Neuroacanthocytosis: new developments in a neglected group of dementing disorders

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Abstract

Neurological abnormalities associated with spiculated, “acanthocytic” red cells in blood have been summarized as neuroacanthocytosis. This is a heterogeneous group of conditions that can now be clearly subdivided on the basis of genetic discoveries. The core neuroacanthocytosis syndromes are autosomal recessive chorea-acanthocytosis (ChAc) and the X-linked McLeod syndrome (MLS). Huntington’s disease-like 2 (HLD2) and pantothenate kinase associated neurodegeneration (PKAN) can now also be included. All of these share dyskinesias, cognitive deterioration and progressive neurodegeneration mainly of the basal ganglia, but they are sufficiently distinct to permit a specific working diagnosis on the basis of clinical, laboratory and imaging findings. In addition, the \textit{VPS13A} (formerly called \textit{CHAC}), \textit{XK}, \textit{JPH3} and \textit{PANK2} genes, respectively, may be examined for mutations. Unfortunately, little is yet known about the normal and abnormal physiology of the protein products of these genes, but they appear to be involved in membrane function and intracellular protein sorting. Since no cures are yet available, development and study of disease models in experimental animals (mouse, \textit{C. elegans}) is a priority for current research. From a clinical point of view, the common occurrence of cardiomyopathy in MLS, the transfusion hazards due to the McLeod Kell phenotype and the possibility of improving the violent trunk spasms and orofacial dyskinesias typical for ChAc (with subsequent lip or tongue mutilations and feeding dystonia) by deep brain surgery or stimulation should be considered in patient management.

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1. Introduction

Neuroacanthocytosis is an umbrella term for neurological conditions that occur together with misshapen acanthocytic red cells (Fig. 1A). One group of disorders is associated with lipid malabsorption and affects primarily the spinal cord, retina and peripheral nervous system. The second group are disorders that primarily affect the brain, in particular the basal ganglia (Fig. 1B). They are associated with a choreatic movement disorder, psychiatric abnormalities and progressive cognitive deterioration, resembling Huntington’s disease (HD) and other HD-like conditions. Although the hallmark of neuroacanthocytosis is an abnormality of circulating cells, the dementia in these disorders is of a primary neurodegenerative, not of a vascular nature. In some patients, particularly those affected by McLeod syndrome, who suffer from associated heart involvement, cardio-embolic strokes could be an additional cause for cognitive impairment. A review of neuroacanthocytosis is warranted because of important
advances in the genetics and the clinical delineation of these conditions.

Some of this new information was collected at the first ever scientific meeting devoted to neuroacanthocytosis held in May 2002 at Seeon, Germany [1]. A follow-up meeting will take place at the Montreal Neurological Institute in April 2005 (see www.naadvocacy.org).

2. The spectrum of neuroacanthocytosis syndromes

The term “acanthocytosis” was coined to describe the spiky deformation of erythrocytes in the Bassen–Kornzweig syndrome of fat malabsorption [2]. A few years later, Levine and Critchley independently described patients from three families who showed a neurological condition with acanthocytes yet normal lipoproteins [3–6]. Neuroacanthocytosis was subsequently adopted as a superordinate term [7,8]—encompassing conditions as diverse as Bassen–Kornzweig abetalipoproteinemia and mitochondrial cytopathies [9] that share the association of neuromuscular manifestations with acanthocytic blood cells.

In the original families of Levine and Critchley, the pattern of inheritance of the neurological and hematological phenotypes appeared autosomal-dominant with partial penetrance. Their families have been lost to follow-up so that these seminal observations have yet to be correlated with the recent molecular discoveries.

Most notably, the genes for McLeod syndrome (MLS)—originally thought to be merely a peculiar Kell blood group phenotype [10]—and for chorea-acanthocytosis (ChAc) [11,12] have since been identified. The McLeod blood group phenotype is characterized by absent Kx erythrocyte antigen, weak Kell glycoprotein antigens and X-linked inheritance [13,14]. Chorea-acanthocytosis denotes the autosomal-recessive type of neuroacanthocytosis that has been most commonly diagnosed after Levine’s and Critchley’s initial reports. Particularly in Japan, their descriptions were picked up as “amyotrophic chorea with acanthocytosis” or “chorea-acanthocytosis” and numerous cases were recognized around 1980 [15–19].

A number of observations, however, remain in which the mode of inheritance does not fit with either of the disorders. Among the families with apparent autosomal-dominant neuroacanthocytosis [20–22], one was characterized by dementia and chorea in the absence of peripheral neuromuscular abnormalities or seizure [23,24]. Neuropathology was similar to Huntington’s disease-like 2 (HDL2), with intranuclear inclusions immunoreactive for ubiquitin and expanded polyglutamine repeats [25]. Subsequent genetic testing led to identification of the family’s disease as a manifestation of HDL2 [26]. Acanthocytes may also occur in Hallervorden–Spatz syndrome (HSS)—now better designated “pantothenate kinase-associated neurodegeneration” (PKAN)—justifying the classification of this autosomal recessive condition with the neuroacanthocytoses [27–30]. There is clinical overlap with the “HARP syndrome”. This relationship has become clear since in both conditions mutations of the PANK2 gene were found [30,31].

There are a few systemic diseases with acanthocytes that secondarily show neurological signs (see Table 1) but this review is focussed on primary neurodegenerative disorders with acanthocytes and will, after a description of current
Table 1  
Syndromes with neurological findings and red cell acanthocytosis

Core neuroacanthocytosis syndromes
• ChAc: Chorea-acanthocytosis
• MLS: McLeod syndrome
• HDL2: Huntington’s disease-like 2
• PKAN: Pantothenate kinase associated neurodegeneration, including the “HARP” subtype

Observations of as yet uncertain status
• New England family of Levine [4]
• Kentucky family of Critchley [71]
• British family of Critchley [6]
• MELAS with acanthocytosis [9]
• FAPED: Familial acanthocytosis with paroxysmal exertion-induced dyskinesias and epilepsy [128]

Neuroacanthocytosis with lipoprotein disorders [32]
• Abetalipoproteinemia
• Familial hypobetalipoproteinemia
• Anderson disease
• Atypical Wolman disease

Acanthocytosis in systemic diseases that are also accompanied by neurological findings [129]
• Severe malnutrition (e.g. anorexia nervosa)
• Cancers, sarcoma
• Thyroid disorders, myxedema
• Splenectomy
• Liver cirrhosis, hepatic encephalopathy
• Psoriasis
• Eales’ disease

molecular knowledge, deal with MLS, ChAc and HDL2 in particular.

