McLeod syndrome: a neurohaematological disorder

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The X-linked McLeod syndrome is defined by absent Kx red blood cell antigen and weak expression of Kell antigens, and this constellation may be accidentally detected in routine screening of apparently healthy blood donors. Most carriers of this McLeod blood group phenotype have acanthocytosis and elevated serum creatine kinase levels and are prone to develop a severe neurological disorder resembling Huntington’s disease. Onset of neurological symptoms ranges between 25 and 60 years, and the penetrance of the disorder appears to be high. Additional symptoms of the McLeod neuroacanthocytosis syndrome that warrant therapeutic and diagnostic considerations include generalized seizures, neuromuscular symptoms leading to weakness and atrophy, and cardiopathy mainly manifesting with atrial fibrillation, malignant arrhythmias and dilated cardiomyopathy. Therefore, asymptomatic carriers of the McLeod blood group phenotype should have a careful genetic counseling, neurological examination and a cardiologic evaluation for the presence of a treatable cardiomyopathy.

Key words: cardiopathy, chorea, McLeod blood group phenotype, myopathy, neuroacanthocytosis syndrome, neurodegeneration.

Introduction

McLeod syndrome (MLS) is an X-linked multisystem disorder that is assigned to the neuroacanthocytosis syndromes (see Table 1 [1,2] and http://www.geneclinics.org/profiles/mcleod). Haematologically, MLS is characterized by the absence of Kx red blood cell (RBC) antigen, weak expression of Kell RBC antigens, acanthocytosis and compensated haemolysis [3]. Asymptomatic carriers of the McLeod blood group phenotype may be accidentally recognized by blood bank testing [3,4]. All McLeod carriers reported up to date have elevated serum creatine kinase (CK) levels. They may develop neurological signs and symptoms with a mean onset age from 30 to 40 years, and high penetrance of the disorder [4–6]. Neuromuscular manifestations include myopathy, sensory-motor axonal neuropathy and cardiomyopathy [1]. Central nervous system (CNS) manifestations are similar to that of Huntington’s disease, and consist of a choreatic movement disorder, ‘subcortical’ neurobehavioural deficits, psychiatric abnormalities and generalized seizures [1,2]. McLeod syndrome is caused by mutations of the XK gene encoding the XK protein, which carries the Kx RBC antigen [7]. Although the exact function of the human XK protein is not yet known, available data suggest an important role for apoptosis regulation. Thus, MLS might be a model disorder to study principal mechanisms that are not only involved in RBC physiology but also in neurodegeneration.

The Kell blood group system

The Kell system was first identified in 1946 by Coombs with the help of his newly developed antiglobulin test [8]. Rhesus incompatibility with the mother, Mrs Kell, had been ruled out as the cause of haemolytic disease in her child. Subsequently, Kell became the third most important blood group system after the ABO and rhesus systems.

The McLeod phenotype of the Kell system was detected by routine screening for allogenic antibodies at Harvard University blood bank in 1960 [3]. The RBCs of the propositus, Hugh McLeod, showed an unexplainably weak reactivity to Kell antisera. Immunohaematologically, the McLeod blood group...
The Kell protein is a 93-kDa glycoprotein that is encoded by the KEL locus on chromosome 7q34. KEL contains 19 exons and shares a consensus sequence with a large family of zinc-dependent endopeptidases [11]. The Kell glycoprotein is a type II red cell membrane protein with a short intracellular amino terminal, a single transmembrane and a large extracellular domain [12]. It shows substantial homology with the M13 subfamily of mammalian neutral endopeptidases, including endothelin converting enzyme-1 (ECE1; 600423). ECE-1 converts big endothelin-3 into endothelin-3, the bioactive peptide [11]. Its extracellular conformation is stabilized by seven intramolecular disulphide bonds preserving endopeptidase activity of KEL protein as well as most of the KEL antigens.

The XK protein contains three exons and is located on Xp21·1. It shares important homologies with the ced-8 protein of the nematode Caenorhabditis elegans where it controls the timing of programmed cell death [13]. The XK protein is predicted to have 10 transmembrane domains and shows structural characteristics of procaryotic and eucaryotic membrane transport proteins [7]. The XK protein carries the Xk RBC antigen [14] and is linked to the Kell glycoprotein by a single disulphide bond (XKcys347-KellCys72) [15].

