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XK-Associated McLeod Syndrome: Nonhematological Manifestations and Relation to VPS13A Disease

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Keywords

Kx antigen · XK protein · Chorein · Neuroacanthocytosis · Bulk lipid transport diseases

Abstract

Background: McLeod syndrome (MLS) is an X-linked multisystemic progressive disorder caused by loss of function mutations in the *XK* gene. The rare blood group phenotype of MLS patients with absent Kx antigen requires the support of specialized transfusion institutions because of the risk of transfusion complications. Acanthocytosis of red blood cells occurs in almost all patients. Nonhematological manifestations of MLS are very similar to those of VPS13A disease (chorea-acanthocytosis), an autosomal-recessive condition. Their shared phenotype apart from acanthocytosis includes movement disorders such as chorea and dystonia, epilepsy, peripheral neuropathy, and muscle involvement, typically with creatine kinase (CK) elevation, cardiomyopathy included. ***Summary:*** In this review, we describe the nonhematological manifestations of MLS in comparison with those of VPS13A disease. While there are many similarities, differences such as mode of inheritance, sex distribution, age at manifestation, severity of heart involvement, frequency of feeding dystonia or of involuntary head drops may help to distinguish these disorders in the clinic. Immunohematological demonstration of the McLeod-Kell phenotype or detection of pathogenic mutations of *XK* (or *VPS13A*, respectively) is the gold standard for distinction. "Neuroacanthocytosis" was often used as an overarching term, but is potentially misleading, as the term does not refer to a defined disease entity. Its use, if continued, must not prevent clinicians to seek a final diagnosis on the basis of molecular findings. The clinical similarity of MLS and VPS13A disease has long suggested some shared pathophysiology. Evidence for molecular interaction between XK, the McLeod protein, and chorein, the *VPS13A* gene product, has recently been put forward: XK forms a complex with chorein/VPS13A, a bulk lipid transporter located at various membrane contact sites. The exact role of XK in this complex needs to be further elucidated. Impairment of bulk lipid transport appears as the common denominator of both MLS and VPS13A disease. A variety of further conditions may in time be added to the "bulk lipid transport diseases," such as the recently recognized disorders caused by mutations in the *VPS13B*, *VPS13C*, and *VPS13D* genes. ***Key Messages:*** (1) Patients diagnosed with the rare red cell McLeod phenotype (McLeod syndrome, MLS) require interdisciplinary collaboration of transfusion medicine specialists, neurologists, and cardiologists for both their hematological and nonhematological disease manifestations. (2) The phenotypical similarity of MLS and VPS13A disease, often leading to either confusion or insufficient diagnostic depth (under the label of "neuroacanthocytosis"), is based on interaction of the respective proteins, XK and chorein, within the cellular machinery for bulk lipid transport. (3) Overall, the term "bulk lipid transport diseases" seems useful for further research on a group of conditions that may not only share pathophysiology, but may also share treatment approaches.

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Introduction

McLeod syndrome (OMIM #300842) is an ultra-rare progressive multisystemic disorder due to pathogenic variants in the *XK* gene with X-chromosomal inheritance [1]. Delineation of the syndrome began in the early 1960s with the description of a hitherto unknown Kell antigen profile in an otherwise healthy 25-year-old male blood donor, then a Harvard dental student, who developed neurological symptoms much later in life [1–3]. The "McLeod blood group phenotype" that necessitates specific transfusion precautions was later found associated with degeneration within the central and peripheral nervous system and with a wide spectrum of neurological signs and symptoms and led to naming of the multisystemic condition as McLeod syndrome (MLS) after the original propositus [1, 4, 5]. Because of the particular "neurohematological" coincidence, diagnosis and management of MLS patients clearly require efforts by multidisciplinary collaboration.