3. Molecular basis

3.1. APOB (apolipoprotein B, familial hypobetalipoproteinemia 1), FHBL2 (familial hypobetalipoproteinemia 2) and MTP (microsomal transfer protein, abetalipoproteinemia)

APOB gene defects are responsible for familial hypobetalipoproteinemia type 1 (FHBL1, MIM 107730) [32]. FHBL1 segregates as an autosomal codominant trait. Obligate heterozygotes for FHBL1 show hypercholesterolemia but are otherwise healthy. Homozygous FHBL1 is rare: patients may be detected at a young age because of fat malabsorption and reduced plasma cholesterol levels. Fat malabsorption results from an inability to form chylomicrons in the intestine, which is a direct effect of the absence of apolipoprotein B (apoB). Subsequent vitamin E deficiency leads to progressive neurologic disease with retinitis pigmentosa and acanthocytosis [32].

For the majority of familial hypobetalipoproteinemia, however, the molecular defect is not known. In one family, linkage to APOB was excluded [33]. Affected members were designated to have FHBL2 (MIM 605019) for which linkage to 3p22–p21.1 was found [34].

Mutations in the gene coding for microsomal triglyceride transfer protein (MTP) are responsible for abetalipoproteinemia (ABL, MIM 200100), the autosomal recessive disease originally described by Bassen and Kornzweig [1,32]. MTP, a dimer composed of the multifunctional enzyme protein disulfide isomerase and a unique 97 kDa subunit, is required for normal assembly and secretion of apo B-containing lipoproteins. In the absence of MTP, apoB cannot be properly lipidated and undergoes rapid degradation. As in FHBL, the resulting vitamin E deficiency causes the neurologic syndrome. Without treatment, patients may soon become wheelchair-bound or bedridden. Early administration of vitamin E arrests the otherwise progressive neuropathy and myopathy. Initial clinical signs are often the diminution and then loss of deep tendon reflexes followed by a progressive loss of position and vibration senses, a spinocerebellar syndrome and muscular weakness. In addition, retarded intellectual development is present in up to one-third of patients. Neuropathology reveals axonal degeneration of the spinocerebellar tracts and demyelination of the fasciculus cuneatus and gracilis. Deficiency of vitamin E also causes damage to the striatum. PET studies show a reduced [18F]fluorodopa uptake in the putamen and caudate, indicating dysfunction of the dopaminergic nigrostriatal projections. Overt clinical signs or symptoms from this system, specifically chorea, dystonia or parkinsonism, however, are not a feature of ABL [35]. Acanthocytic red cell deformation possibly results from decreased membrane fluidity due to altered lipid composition [32].

3.2. VPS13A (CHAC, chorein, chorea-acanthocytosis)

The molecular basis for chorea-acanthocytosis (ChAc, MIM 200150) was elucidated only recently. Through a linkage study of 11 families of different geographical origin the VPS13A locus was mapped to chromosome 9q21 [36]. Subsequently, a novel gene from this region was identified and found to be mutated in ChAc patients [11,12]. The VPS13A gene is organised in 73 exons spanning a chromosomal region of about 250 kb. There are two splicing variants of 10 kb (exons 1–69) and 11 kb (exons 1–68, 70–73) that encode for proteins of 3095 and 3174 amino acids, respectively. The longer protein product was named chorein [12]. VPS13A shows a ubiquitous pattern of expression, the two variants have been found in all tissues investigated. In particular, VPS13A expression could be detected in those tissues that are related to the clinical condition of ChAc, namely erythroid precursors, skeletal muscle and brain, where equal levels of transcript were found in several areas (including frontal lobe and putamen).

At present, 71 VPS13A mutations have been reported [11,12,37]. They seem to be evenly distributed throughout the gene with no obvious clustering. Most of them were found to be unique to the proband or family studied, indicating a strong allelic heterogeneity with no single
mutation causing the majority of ChAc cases in the population. Seventy-one percent of the reported mutations are either small deletions or insertions leading to a frameshift, or gross deletions and nonsense mutations. All these changes either introduce or are predicted to introduce a premature stop codon. This could lead to the production of a truncated protein product, alternatively to the degradation of the corresponding messenger RNA through nonsense-mediated mRNA decay [38]. This is in accordance with the recessive inheritance of chorea-​acanthocytosis, where lack of chorein is the primary cause of the disease. Twenty-​two percent of the mutations affect splicing. This relatively high percentage of splice-​site mutations could be explained by the 144 splice-​sites of VPS13A that presumably represent quite a large target for mutation. Although no experiments were carried out on patient RNA, it is likely that these mutations affected normal splicing of the gene. Only 7% of the reported mutations (5 out of 71) are missense. They are non-​conservative substitutions and were not found in control chromosomes, which suggests that they do not represent benign polymorphisms. Since most of the mutations described are predicted to be loss of function mutations, it is difficult to draw any conclusion regarding a possible genotype–phenotype correlation. The documentation of a family with autosomal-​dominant inheritance of a typical ChAc phenotype with an associated chorein mutation [22] suggests a possible dominant negative effect.

Chorein shows a good degree of sequence similarity (23–27% identity, 40–46% positivity) with four proteins of comparable size: two putative protein products of C. elegans and D. melanogaster, the protein Vps13 of S. cerevisiae and its S. pombe orthologue. The degree of homology significantly increases in the NH2-​and COOH-​terminal regions where matches can be found with additional proteins.