Databank analysis demonstrated that the human XK gene belongs to a gene family with several different members [16]. Sequence similarity searches identified a family of nine full-length human genes related to ced-8, as well as a series of eight Y chromosome–linked partial sequences. Sequence comparisons confirmed that previously identified highly conserved motifs in ced-8 and XK are shared with the related genes. Several residues in these motifs were identical between ced-8 and other family members, but not conserved with XK [17]. Recently, two cDNAs, XPLAC and XTES, have been cloned. XPLAC, like XK, has three exons and is located on X chromosome at q22·1, while XTES has four exons and is located at 22q11·1. While XK is ubiquitously expressed, XPLAC predominantly in placenta and adrenal gland, and XTES is exclusively expressed in primate testis [16].

Several studies demonstrated that XK and Kell are co-expressed in erythroid tissue [7,16,18,19]. In the erythroid tissue, Kell and XK most probably formed a functional complex, as Kell antigen expression, as well as Kell protein density on the RBC membrane, was dependent on the expression of XK protein [20,21]. In other tissues, however, the Kell and XK protein had a differential expression pattern. In skeletal muscle, there was no colocalization of Kell and XK [22]. In rodent and human brain, XK was expressed in intracellular compartments of neurons, whereas Kell expression was restricted to RBCs in cerebral vessels [19]. Another study showed that XK, but not Kell, was significantly expressed in brain, spinal cord, muscle, heart, small intestine, stomach, bladder and kidney [23]. In brain, XK was predominantly expressed in neuronal cells [23]. Co-expression of Kell and XK in erythroid tissues and the different expressions in non-erythroid tissues suggests that XK may have a complementary haematological function with Kell and a separate role in other tissues.

### Molecular basis

The Kell protein is a 93-kDa glycoprotein that is encoded by the KEL gene on chromosome 7q34. KEL contains 19 exons and shares a consensus sequence with a large family of zinc–dependent endopeptidases [11]. The Kell glycoprotein is a type II red cell membrane protein with a short intracellular amino terminal, a single transmembrane and a large extracellular domain [12]. It shows substantial homology with the M13 subfamily of mammalian neutral endopeptidases, including endothelin converting enzyme-1 (ECE1; 600423). ECE-1 converts big endothelin-3 into endothelin-3, the bioactive peptide [11]. Its extracellular conformation is stabilized by seven intramolecular disulphide bonds preserving endopeptidase activity of KEL protein as well as most of the KEL antigens.

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### Immunohaematology

At present, 35 mutations of the KEL locus are characterized [24]. At the moment, the International Society of Blood Transfusion (ISBT) recognizes 31 distinct antigens of the Kell system, including four pairs of antithetical antigens and one triplet, 18 antigens with high frequency and 10 of low frequency (Table 2). According to the ISBT, the Kell antigens are numbered from K1 to K31, including two obsolete antigens [25]. Most KEL blood group polymorphisms are located in the extracellular, amino-terminal half of the protein (exon 6–10) while the carboxy-terminal half of the protein (exon 11–19)