The "McLeod blood group phenotype" results from absence of the Kx antigen (located at an extracellular loop of the transmembrane protein XK) and an associated reduced expression of antigens of the Kell blood group system [5, 6]. MLS therefore affects both the XK (ISBT 019) and KEL (ISBT 06) systems [4, 7]. Kx+ transfusions should be strictly avoided for all individuals carrying the McLeod blood phenotype: this implicates the need for support from specialized transfusion institutions with immunohematological expertise. Because of the rarity of compatible units of stored blood, autologous donation prior to an anticipated need or blood donation for long-term cryopreservation, banking and interinstitutional, world-wide exchange of blood units are required. The impact on blood banking and cryopreservation of the presence of acanthocytic red cells and of subsequent chronic-compensated hemolysis in MLS [4] so far has not been systematically studied. Single case observations, however, indicate the absence of major issues with freezing and thawing of McLeod blood [8, 9].

Acanthocytosis of red blood cells occurs in almost all patients, but was first recognized as a feature of the McLeod propositus only years after the immunohematological definition [10]. Our recent chance observation of slowed erythrocyte sedimentation of acanthocytic blood was confirmed by systematic analysis that showed a clear inverse correlation of acanthocyte proportion and sedimentation rate [11].

Compensated, usually clinically asymptomatic hemolysis with decreased erythrocyte lifespan [12] probably underlies the hepatosplenomegaly seen in around half of the cases [1], and the commonly elevated levels of aspartate and alanine transaminases and of lactate dehydrogenase in MLS may relate to such liver involvement [13].

MLS and the clinically similar, yet autosomal-recessive VPS13A disease (also known as chorea-acanthocytosis; OMIM #200150), with an estimated prevalence of 1:10,000,000 and 1:1,000,000, respectively, may also be called "core neuroacanthocytosis syndromes" [14–16]. The term "neuroacanthocytosis," however, is no longer recommended, as it blurs the distinction of genetically separate conditions [14]. In the past, the term was used in an even broader sense: neurological disorders associated with acanthocytosis comprise pantothenate kinase-associated neurodegeneration (OMIM #606157) as well as disorders of lipid absorption, with peripheral neuropathy and cerebellar signs, such as abetalipoproteinemia (Bassen-Kornzweig syndrome; OMIM #200100) or familial hypobetalipoproteinemia (FHBL1, OMIM #615558; FHBL2, OMIM #605019) [14].

In the present article, we review the nonhematological manifestations of MLS in comparison to VPS13A disease and point out the molecular evidence that may explain the similarity of the two conditions.

XK and VPS13A Genes, Mode of Inheritance

MLS is caused by pathogenic variants in the *XK* gene which is located at the p21.1 region of the X chromosome [17], in close proximity to the *CYBB* gene that codes for cytochrome b558, subunit β (also known as NADPH oxidase 2 and relevant for the microbicidal system of phagocytes). Deletions or partial deletions of the two genes thus lead to a contiguous gene deletion syndrome that combines MLS with chronic granulomatous disease (OMIM #306400). As the latter often requires blood transfusion [18], MLS ought to be ruled out in chronic granulomatous disease patients prior to allogenic transfusions in order to avoid alloimmunization and subsequent posttransfusion complications [19]. Larger deletions of the Xp21 region may additionally involve genes associated with Duchenne muscular dystrophy (OMIM #310200), retinitis pigmentosa (OMIM #300029) and ornithine transcarbamylase deficiency (OMIM #311250), respectively [1]. Partial inclusion of the *PRRG1* gene that codes for transmembrane γ-carboxyglutamic acid protein 1 has recently been found included in an MLS patient´s deletion, without any as yet clinically tangible consequence [20]. Due to the X-chromosomal mode of inheritance, most individuals clinically affected by MLS are male. Exceptionally, heterozygous female gene carriers may develop symptoms, too [21–25], which is likely due to skewed X-chromosome inactivation [26]. Commonly, however, females with a single *XK* mutation will not be affected. Females homozygous for *XK* gene mutations have not yet been recognized.

VPS13A disease, also known as chorea-acanthocytosis [14], is caused by pathogenic variants in the *VPS13A* gene, located at the q21.2 region of chromosome 9. Ini-

tially, the gene was called *CHAC* and its product was called chorein [27, 28]. As expected with autosomal-recessive inheritance, females and males likewise are affected by VPS13A disease without an as yet obvious genotype-phenotype correlation [29].