Little is known about the function of chorein. Amino-​acid sequence analysis failed to identify conserved domains or identifiable structural features. The only identifiable motifs were 10 tetra-trico peptide repeats (TPR), a stretch of 34 amino acids with a loose consensus that is known to mediate protein–protein interaction [39]. The presence of transmembrane domains could not be unequivocally determined using several prediction programs.

3.3. JPH3 (autosomal-​dominant neuroacanthocytosis, Huntington’s disease-​like 2)

Huntington’s disease-​like 2 (HDL2, MIM 605268) is due to an uninterrupted CTG/CAG trinucleotide repeat expansion located within a variably spliced exon (labeled 2A) between exon 1 and exon 2B of the junctophilin-3 gene (JPH3) on chromosome 16q24.3 [40]. The repeat size is polymorphic, ranging from 6 to 27 CTG/CAG triplets in the normal population, whereas affected individuals have repeat expansions of 41–58 triplets. At present, it appears that this expansion is not expressed and the significance of the positive immunoreactivity of the inclusion bodies for expanded polyglutamine repeats remains to be determined.

Genetic analysis indicated that three patients affected by an autosomal-​dominant form of neuroacanthocytosis had an expansion of the CTG/CAG repeat within JPH3, consistent with the diagnosis of HDL2. Conversely, acanthocytes were detected in one patient from a new, third HDL2 family from Mexico, but not in two other patients from this family. Three additional HDL2 patients also did not show acanthocytosis. Thus, all affected members of the neuroacanthocytosis family had the HDL2 mutation, whereas it appears that some, but not all, patients with an HDL2 mutation may develop acanthocytosis [26]. There was no apparent correlation between the phenotype, the size of the triplet expansion and the presence of acanthocytosis [24].

Junctophilin-3, the protein product of the gene associated with HDL2, appears to be involved in junctional membrane structures and may play a role in the regulation of calcium [40]. Interestingly, the proteins responsible for other neuroacanthocytosis syndromes also appear to have a role in membrane structure. Acanthocytosis in HDL2 may be mediated by a functional loss or alteration of the junctophilin-3 protein.

Mice without junctophilin-3 show impaired motor coordination, but examination of neuropathology has been limited [41].

3.4. PANK2 (pantothenate kinase-​associated neurodegeneration)

Hallervorden-–Spatz syndrome (HSS), an autosomal recessive disorder, in its classic form presents with dystonia, dysarthria and rigidity in childhood, as well as with retinitis pigmentosa. Eight percent in a larger series had acanthocytosis [30], thus confirming earlier findings in single cases [27–29]. The classical form leads to early death. In an atypical form, onset is later and progression slower and more variable. In both, iron is deposited in the basal ganglia [42]. Alternative names thus are “neurodegeneration with axonal spheroids and iron deposition” and “neurodegeneration with brain iron accumulation type 1 (NBIA1)”. Most cases were found to have a mutation of the PANK2 gene and can now be classified under the most recent designation of “pantothenate kinase-​associated neurodegeneration” (PKAN, MIM 234200). A minority of cases, however, do not carry a mutation of this gene [30]. PANK2, the gene for pantothenate kinase 2, encodes a key regulatory enzyme in the biosynthesis of coenzyme A from pantothenate (vitamin B5). Coenzyme A plays a central role in several important pathways, including phospholipid biosynthesis and, therefore, membranogenesis. PKAN is the first identified inborn error of pantothenate metabolism [43].

Even if the true prevalence of acanthocytosis is probably underestimated, PKAN can rightly be classified with the
neuroacanthocytosis syndromes, along with its variant “HARP.” This term had been coined in 1992 on the occasion of a single observation for the constellation of hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration [44], but has become expendable along with the whole idea of prebetalipoprotein significance [50].

3.5. XK (McLeod syndrome)

The X-chromosomal XK gene encodes the XK protein, a membrane transport protein of yet unknown function, which contains the Kx erythrocyte antigen [10]. Its absence is associated with McLeod syndrome (MLS, MIM 314850). Most disease-causing XK mutations comprise deletions, nonsense mutations or splice site mutations predicting an absent or truncated XK protein devoid of the Kell protein binding site. No clear phenotype–genotype correlation was observed [10,47,48]. One XK missense mutation was associated with a prototypic neuroacanthocytosis phenotype [48]. In contrast, carriers of another XK missense mutation had the McLeod blood group phenotype without evidence for CNS or neuromuscular involvement [49]. The XK protein is linked to the Kell glycoprotein and the two proteins form a functional complex of as yet unknown significance [50].

4. Clinical approach

In spite of the genetic progress presented above, molecular diagnosis so far plays a minor role in the clinical work-up of patients with suspected neuroacanthocytosis—except for an initial exclusion of an HD or DRPLA mutation (see also Table 2). However, identification of the mode of inheritance of the disease is important for genetic counseling and may be facilitated if the correct molecular diagnosis is made. Many of the procedures necessary for testing for the core syndromes are not easily accessible, which is particularly true for the VPS13A gene with its huge size and great variety of mutations. At present, VPS13A gene analysis is only available on a research basis in Oxford and in Japan [12,22,37] and takes rather long. Protein assays for chorein are a promising alternative [51].

Genetic diagnosis for MLS is more widely available (Zürich, Bristol, Oxford, New York, Sydney and Japan; for a current directory of laboratories working on ChAc and MLS, respectively, see www.genetests.org), but should not be performed as the initial diagnostic test. Instead, every patient, male or female, with suspected neuroacanthocytosis ought to receive thorough Kell blood group typing. Routine procedures are insufficient and specific antibodies that are needed to rule out or confirm the weak expression of Kell antigens typical for the McLeod red cell phenotype must be used.

Accurate determination of acanthocytosis can be challenging. Hematology labs may not follow the procedures that have been established particularly for this context [52] and neurologists commonly have too little experience with blood work. Some of the instances of late-appearing acanthocytes [53] or of “neuroacanthocytosis without acanthocytes” [54,55] are possibly due to the technicalities of acanthocyte determinations. The procedure that is evaluated best uses full blood samples in 1:1 dilution with heparinized saline. After incubation on a shaker at room temperature for 30 to 120 min, wet cell monolayers for viewing under a phase-contrast microscope are prepared. All red blood cells with spicules, which are irregular in shape and orientation/distribution (corresponding to type AI/All acanthocytes and echinocytes of Feinberg et al. [52]) are counted. Normal controls show less than 6.3% acanthocytic/echinocytic red blood cells of their total erythrocytes [56]. Confirmation of erythrocyte morphology by scanning electron microscopy is helpful if available.