### Table 1 Neuroacanthocytosis syndromes [1]

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
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<tbody>
<tr>
<td>Core neuroacanthocytosis syndromes</td>
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<tr>
<td>Chorea-acanthocytosis (ChAc)</td>
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<tr>
<td>McLeod syndrome (MLS)</td>
<td></td>
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<tr>
<td>Huntington’s disease–like 2 (HDL2)</td>
<td></td>
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<tr>
<td>Pantothenate kinase associated neurodegeneration (PKAN; including</td>
<td></td>
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<tr>
<td>HARP subtype)</td>
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<tr>
<td>Neuroacanthocytosis with lipoprotein disorders</td>
<td></td>
</tr>
<tr>
<td>Abetalipoproteinemia (Bassen–Kornzweig syndrome)</td>
<td></td>
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<tr>
<td>Familial hypobetalipoproteinemia</td>
<td></td>
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<tr>
<td>Anderson disease</td>
<td></td>
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<tr>
<td>Atypical Wolman disease</td>
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<tr>
<td>Acanthocytosis in systemic diseases where neurological findings may also</td>
<td></td>
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<tr>
<td>be present</td>
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<tr>
<td>Severe malnutrition (e.g. anorexia nervosa)</td>
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<tr>
<td>Cancers, sarcoma</td>
<td></td>
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<tr>
<td>Thyroid disorders, myxoedema</td>
<td></td>
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<tr>
<td>Splenectomy</td>
<td></td>
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<tr>
<td>Liver cirrhosis, hepatic encephalopathy</td>
<td></td>
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<tr>
<td>Psoriasis</td>
<td></td>
</tr>
<tr>
<td>Eales’ disease</td>
<td></td>
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<tr>
<td>MELAS</td>
<td></td>
</tr>
<tr>
<td>HARP, hypobetalipoproteinemia, acanthocytosis, retinitis pigmentosa,</td>
<td></td>
</tr>
<tr>
<td>palidal degeneration; MELAS, mitochondrial encephalopathy with lactic</td>
<td></td>
</tr>
<tr>
<td>acidosis and stroke-like episodes.</td>
<td></td>
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</tbody>
</table>

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is phylogenetically conserved preserving the endopeptidase activity [12]. Some of the polymorphism are located in the active part of the protein, among those the antithetical pair K6/K7 (Js²/Sutter a, K6[Jsa]/Js b, Sutter b, K7), which is characterized by C1910T (Leu597Pro) in exon 17 [12]. However, a functionally active Kell glycoprotein for humans might not be essential as there are numerous K0 phenotypes that do not exhibit clinical deficiencies.

Table 2 gives an overview of the currently recognized Kell protein antigens and their underlying molecular mechanisms and shows the systematic nomenclature of Kell antigens as suggested by the ISBT in perspective to the historical and generic nomenclature of the Kell antigens [25]. Besides the Kell protein antigen polymorphisms there are numerous mutations at the KEL locus that create a K0 or Kmod phenotype. Most of these mutations are point mutations, frameshift mutations or splice site mutations that lead to protein truncation or accelerated protein degradation [25–28]. In addition, several mutations in the coding sequence of the KEL locus are associated with weak expression of the Kell epitopes. These phenotypes are assigned to Kmod phenotypes [29]. K0 and Kmod phenotypes are characterized by strongly expressed Kx antigen. In contrast, McLeod phenotypes lack the Kx antigen and the RBCs present weak or missing expression of all Kell epitopes.

The formerly KEL15 (Kx) antigen has been regrouped into the new antigen system 019 (XK019001), as it was discovered that the XK protein is a product of the XK locus on chromosome Xp21·1. The XK protein carries only one single antigen, Kx. The absence of Kx reflects loss of XK protein on the RBC membrane, which might be due to mutational, transcriptional