VPS13A is part of a mammalian gene family of 4 paralogues [30]. Mutations in the other *VPS13* family genes are also associated with neurodevelopmental or neurodegenerative diseases. *VPS13B* (*COH1*) variants underlie Cohen syndrome [31], and *VPS13C* variants have been observed in early-onset Parkinson's [32, 33] and in Lewy body disease [34]. VPS13D disease may start with movement disorders in early childhood and was diagnosed also in cases initially labeled as recessive spinocerebellar ataxia type 4 or spinocerebellar ataxia with saccadic intrusions [35].

Nonhematological Manifestations of MLS

Multiple systems are affected in MLS, mainly the blood, the central and peripheral nervous system, the skeletal muscle, and the heart [36]. The McLeod blood phenotype is present at birth in male *XK* mutation carriers, while the time of first occurrence of red cell acanthocytosis is still a matter of speculation. In contrast, signs and symptoms from nonhematological involvement usually develop after the age of 30 years, with a broad range of variability [1, 4, 20, 23]. Overall, these manifestations of MLS often cause severe disability and may reduce or abolish independent living and shorten life expectancy [37].

Central nervous system manifestation of MLS is typically with "huntingtonism," a progressive triple disorder of movement, behavior, and cognition. To which extent each domain is affected, varies among MLS individuals, but symptoms seem to correlate with progressive degeneration of the basal ganglia. There is progressive widening of the anterior horn of the lateral ventricles due to caudate nucleus atrophy [38] and MRI volumetry shows an inverse correlation of basal ganglia volumes with duration of disease and, in particular, a decrease in caudate volume with disease progression [39, 40]. FDG-PET reveals bilaterally reduced striatal glucose uptake [41, 42] and post mortem studies show the atrophy of the striatum more pronounced than that of the globus pallidus [43, 44]. In the exceptional "L family" female mutation carrier [26], the substantia nigra was felt unaffected, as was her brainstem, subthalamic nucleus, thalamus, cerebral cortex, cerebellum, and spinal cord [45, 46]. A recent male case confirmed the normal findings in subthalamic nucleus, thalamus, and substantia nigra, and displayed no neuronal or glial inclusions with TDP 43, α-synuclein and p62 immunohistochemistry. Only few τ-positive neuronal and glial inclusions, compatible with aging, were detected [47].

Disorders of movement often are the presenting manifestations of MLS, most commonly hyperkinesia, i.e., chorea, which develops over time in 95% of the patients [36]. Chorea can affect all parts of the body [48]. Dystonia can also occur as can parkinsonism, the latter typically later into the disease [1, 36]. Involuntary facial and perioral contractions as well as unintended vocalizations may be present [1, 48]. Dysarthria impacts communication and social participation. Dysphagia may impair caloric intake and lead to complications such as aspiration and recurrent pneumonia [37]. In addition to these well-established features, less common manifestations occur in single MLS patients, such as involuntary tongue and cheek biting, feeding dystonia, and head drops [49, 50], findings that are much more typical in VPS13A disease.

Behavioral and cognitive manifestations of MLS, even if commonly observed, as yet await systematic prospective study. Both figurative and verbal memory is impaired, the latter with documented progression, and there is executive ("frontal") dysfunction [51]. Changes of behavior and/or personality occur in about 80% of the patients [36], and depression, anxiety, psychosis, irritability, and obsessive-compulsive disorder have been reported [1, 39, 52, 53].

About 40% of patients are diagnosed with epilepsy, which in half of these is the very first presentation of MLS [36]. Seizures are commonly described as generalized, yet little is known about the exact semiology or pathogenesis.

Neuromuscular manifestations are obvious from the regular findings of diminished or absent deep tendon reflexes and of, even excessive, hyperCKemia [54, 55]. The high levels of transaminases (ALT/AST) and LDH, mentioned in relation to hepatomegaly, might alternatively originate from muscle affection. MLS may be considered a primary myopathy [56]. As sensory and motor axonal polyneuropathy is very common [1, 23, 39, 57], muscle atrophy and weakness have thus been interpreted predominantly due to motor neuropathy [3]. Muscle biopsies show both neurogenic and myopathic changes [1, 3, 57, 58]. MLS thus seems to be a mixed neuromuscular condition with an individually variable proportion of the two components. Clinically relevant impairment occurs in about half of MLS individuals [1], such as pronounced bilateral foot drop, but also axially predominant weakness [59]. Of interest are biopsy findings that suggest additional inflammatory changes in muscle [57, 59, 60] and correspond to comparable observations in the heart [61].