Given these intricacies, it often is useful to concentrate on basic serum values, such as creatine kinase, muscle and liver transaminases, and LDH that may be abnormal in neuroacanthocytosis. Some patients may also have an anemia as a result of the shorter lives of deformed red cells.

Lipoprotein electrophoresis is necessary in every patient to search for the neuroacanthocytosis subtypes associated with lipid disorders. Vitamin E substitution is their treatment of choice and measurement of vitamin E levels thus is a laboratory procedure of immediate therapeutic consequence when neuroacanthocytosis is suspected.

Genetic testing for HDL2 is more accessible as it relies upon detection of a trinucleotide repeat expansion and is available in a small number of laboratories.

To distinguish Lesch–Nyhan syndrome and Wilson disease, respectively, uric acid, and ceruloplasmin and urinary copper must be determined. Patients with Lesch–Nyhan syndrome show self-injurious behavior (biting the fingers, hands, lips and cheeks; banging the head or limbs) somewhat reminiscent of ChAc. However, they usually present with hypotonia and developmental delay, evident by 3 to 6 months of age, and rarely learn to walk. Wilson disease better fits the age range to be considered in neuroacanthocytosis and is characterized by movement disorder, psychiatric disturbance including dementia and liver dysfunction.

Brain imaging, preferably with MRI, in MLS and ChAc may show atrophy of putamen and the caudate nucleus which can be best appreciated on coronal sections but MRI may also disclose the signal changes in the basal ganglia typical for aceruloplasminemia, neuroferritinoopathy, Wilson disease and PKAN, with the so-called “eye of the tiger sign” in the latter, due to central hyperintensity [30].

Pigmentary retinopathy may be found in PKAN, the lipoprotein disorders and in some cases of MLS with larger deletions affecting neighboring X-chromosomal genes. The eye exam should also consider the possibility of corneal
<table>
<thead>
<tr>
<th>Disease</th>
<th>MIM</th>
<th>Inheritance</th>
<th>Gene, protein</th>
<th>Chromosome</th>
<th>Clinical features</th>
<th>Morphology</th>
<th>Usual age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington’s disease</td>
<td>143100</td>
<td>AD</td>
<td>IT15, huntingtin</td>
<td>4p16.3</td>
<td>Ch, Dyt, Park, At, Dem, Sz</td>
<td>Atrophy of CN, Put, cerebral cortex</td>
<td>30–40 years, but inversely related to repeat size</td>
</tr>
<tr>
<td>HDL1 (Huntington’s disease-like 1)</td>
<td>603218</td>
<td>AD</td>
<td>PRNP, prion protein</td>
<td>20pter-p12</td>
<td>Ch, rigidity, At, Dem, Sz, mania, depression</td>
<td>Atrophy of cerebellar molecular layer with Kuru plaques, also in thalamus</td>
<td>23–41 years</td>
</tr>
<tr>
<td>HDL2</td>
<td>606438</td>
<td>AD</td>
<td>JPH3, junctophilin-3</td>
<td>16q24.3</td>
<td>Ch, Dyt, Park, At, Dem, Sz, mania, depression</td>
<td>Atrophy of CN and Put</td>
<td>35–40 years, but inversely related to repeat size</td>
</tr>
<tr>
<td>HDL4</td>
<td>single case [130]</td>
<td>AD</td>
<td>Gene and protein not identified</td>
<td>–</td>
<td>Ch, rigidity, Trem, gait difficulty, dysarthria, Dem, Sz</td>
<td></td>
<td>38 years (died age 71)</td>
</tr>
<tr>
<td>Dentato-rubro-pallido-Luysian atrophy</td>
<td>125370</td>
<td>AD</td>
<td>DRPLA, atrophin-1</td>
<td>12p13.31</td>
<td>Ch, myoclonus, At, Sz</td>
<td>Atrophy of GP and DN, RN and subthalamic nucleus</td>
<td>About 20 years, but inversely related to repeat size</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td>606159</td>
<td>AD</td>
<td>FTL, ferritin light chain polypeptide</td>
<td>19q13.3-4</td>
<td>Choroathetosis, Dyt, spasticity, rigidity, no dementia</td>
<td>Iron deposition in CN, Put, GP, DN, SN, basal ganglia cavitation, T2 signal increase [131]</td>
<td>40–55 years</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 3</td>
<td>109150</td>
<td>AD</td>
<td>MJD, ataxin-3</td>
<td>14q24.3-q31</td>
<td>Ch, Dyt, Park, Trem, At, spasticity, ocular motor disorder, Dem</td>
<td>Cell loss in Put, SN, pons, spinal chord anterior horn</td>
<td>35–40 years, but inversely related to repeat size</td>
</tr>
<tr>
<td>Spinocerebellar ataxia type 17</td>
<td>600075</td>
<td>AD</td>
<td>TBP, TATA box-binding protein</td>
<td>6q27</td>
<td>Ch, Dyt, rigidity, At, spasticity, Dem</td>
<td>Cerebellar and pontine atrophy, cell loss in CN, Put, less in Thal, cerebral cortex</td>
<td>6–30 years</td>
</tr>
<tr>
<td>Benign hereditary chorea</td>
<td>118700</td>
<td>AD</td>
<td>TITF-1, thyroid transcription factor 1, and others</td>
<td>14q-13.1</td>
<td>Ch, At, delayed motor development, normal intelligence</td>
<td>No gross atrophy, FDG-PET normal, non-specific astrocytosis [132]</td>
<td>Childhood</td>
</tr>
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<td>Condition</td>
<td>OMIM</td>
<td>Inheritance</td>
<td>Gene/Protein</td>
<td>Chromosome</td>
<td>Description</td>
<td>Age of Onset</td>
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<td>Chorea-acanthocytosis</td>
<td>200150</td>
<td>AR</td>
<td>VPS13A (CHAC), chorein</td>
<td>9q21</td>
<td>Ch, Dyt, Park, orofacial dyskinesias, Sz, neuropathy</td>
<td>20–50 years</td>
<td></td>
</tr>
<tr>
<td>HDL3</td>
<td>604802</td>
<td>AR</td>
<td>HDL3, gene and protein not identified</td>
<td>4p15.3</td>
<td>Ch, Dyt, spasticity, At, Dem, Sz</td>
<td>Childhood</td>
<td></td>
</tr>
<tr>
<td>Wilson disease</td>
<td>277900</td>
<td>AR</td>
<td>ATP7B, copper transporting P-type ATPase</td>
<td>13q14.3-q21.1</td>
<td>Dysarthria, Dyt, Park, Trem, dysphagia, cognitive and behavioural change, liver disease</td>
<td>&lt;40 years</td>
<td></td>
</tr>
<tr>
<td>Aceruloplasminemia</td>
<td>604290</td>
<td>AR</td>
<td>CP, ceruloplasmin</td>
<td>3q23-4</td>
<td>Ch, Dyt, At, Dem, diabetes</td>
<td>30–50 years</td>
<td></td>
</tr>
<tr>
<td>Pantothenate kinase associated neurodegeneration, including HARP</td>
<td>234200</td>
<td>AR</td>
<td>PANK2, pantothenate kinase 2</td>
<td>20p13</td>
<td>Choreoathetosis, Dyt, dysarthria, rigidity, spasticity, Dem</td>
<td>Childhood&lt;6 years, but also adult-onset subtype</td>
<td></td>
</tr>
<tr>
<td>Karak syndrome</td>
<td>single family</td>
<td>AR or X</td>
<td>Gene and protein not identified</td>
<td>–</td>
<td>Ch, Dyt, At</td>
<td>6 years</td>
<td></td>
</tr>
<tr>
<td>McLeod syndrome</td>
<td>314850</td>
<td>X</td>
<td>XK, XK Kell blood group protein</td>
<td>Xp21</td>
<td>Ch, Dyt, Park, Sz, neuropathy, myopathy, cardiomyopathy</td>
<td>40–70 years</td>
<td></td>
</tr>
<tr>
<td>Lubag, X-linked dystonia-parkinsonism</td>
<td>314250</td>
<td>X</td>
<td>DYT3, gene and protein not identified</td>
<td>Xq13.1</td>
<td>Dyt, segmental or generalised, commonly with Park (may be preceding)</td>
<td>12–56 years</td>
<td></td>
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<tr>
<td>Lesch–Nyhan syndrome</td>
<td>300322</td>
<td>X</td>
<td>HPRT, hypoxanthine guanine phosphoribosyltransferase 1</td>
<td>Xq26-27.2</td>
<td>Choreoathetosis, spasticity, mental retardation, biting of fingers and lips, short stature, renal calculi</td>
<td>Childhood (median onset 2 years)</td>
<td></td>
</tr>
</tbody>
</table>