### Table 2 Antigens of the Kell blood group system as recognized by the ISBT (October 2006)

<table>
<thead>
<tr>
<th>Number</th>
<th>ISBT nomenclature</th>
<th>Symbol</th>
<th>Generic name</th>
<th>Mutation</th>
<th>Exon</th>
<th>AA</th>
<th>Prevalence</th>
<th>Antithetic</th>
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<td>001</td>
<td>KEL1</td>
<td>K, Kell, K1</td>
<td>T698C</td>
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<td>Thr193Met</td>
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<tr>
<td>002</td>
<td>KEL2</td>
<td>K, Celano, K2</td>
<td>C698T</td>
<td>6</td>
<td>Met193Thr</td>
<td>High</td>
<td>1</td>
<td></td>
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<tr>
<td>003</td>
<td>KEL3</td>
<td>Kp⁴, K3</td>
<td>T616C</td>
<td>8</td>
<td>Arg281Trp</td>
<td>Low</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>004</td>
<td>KEL4</td>
<td>Kp⁵, K4</td>
<td>C616T</td>
<td>8</td>
<td>Thr281Arg</td>
<td>High</td>
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<tr>
<td>005</td>
<td>KEL5</td>
<td>Ku, K5</td>
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<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td>006</td>
<td>KEL6</td>
<td>Js², Sutter a, K6</td>
<td>C1910T</td>
<td>17</td>
<td>Leu597Pro</td>
<td>Low</td>
<td>3</td>
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<tr>
<td>007</td>
<td>KEL7</td>
<td>Js², Sutter b, K7</td>
<td>T1910C</td>
<td>17</td>
<td>Pro597Leu</td>
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<tr>
<td>008</td>
<td>obsolete</td>
<td>Kw</td>
<td>n.a.</td>
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<td>n.a.</td>
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<tr>
<td>009</td>
<td>obsolete</td>
<td>Kl</td>
<td>n.a.</td>
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<td>n.a.</td>
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<tr>
<td>010</td>
<td>KEL10</td>
<td>U, K10</td>
<td>T601A</td>
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<td>Glu494Val</td>
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<tr>
<td>011</td>
<td>KEL11</td>
<td>Côte, K11</td>
<td>T1026C</td>
<td>8</td>
<td>Val302Ala</td>
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<tr>
<td>012</td>
<td>KEL12</td>
<td>Boc, K12</td>
<td>A1763G</td>
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<td>His548Arg</td>
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<tr>
<td>013</td>
<td>KEL13</td>
<td>SGRO, K13</td>
<td>T106C</td>
<td>9</td>
<td>Leu329Pro</td>
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<td></td>
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<td>G1716A</td>
<td>15</td>
<td>Trp532Stop</td>
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<td>KEL14</td>
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<td>015</td>
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<td>KEL17</td>
<td>Wk⁶, K17</td>
<td>C1025T</td>
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<td>Val302Ala</td>
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<tr>
<td>018</td>
<td>KEL18</td>
<td>K18</td>
<td>C508T</td>
<td>4</td>
<td>Arg130Trp</td>
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<td></td>
<td></td>
<td></td>
<td>G509A</td>
<td>Arg130Gln</td>
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<td>KEL19</td>
<td>K19</td>
<td>G1595A</td>
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<td>Arg492Gln</td>
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<tr>
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<td>n.d.</td>
<td>n.d.</td>
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<tr>
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<td>Ala322Val</td>
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<td>Arg382Gln</td>
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<td>KEL24</td>
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<td>6</td>
<td>Pro308Arg</td>
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<td>025</td>
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<td>VLAN</td>
<td>A863G</td>
<td>8</td>
<td>Gln248Arg</td>
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<td>026</td>
<td>KEL26</td>
<td>TOU</td>
<td>G1337A</td>
<td>11</td>
<td>Arg406Gln</td>
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<tr>
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<td>KEL27</td>
<td>RAZ</td>
<td>G865A</td>
<td>8</td>
<td>Gln249Lys</td>
<td>High</td>
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<tr>
<td>029</td>
<td>KEL29</td>
<td>KALT</td>
<td>G1988A</td>
<td>17</td>
<td>Arg623Gln</td>
<td>High</td>
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<tr>
<td>030</td>
<td>KEL30</td>
<td>KTIM</td>
<td>G1033A</td>
<td>8</td>
<td>Asp305Asn</td>
<td>High</td>
<td></td>
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</tr>
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</table>

n.d., not defined; n.a., not applicable.
or translational deficiency of the XK gene [30,31]. XK is located close to the locus of CGD, Duchenne muscle dystrophia and retinitis pigmentosa on the X chromosome Xp21·1. Its alteration is necessary but not predictive of the neurological manifestation of MLS [4,6,32–34]. Kx negativity of RBC reflects the serologically specific finding of the McLeod phenotype. The associated abortive expression of Kell protein, reflected by low or missing reactivity of all Kell antigens, serves as a major surrogate for the presence of dysfunctional XK mutations.

Transfusion hazards

Boys with X-linked chronic granulomatous disease (CGD) (see below) are at risk of developing anti-Kx antibodies, which may lead to serious transfusion hazards when receiving multiple transfusions [35]. Rarely, carriers of the McLeod phenotype without CGD may develop anti-Kx antibodies [36]. Therefore, transfusion hazards must be considered in all carriers of the McLeod phenotype due to alloergic antibody production, which occurs exclusively in male carriers of the McLeod mutation and requires previous exposure to Kx antigens as a result of homologous blood transfusion. Autologous blood banking for males with the McLeod blood group phenotype should be considered before carrying out elective surgical procedures that may possibly require transfusions. Female carriers of McLeod mutations are always hemizygous mutation carriers and therefore not prone to anti-Kx generation.

