Neurol 2006;59:248-256.

Venco P, Dusi S, Valletta L, Tiranti V. Alteration of the coenzyme A biosynthetic pathway in neurodegeneration with brain iron accumulation syndromes. Biochem Soc Trans 2014;42:1069-1074.

Hört Engel K, Prokisch H, Meitinger T. An isoform of hPANK2, deficient in pantothenate kinase-associated neurodegeneration, localizes to mitochondria. Hum Mol Genet 2003;12:321-327.

Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. J Mov Disord 2015;8:1-13.

Gregory A, Polster BJ, Hayflick SJ. Clinical and genetic delineation of neurodegeneration with brain iron accumulation. J Med Genet 2009;46:73-80.

Zolkhipi Z, Dahmoush H, Saunders DE, Chong WK, Surtees R. Pantothenate kinase 2 mutation with classic pantothenate-kinase-associated neurodegeneration without ‘eye-of-the-tiger’ sign on MRI in a pair of siblings. Pediatr Radiol 2006;36:884-886.

McNeill A, Birkhall D, Hayflick SJ, Gregory A, Schenk JF, Zimmerman EA, et al. T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. Neurology 2008;70:1614-1619.

Amaral LL, Gaddikeri S, Chapman PR, Roy R, Gaddikeri RS, Marussi VH, et al. Neurodegeneration with Brain Iron Accumulation: Clinico-radiological Approach to Diagnosis. J Neuroimaging 2014 Dec 24 [Epub]. http://dx.doi.org/10.1111/jon.12195.

Krause M, Fogel W, Tronnier V, Pohle S, Hört Engel K, Thyen U, et al. Long-term benefit to pallidal deep brain stimulation in a case of dystonia secondary to pantothenate kinase-associated neurodegeneration. Mov Disord 2006;21:2255-2257.

Castelnau P, Cif L, Valente EM, Vayssiere N, Hemm S, Gannau A, et al. Pallidal stimulation improves pantothenate kinase-associated neurodegeneration. Ann Neurol 2005;57:738-741.

Mikati MA, Yehya A, Darwish H, Karam P, Comair Y. Deep brain stimulation as a mode of treatment of early onset pantothenate kinase-associated neurodegeneration. Eur J Paediatr Neurol 2009;13:61-64.

Cossu G, Abbuzzese G, Matta G, Murgia D, Melis M, Ricchi V, et al. Efficacy and safety of deferiprone for the treatment of pantothenate kinase-associated neurodegeneration (PKAN) and neurodegeneration with brain iron accumulation (NBIA): results from a four years follow-up. Parkinsonism Relat Disord 2014;20:651-654.

Prohaska R, Sibon OC, Rudnicki DD, Dank A, Hayflick SJ, Verhaag EM, et al. Brain, blood, and iron: perspectives on the roles of erythrocytes and iron in neurodegeneration. Neurobiol Dis 2012;46:607-624.

Irvine G, Irvine G. An Ultra-rare Disease? Where Do We Go from Here? Tremor Other Hyperkinet Mov (N Y) 2013;3. pii: tre-03-179-4181-1. eCollection 2013.