deposition of copper (Kayser–Fleischer ring). The multisystem nature of the disorders under discussion calls for additional tests for possible involvement of liver and spleen (hepatosplenomegaly may be seen in MLS, liver cirrhosis in Wilson disease, etc.) and other organ systems, but should at least focus on peripheral nerve, on muscle and on the heart. Cardiomyopathy is a serious, yet treatable complication of MLS. It should also be noted that ChAc can be easily mistaken for Tourette’s syndrome initially, since both conditions share motor and vocal tics as well as obsessive-compulsive features [57].

Finally, the need for a thorough documentation of the family history must be emphasized.

Genetic basal ganglia diseases that may be considered in the differential diagnosis of neuroacanthocytosis syndrome are listed in Table 2. The clinical features of ChAc, HDL2 and of MLS are detailed below and in Table 3.

Treatment of all these disorders is limited to symptomatic therapies for the movement and psychiatric features, and control of seizures if present. Psychiatric symptoms may respond to anti-psychotics or antidepressants. Hyperkinetic movements may be reduced by the use of benzodiazepines, anti-dopaminergic agents or anticonvulsants. Patients with parkinsonian syndrome do not tend to respond to dopaminergic medications. Stimulation of thalamic or pallidal targets as well as pallidotomy have been used in ChAc, but with only partial success [58–60].

In McLeod syndrome, transfusion with Kell-positive blood may result in the generation of anti-Kell antibodies, which may cause hemolysis on subsequent transfusion. Ideally, patients should bank their own blood for autologous transfusion. If this is not possible, following transfusion they should be monitored for the development of anti-Kell antibodies and transfused with Kell-negative blood if further transfusion is needed.

4.1. Chorea-acanthocytosis

Mean age of onset in ChAc is about 35 years of age, although it can develop as early as the first decade or as late as the seventh decade. It runs a chronic progressive course and may lead to major disability within a few years. Some patients are bed-ridden or wheelchair dependent by the third decade [61,62]. Life expectancy is reduced and several instances of death during epileptic seizures have been reported. Age at death ranges from 28 to 61 years.

In ChAc, the movement disorder is mostly chorea, but some individuals present with a parkinsonian syndrome. Unsteadiness of stance and the patients’ bizarre gait seem to have choreiform as well as dystonic components. Falls may also result from impaired postural reflexes, sudden buckling of knees and equinovarus foot deformity, the latter related to dystonia as well as atrophy of the peroneal muscles. Ambulation may be severely impaired. Violent trunk spasms may occur with sudden flexion or extension movements and head banging [58]. Most characteristic for ChAc are the involuntary movements that affect face, mouth, tongue, pharynx and larynx. Involuntary vocalizations are present in about two thirds of patients. There may be bruxism, spitting or involuntary belching. Continuous tongue and lip biting can lead to mutilation [12] which patients typically try to avoid by keeping an object such as a handkerchief between their teeth [55].