Laboratory findings

Most carriers of the McLeod blood group phenotype have significant RBC acanthocytosis (Fig. 1). However, examination for RBC acanthocytosis has to be done according to a standardized protocol with 1 : 1 dilution of the blood in heparinized saline and phase contrast microscopy [37]. Additional laboratory findings in most McLeod patients include compensated haemolysis and elevated serum CK levels [4–6,9,33].

Hepatosplenomegaly was found in about a third of McLeod patients and MLS may rarely present as hepatic disease [4,38]. More likely, hepatosplenomegaly is due to an MLS-associated extravascular haemolytic state. Absence of the XK protein in the RBC membrane leads to a lipid imbalance between the inner and outer leaflet of the RBC membrane involving phosphatidylserine (PS), which is normally enriched in the inner leaflet. Diminished PS in the inner leaflet causes shrinkage and acanthocytic deformation of the RBC [39]. Although McLeod RBC have normal adenosine triphosphate (ATP) levels, normal range of glycolytic and non-glycolytic enzymes, and normal osmotic fragility [39], they are eliminated from circulation more rapidly than normal RBC by the reticuloendothelial system (RES) due to overexpression of PS on the outer membrane leaflet [40–42]. Clinically, this leads to MLS-associated non-immune mediated, extravascular haemolysis. Maintenance of lipid bilayer asymmetry and normal RBC shape are dependent on ATP and Ca2+ consuming processes [43,44]. Therefore, the abnormalities of McLeod RBC might be explained by the absence of XK protein that may interfere with transmembrane transport of essential metabolites.

McLeod syndrome and chronic granulomatous disease

CGD is an inherited disorder of phagocyte function, characterized by recurrent bacterial and fungal infections and by granuloma [45]. Neutrophils, monocytes/macrophages and eosinophils of CGD patients cannot generate microbicidal oxygen metabolites due to a defect in any of the four components of the phagocyte nicotinamide adenine dinucleotide phosphate oxidase, namely, gp91–, p22–, p47– and p67–phox [46]. Three of these subtypes are autosomal recessive disorders, namely, cytochrome b negative CGD caused by mutations in the gene encoding p22–phox (CYBA; MIM-Nr. 233690), cytochrome b positive CGD type I caused by mutation in the NCF1 gene that encodes the p47–phox (phagocyte oxidase) protein (MIM-Nr. 233700), cytochrome b positive CGD type II caused by mutation in the NCF2 gene that encodes the p67–phox (phagocyte oxidase) protein (MIM-Nr. 233710). X-linked CGD is caused by mutations in the gene encoding p91–phox (CYBB; MIM-Nr. 306400). A vast number of different CYBB
mutations including deletions, insertions, missense, non-sense and splice site mutations have been identified to date [47]. Rarely, large deletions may cause a contiguous gene syndrome including the loci for Duchenne muscular dystrophy (MIM-Nr. 310200), X-linked retinitis pigmentosa (MIM-Nr. 300389), and the McLeod blood group phenotype [10,48,49]. Only a minority of boys with X-linked CGD carry the McLeod blood group phenotype. There are no reports demonstrating that these boys have CNS or neuromuscular manifestations of MLS, most probably because these manifestations have a late adult onset. However, these boys are at risk to develop anti-Kx antibodies, which may lead to serious transfusion hazards when receiving multiple transfusions as indicated above [35].

From haematology to neurology

Marsh and colleagues demonstrated that male carriers of the McLeod blood group phenotype have elevated serum levels of CK reflecting muscle cell pathology [50]. Subsequently, it was recognized that McLeod carriers had a 'neurological disorder characterized by involuntary dystonic or choreiform movements, areflexia, wasting of limb muscles, elevated CK, and congestive cardiomyopathy' [51]. This first short description of 1981 as well as the subsequent clinical observations defines the MLS as a multisystem disorder with haematological, neuromuscular and CNS involvement [4–6,52].