Swallowing is often impaired resulting in dysphagia with reduced caloric intake and weight loss to the point of cachexia [61]. Uncontrolled dystonic tongue protrusions tend to push food out of the patient’s mouth (feeding dystonia) [62]. Patients may develop a technique of swallowing by tipping their heads back and facing the ceiling.

Dysarthria is common. Slurred speech may be a presenting symptom [61] and patients may become mute in the course of the disease [62]. As the hyperkinetic orofacial state progresses to mutism, the choreiform and dystonic syndrome gradually evolves into parkinsonism in about one third of patients. There may be increased muscle

Table 3

Clinical comparison of chorea-acanthocytosis (ChAc) and McLeod syndrome (MLS)

<table>
<thead>
<tr>
<th>Finding</th>
<th>% affected in ChAc</th>
<th>% affected in MLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak Kell antigens</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Elevation of CK</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>Elevation of LDH</td>
<td>75</td>
<td>91</td>
</tr>
<tr>
<td>Elevation of AST</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>Elevation of ALT</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Elevation of γGT</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Reduction of haptoglobin</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>Areflexia: ankles</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Areflexia: arms</td>
<td>85</td>
<td>62</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>54</td>
<td>65</td>
</tr>
<tr>
<td>Muscle biopsy: myopathic</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td>Muscle biopsy: neuropathic</td>
<td>100</td>
<td>64</td>
</tr>
<tr>
<td>Electromyography: myopathic</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Electromyography: neuropathic</td>
<td>67</td>
<td>79</td>
</tr>
<tr>
<td>Palliphaesthesia feet</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>Seizures</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>Neuropsychiatric findings</td>
<td>60</td>
<td>83</td>
</tr>
<tr>
<td>Cognitive changes</td>
<td>73</td>
<td>54</td>
</tr>
<tr>
<td>Chorea</td>
<td>85</td>
<td>94</td>
</tr>
<tr>
<td>Dystonia</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>Hyperkinesia face</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Involuntary vocalisations</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td>Tongue and lip biting</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>88</td>
<td>77</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>62</td>
<td>10</td>
</tr>
<tr>
<td>Parkinsonian features</td>
<td>32</td>
<td>19</td>
</tr>
</tbody>
</table>

The percentages of affected subjects tested for each clinical feature are given: for ChAc, the data refer to 9 women and 11 men from the families reported in Rampoldi et al. [11]; for MLS to 22 men collected by Danek et al. [48].
Epilepsy, usually as grand mal seizures, is observed in almost half the patients and can be the initial manifestation [62]. Neuropathic and myopathic involvement cause ankle areflexia in almost all patients and distally pronounced muscle atrophy and weakness in at least half. Sensory loss is usually slight or may only be detected as reduced vibration sense. Increased serum concentration of muscle creatine phosphokinase is observed in the majority of patients. In contrast to MLS, cardiomyopathy is uncommon.

4.2. Huntington’s disease-like 2

HDL2 manifests in the third or fourth decade and takes a severe progressive course with a bedridden, nonverbal state about 10 to 15 years after onset [25]. The range of phenotype is similar to that observed in HD. There is marked variation: a presentation with chorea or parkinsonism may change with evolution of the disease. Dystonia is frequent. In contrast to ChAc, however, feeding dystonia or orofacial dyskinesias with self-mutilation are not prominent, although weight loss is a characteristic feature. Early signs are often behavioral. With the exception of one Mexican pedigree, all patients reported to date have been of African ancestry [24,63,64]. Involvement of multiple organ systems, as in other neuroacanthocytosis syndromes, is not apparent.

4.3. McLeod syndrome

Male carriers of the McLeod blood group phenotype are prone to develop a multi-system disorder with hematological, neuromuscular and central nervous system (CNS) involvement. Onset ranges between 18 years and 61 years, with a mean of about 35 years [47,48,65–67]. Rarely, manifesting female heterozygous mutation carriers have been identified [67,68].

CNS manifestations of MLS resemble HD and include the prototypic triad of chorea, cognitive impairment and psychiatric symptoms.

About one third of McLeod patients present with a choreatic movement disorder. During the disease course, the majority develops chorea or other involuntary movements such as facial dyskinesia, dystarthritis and involuntary vocalizations [47,48,67,69]. In contrast to patients with ChAc, only few MLS patients develop lip or tongue biting, dysphagia, dystonia or extrapyramidal symptoms [48,67,70,71].

About 20% of MLS patients present with generalized seizures and up to 40% have seizures during the course of the disease [48,67].

Almost all show absence of deep tendon reflexes, indicative of a sensory-motor axonopathy [47,48,67]. All McLeod blood group phenotype carriers examined so far had elevated serum CK levels up to 4000 U/l [14,47,48,67,72,73]. About half of the patients develop muscle weakness during the disease course, but only a minority had severe weakness [14,47,48,67,68,72]. In addition, one case of severe rhabdomyolysis was reported [74]. In an immunohistochemical study, McLeod skeletal muscle failed to show a specific staining pattern for XK and Kell, in contrast to controls where Kell immunohistochemistry stains sarcoplasmic membranes and XK immunohistochemistry shows a type 2 fiber-specific intracellular staining. XK protein may play a crucial role for the integrity of normal muscle [75].

About 60% developed cardiac manifestations including dilated cardiomyopathy, atrial fibrillation and tachyarrhythmia [48,66,76–78]. Due to the possibility of curative interventions, MLS patients should be carefully monitored for cardiac disease.

Carriers of the McLeod blood group phenotype have non-symptomatic erythrocyte acanthocytosis and compensated hemolysis [14,47,48,67]. In about one third, a non-symptomatic hepato-splenomegaly was found [48]. If MLS patients receive multiple blood transfusions, hemolysis may be a problem following the production of anti-Kell antibodies.

5. Dementia and psychiatric disorders in neuroacanthocytosis

Impairment of higher brain function in neuroacanthocytosis, in addition to movement disorders and seizures was already noted in Levine’s family [4,79] as well as in the patients of Critchley [5,6]. Hardie and collaborators, in their mixed case series, summarized the changes as a “frontosubcortical dementia” [67,80].

In molecularly diagnosed ChAc, half of the patients show some impairment of higher cerebral function already at presentation, with the earliest manifestations below the age of 10. Of two siblings, the girl had developed behavioral problems in school, including ritualistic touching and kissing of objects. At age 24, her IQ was low. Her brother was diagnosed as dyslexic, with poor visuospatial skills, writing and spelling. His educational attainments were below average when he left school aged 16 years [67]. Another young man was diagnosed with schizophrenia in adolescence and neurological signs were noted only many years later [81]. Personality change may be another presenting symptom. Practically all patients develop cognitive or neuropsychiatric features by the fourth decade.

There is a wide range of neuropsychiatric abnormalities, many compatible with a frontal lobe syndrome. Changes in social behavior and personality are common (disinhibition, including sexual disinhibition, decreased social skills, aggressive or immature, child-like behavior). There may also be neglect of personal affairs and hygiene, apathy but also hyperactivity, impulsivity, agitation, distractability,
obsessive-compulsive features, emotional lability, depression, anxiety and paranoia.

ChAc is a dementing disease: a discrepancy between expected general intelligence and their actual test performance is frequently seen [82]. The deficits usually affect memory and executive functions. In comparison to MLS, they appear more common, manifest at a younger age and are compounded by the more pronounced neuropsychiatric manifestations of ChAc.

In HDL2, all members of the original family developed profound dementia and displayed psychiatric manifestations, such as depression, anxiety, irritability, apathy, perseverative behavior, delusions and possibly hallucinations [25]. Less severe cases have been seen, for example, one patient who lost his job because of progressive memory deficit, personality changes, depression and difficulties managing his finances at age 53 [24]. His cognitive deficit was thought mild on examination (Mini-Mental score 25/30) and may be related to the smaller size of the pathologic triplet repeat expansion (44 repeats) [24]. In another family, the contribution of the HDL2 mutation is difficult to differentiate from an influence of the fragile X mutation status that was present in addition [23].

During the course of MLS, at least one half of the patients show cognitive or neuropsychiatric features [47,48,83]. In a Swiss family [47], they often were the presenting symptom: the propositus had developed a decrease in social competence at age 25, with complete social withdrawal by the age of 49. On testing, he was disoriented for time and location and showed mild dementia. Aphasia, apraxia or visuoperceptual deficits were not found but some family members demonstrated moderate deficits in figurative memory and verbal as well as figurative fluency tasks. Complete sparing of higher functions (e.g. [69], case 6), unfortunately, may only be temporary since many MLS features develop in an age-dependent manner and cognitive changes commonly manifest in older age groups, with a range from the mid thirties to the sixties.

Onset of psychiatric features is after 25 years of age and self-neglect and personality change are noted most commonly. Inappropriate conduct (including exhibitionism), hoarding, obsessive-compulsive features, anxiety, emotional lability, depression, paranoia and hallucinations can also occur. As in ChAc, schizophrenia may be the initial manifestation of MLS at a stage with no clear-cut neurological signs [84].

The neuroimaging correlates of dementia in these neuroacanthocytosis syndromes are atrophy of the basal ganglia [47,48,53] and, in the case of HDL2, additional pronounced cortical volume loss [23,25,63]. As a yet unexplained finding, there are single case observations of white matter changes in MLS as well as in a patient with a clinical diagnosis of ChAc [85]. Imaging of local metabolism or of striatal receptors with PET or SPECT confirms the involvement of the basal ganglia [83,86], in MLS even before overt disease manifestation or in female mutation carriers [47,73].

6. Brain pathology

Histological data are available for only few molecularly classified cases of neuroacanthocytosis. Thirteen post-mortem reports without a clear genetic diagnosis are on record [52,55,87–98]. This, unfortunately, is also true for those cases with additional neurochemical studies: glutamic acid decarboxylase (GAD) and choline acetyltransferase levels were reported to be normal in caudate nucleus and putamen; GAD was increased in the substantia nigra. Substance P and dopamine metabolites were reduced in some of the brains [87,89,95,99].

Possibly all of the unclassified post-mortem cases represent instances of ChAc, yet VPS13A mutations [11,37] have been proven in only four: in case 2 from the series of Hardie et al. [67,93,94], two brothers from Mexico [61] and a French patient [58,100–102]. With respect to MLS, much less information is available. One male from the New Zealand family [103] was described in a book chapter and an abstract [104,105], whereas the second patient, the most severely affected manifesting female mutation carrier known so far, perhaps is atypical [67,93,94,106].

The findings in both conditions are very similar as seen with the conventional methods that were applied. There is marked striatal atrophy, with loss of nerve cells and reactive astrocytic gliosis on microscopy. The head of the caudate nucleus is most affected. Putamen and globus pallidus are more involved in ChAc than in MLS. In ChAc, the thalamus showed some increased glosis [61,67,100,102]. In the MLS case from New Zealand, slight white matter myelin pallor was noted.

Only in ChAc have clear changes been found in the substantia nigra [61,67]. In one case, nerve cell loss was practically complete in the pars reticulata and was less marked in the pars compacta. Notably, Lewy bodies were absent [93,94]. No definite abnormalities were detected in other brain structures in either ChAc and MLS: the cortex in particular was spared.

In contrast, in HDL2, severe cortical atrophy diffusely involved all lobes and was most conspicuous in the cingulum. Caudate and putamen were also severely affected by atrophy, neuronal loss and gliosis, with a gradient very similar to that seen in HD. Some of the scattered residual, large-caliber neurons were identified as interneurons by somatostatin-immunoreactivity. Lesser degrees of neuronal loss were present in all areas of neocortex sampled (mainly large layer III pyramidal neurons), as well as in globus pallidus, substantia nigra, locus ceruleus and amygdala. On immunohistochemistry, ubiquitinated intranuclear neuronal inclusions were found throughout all areas of the cerebral cortex, the substantia
nigra, the thalamus and were most numerous in the insula. In the basal ganglia, they were not detected [23]. This finding is also reminiscent of HD.

### 7. Pathogenesis

The mechanisms leading from genes to clinical manifestations in the neuroacanthocytosis syndromes are still far from being understood.