Central nervous system involvement

Central nervous system manifestations of MLS closely resemble Huntington's disease. Symptoms and signs comprise the prototypic triad of a progressive neurodegenerative basal ganglia disease including:

- choreatic movement disorder,
- ‘subcortical’ cognitive impairment, and
- psychiatric symptoms.

Movement disorder

Choreatic movements are the presenting sign in about 30% of McLeod patients [4–6,53]. Abnormal motor findings may be subtle such as a slight generalized restlessness with frequent changes of posture or with tic-like movements [4,6,53]. During the course of the disorder, however, the majority of patients develop chorea [4–6]. Additional involuntary movements include facial dyskinesia and dysarthria as well as involuntary vocalization [4–6,53]. There is considerable inter- and intrafamilial variability with respect to the type and the severity of the movement disorder [6]. In contrast to autosomal recessive chorea-acanthocytosis (ChAc; MIM 200150; Levine–Crichley syndrome), only very few McLeod patients have habitual lip or tongue biting, dysphagia, dystonia or extrapyramidal signs [2,4,5].

Cognitive impairment

Cognitive impairment is not a major presenting finding in MLS. During the course of the disease, however, about 50% of the patients show cognitive decline [4–6,54,55]. The data available suggest a 'subcortical' pattern of cognitive deficits similar to Huntington's disease [56]. Severity of cognitive alterations shows a remarkable intrafamilial variability and ranges from slight memory impairment to frank dementia [6].

Psychiatric abnormalities

About 20% of McLeod patients manifest with psychiatric abnormalities including personality disorder, anxiety, depression, obsessive-compulsive disorder, bipolar disorder, or schizoaffective disorder [4–6,57]. A psychiatric presentation may predate in certain families [6] and develop in a majority of McLeod patients during the course of disease [4–6]. The spectrum of psychiatric abnormalities is comparable to other neurodegenerative basal ganglia disorders such as Huntington's disease [56,58].

Seizures

About 20% of McLeod patients may present with generalized seizures and up to 40% experience them during the course of disease, most probably with secondary generalization [4,5].

Neuroradiology

Computed tomography and magnetic resonance imaging studies demonstrate atrophy of caudate nucleus and putamen, particularly with advanced disease [4–6]. Exceptionally, there may also be white matter changes [59]. 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) demonstrates impaired striatal glucose metabolism (Fig. 2) [6,60], but no impairment of glucose metabolism was found in the cerebral cortex by quantified FDG-PET [6]. Magnetic resonance spectroscopy demonstrates subtle metabolic abnormalities in different extrastriatal brain regions related to the psychiatric and cognitive findings [61].

Pathology

Neuropathological examination of one McLeod patient revealed marked neuronal loss and astrocytic gliosis in caudate nucleus and putamen. In contrast, no alterations were found in cortex, thalamus, subthalamic nucleus, brainstem and cerebellum [5,62]. Similar findings were observed in the exceptional case of a female XK mutation carrier who clinically manifested MLS [Case 5 of [5] and [63]]. Although the prominent psychiatric and cognitive manifestations in McLeod patients indicate a significant and widespread
cortical, rather than purely subcortical dysfunction, the cerebral pathological alterations were restricted to the striatum. Therefore, the clinical symptoms may be explained by a neuronal dysfunction due to impaired basal ganglia – cortical circuits [57].

**Neuromuscular involvement**

**Axonopathy**

All McLeod patients reported up to date lack deep tendon reflexes, at least at the ankles [4–6]. About a third of McLeod patients have reduced vibration sense in the feet, but only a minority of patients have sensory symptoms [4–6]. Neurography demonstrates a sensory-motor axonal neuropathy, and electromyography may reveal myopathic as well as neurogenic changes [4,5].

**Myopathy**

Elevated serum CK levels as a sign of subclinical or manifest myopathy are present in virtually all carriers of the McLeod blood group [4–6,64]. CK elevation is usually mild and is usually < 4000 U/l. About 50% of McLeod patients have a clinically significant muscle weakness or atrophy. The deterioration rate of the myopathy is slow, and only a minority of McLeod patients develop severe weakness or rhabdomyolysis [65,66]. In one patient, the findings resembled inflammatory changes [67].