With respect to XK, there is converging evidence that the XK-Kell-complex might play an important role in muscle and nerve cell physiology [107]. The Kell protein is an endothelin-3 converting enzyme generating the bioactive endothelin-3 [108,109]. Endothelin is a neutrophoric factor at low concentrations and a cytotoxic factor at high concentrations [110,111]. However, no acanthocytosis, cerebral or neuromuscular involvement has yet been described in individuals who lack the Kell protein, as indicated by the K0-phenotype of their red cells [112].

On the other hand, the XK protein has been found to share important homologies with the nematode C. elegans, in which it functions as a cell death effector downstream of the caspase-ced-3 [107]. The human homologue of ced-3, caspase-8, plays a crucial role in the striatal neurodegeneration in Huntington’s disease [113,114]. XK dysfunction might cause apoptosis dysregulation, and should be considered as a major cause of myopathy and striatal neurodegeneration in McLeod syndrome.

For ChAc, hints for understanding the function of chorein may be gathered from functional studies of its S. cerevisiae homologue Vps13. Vps13 is required for proper trafficking of protein Kex2p, and to a lesser extent Vps10 and Ste13, between the Trans Golgi Network (TGN) and the pre-vacuolar compartment, corresponding to the multivesicular body/late endosome in animal cells [115]. It is reasonable to assume a role for chorein similar to that of its yeast counterpart. Indeed, chorein might control one or more steps in the cycling of proteins through the TGN to early and late endosomes, lysosomes and the plasma membrane.

Scrutiny of database information has resulted in the identification of the new human gene family, VLG. In addition to VPS13A, “Vps13-like genes” were identified on chromosomes 1, 8 and 15 [116]. One of them has recently been reported as COHI, involved in Cohen syndrome (MIM 216550). This autosomal recessive disorder is quite unlike ChAc and comprises nonprogressive psychomotor retardation with a cheerful disposition, microcephaly, facial dysmorphism, childhood hypotonia and joint laxity, progressive retinochoroidal dystrophy, myopia and intermittent isolated neutropenia [117]. All four VLG genes are widely expressed in human tissues and their gene products probably are involved in the transport of different proteins, such as the proprotein convertases, homologous to the yeast Kex2p, which also constitute a protein and gene family in higher species [116].

Triplet repeat diseases such as Huntington’s disease and HDL2 share a number of common features, including the formation of intracellular insoluble protein aggregates by the mutant protein. N-terminal fragments of the Huntington’s disease gene product, including the expanded polyglutamine (polyGln) tract, are toxic to cells and mice [118–120]. In this context, a role for transglutaminases, a class of cross-linking enzymes, has been proposed: the polyGln domain in the altered protein could result in increased substrate for tissue transglutaminase (tTGase) and therefore contribute to aggregate formation in Huntington’s disease brain [121]. This Ca^{2+}-dependent enzyme has been implicated in a number of cellular processes including cell attachment, axonal growth and regeneration, as well as cell growth regulation and apoptosis (for review, see [122]). In vitro, in the presence of tTGase, purified glyceraldehyde-3-phosphate dehydrogenase (GAPDH)—a key glycolytic enzyme that binds tightly to the polyGln domains—covalently attaches to polyGln peptides. This results in the formation of high molecular weight aggregates, depending on the length of polyGln stretches. Extracts of a Balb-c 3T3 fibroblast cell line overexpressing human tTGase were able to induce the formation of insoluble aggregates incorporating GAPDH [123]. In addition, when tTGase in HD fibroblasts is activated by a calcium ionophore, levels of the expanded huntingtin fragment increase, and insoluble high-molecular-weight aggregates appear, along with evidence of apoptosis [124]. Interestingly, patients with a clinical diagnosis of ChAc showed increased amounts of tTGase-derived Nε-(γ-glutamyl)lysine isopeptide cross-links in erythrocytes and muscle [125]. Immunohistochemistry demonstrated abnormal accumulation of tTGase products, as well as of proteinaceous bodies in ChAc muscles. The striking similarity of these aggregates suggests that the diverse neurological disorders may have a common pathogenesis related to abnormal protein conformation [126] and the aggregates may be toxic via the recruitment of factors that are normally central to cell function, viability and structure (for review, see [127]).

### 8. Animal models

Mouse models for HDL2 [41] and MLS are already available, the latter unfortunately still unpublished. There are also attempts to create an MLS model in C. elegans.

JPH3 knockout mice demonstrated motor incoordination, but no signs of neurodegeneration, nor of changes in junctional membrane structures were found up to the age of 12 weeks [41]. Examination of older mice may be more revealing.

To understand chorein’s function, VPS13A knock-out mice are now required. VPS13A murine homologue (mVPS13A) localises to mouse chromosome 19 and is
Fig. 2. Murine homologue of VPS13A. (A) Schematic representation of mVPS13A genomic structure (boxed) as available from UCSC database (http://www.genome.ucsc.edu). Partial transcripts matching with mVPS13A are indicated. (B) Alignment of human and murine VPS13A protein products. Identities are highlighted.
organised in 72 exons, over a region of approximately 180 kb (Fig. 2A). The transcript has an open reading frame of 9474 bp, encoding a protein of 3157 amino acids. In silico analysis shows that mVPS13A has a very similar expression profile to its human counterpart, being found in all tissues analysed. The similarity between the human and the murine proteins is highly significant with more than 90% of the residues being conserved in the two species (Fig. 2B). The targeting construct aiming to delete exons 6 and 7 has already been built and will bring the remaining downstream sequences out of frame and completely inactivate the gene. The targeting vector has been electroporated into embryonic stem cells, which presently are being screened to identify the desired clone.

VPS13A null mice will represent an invaluable tool to advance our understanding of the molecular and physiological abnormalities triggered by the disease and will be very powerful if studied in parallel with HDL2 and MLS mice. Even if distinct mutations underlie the different types of neuroacanthocytosis, there must be one common final pathway that leads to changes in neurons as well as in red blood cells. Mouse models should be able to solve this intriguing question and might provide the essential clues in the search for a cure of these yet untreatable conditions.

References