**Cardiomyopathy**

Cardiac manifestations of MLS include congestive cardiomyopathy, dilated cardiomyopathy, atrial fibrillation and tachyarrhythmia [68–70]. Up to 60% of McLeod patients develop cardiac manifestations during the course of the disease [4]. Cardiac problems such as malignant arrhythmia or heart failure might be an important cause of death [4]. Due to the possibility of a curative intervention, McLeod patient should be carefully monitored for cardiac disease.

**Histopathology**

Sural nerve biopsies display an unspecific sensory-motor axonal neuropathy [5]. Histological findings of skeletal muscle in McLeod patients reveal fibre type grouping, type 1-fibre predominance, type 2-fibre atrophy, increased variability in fibre size, and increased central nucleation [22,64]. In normal skeletal muscle, XK immunohistochemistry reveals a type 2 fibre-specific intracellular staining possibly confined to the sarcoplasmic reticulum. XK staining is absent in McLeod myopathy. This finding correlates to the observed type 2-fibre atrophy, and suggests that the XK protein is crucial for the maintenance of normal structure and function [22]. Cardiac muscle needle biopsy in one patient showed non-specific findings of hypertrophy with some dilatations [69].

**Manifesting female McLeod carriers**

Two female heterozygotes were reported to develop the typical McLeod phenotype [5,65]. In one McLeod family, female McLeod mutation carriers had slight cognitive deficits [6]. In addition, reduction of striatal glucose uptake was seen with quantified cerebral FDG-PET indicating subtle CNS involvement in heterozygotes without manifest movement disorder [6]. The most probable reason for these findings is an unfavourable inactivation of the chromosome carrying the normal XK gene (Lyon effect), as was demonstrated in one heterozygote [5,63]. Female heterozygotes with or without clinical manifestation of the MLS may demonstrate a Kell blood group chimerism detectable by Kell antigen flow cytometry (Fig. 3).
Disease course and therapy

Patients with MLS usually show a slow progression of disease with a mean onset between 30 and 40 years of age [4–6]. Disease duration ranged from 7 to 51 years, and mean age at death was 53 years, ranging from 31 to 69 years [4–6,70]. Hugh McLeod, the original propositus, recently died at the age of 69 after he had developed all major MLS manifestations.
(personal communications by Dr Ruth Walker, New York).
Cardiovascular events, epileptic seizures and aspiration pneumonia might be the major causes of death in older McLeod patients [4–6]. At present, no causal or preventative therapy is available to alter the progression of the syndrome. Recognition of treatable MLS complications, for example cardiac problems and seizures, is presently the most important issue. Because of possible rhabdomyolysis, serum CK levels should be carefully monitored, in particular if excessive movement disorder or neuroleptic medication are present [66]. Psychiatric problems should be treated according to the clinical presentation. Dopamine antagonists such as tiapride, clozapine or quetiapine may be useful to ameliorate choreatic movements. And last but not least, an extended and continuous multidisciplinary psychosocial support should be provided for patients and their families.

Challenging diagnosis of McLeod syndrome
The diagnosis of MLS is based on the immunohematological findings of absent Kx antigen and weak Kell antigens. Carriers of the McLeod blood group phenotype may therefore be recognized in blood banks. In most carriers, neurological data are not available, and cognitive, neuromuscular, cardiac and neuroimaging examinations are rarely performed [3,71]. Long-term follow-up of McLeod phenotype carriers, however, including the eponymous index case, demonstrate development of neurological manifestations during the course of disease [4]. There is converging evidence that the clinical penetrance of MLS is high, in particular after the age of 50 [4–6]. Yet, because of the gradual onset and wide diversity of signs and symptoms, the diagnosis is frequently delayed and often mistaken for familial haemolytic anaemia, hepatopathy [38], Huntington’s disease, Tourette’s syndrome, myopathy or spinal muscle atrophy.

Conclusions
Carriers of the McLeod blood group phenotype are prone to develop a severe neurological disorder that resembles Huntington’s disease but shows additional neuromuscular and cardiac manifestations. If such carriers are recognized in blood donation programmes, genetic counseling, neurological and cardiologic examination as well as follow-up examinations in a specialized neurological centre are warranted.

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