Heart involvement in MLS is potentially life-threatening and comprises organ failure, dilated cardiomyopathy, and arrhythmias such as ventricular tachycardia [58, 61–64]. Heart muscle fibrosis may be detected on histology [58, 63]. Its presence can also be inferred from cardiac MRI [64].

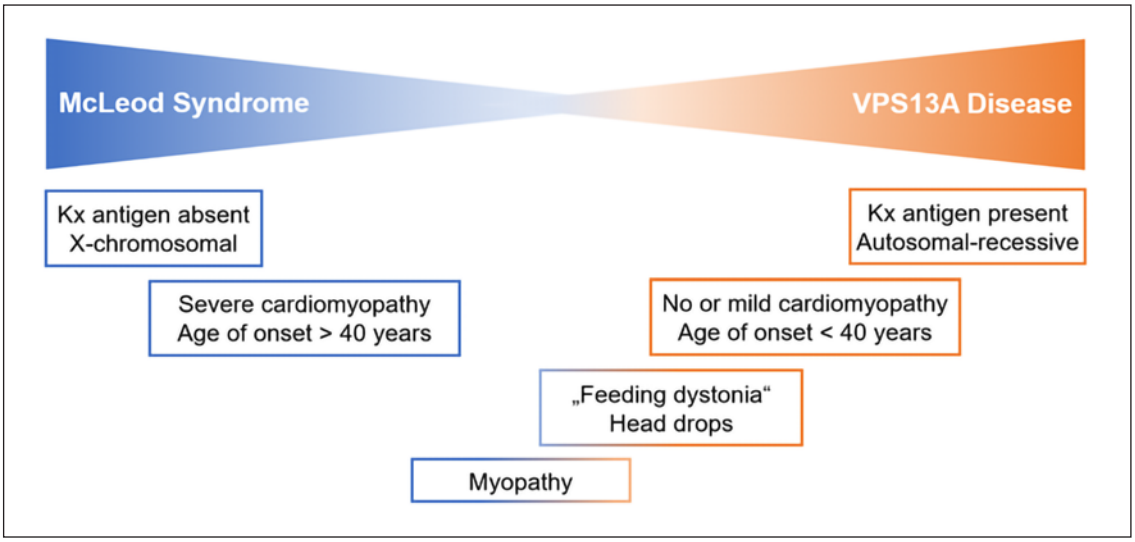

Fig. 1. McLeod syndrome (MLS) and VPS13A disease (chorea-acanthocytosis) are phenotypically very similar neurohematological disorders. Certain features, such as cardiomyopathy or involuntary movements that interfere with chewing and swallowing (feeding dystonia), may be less common in one of the two, but presence of the Kell-McLeod phenotype (absence of Kx antigen) is the main distinguishing feature.

MLS and VPS13A disease behave as phenocopies with respect to many nonhematological manifestations. Apart from their respective mode of inheritance, X-linked or autosomal-recessive (with resultant sex distribution), the only phenotypical feature to tell the two disorders apart with high certainty is the presence or absence of the McLeod-Kell phenotype, i.e., weak Kell antigen expression in combination with absent Kx antigen.

Some additional features may help in distinguishing MLS from VPS13A disease (Fig. 1). In MLS, nonhematological manifestations occur at a later age, and cardiac involvement is more severe. Episodes of sudden loss of muscle tone in the neck, trunk, or legs (leading to head drops, "clasping behavior," or the peculiar "rubber-man-like appearance/gait") as well as tongue protrusion/feeding dystonia seem more typical for VPS13A disease. Nevertheless, proper distinction of the two disorders requires molecular characterization, preferably on both the levels of their genes and the corresponding proteins, XK and chorein.

It is not yet clear how to interpret the novel observation of a 67-year-old male with a suggestive neurological syndrome but normal Kell phenotype in spite of a possibly pathogenic *XK* missense mutation [65]. This appears as the reverse of situations where the McLeod red cell phenotype is detected but nonhematological manifestations are not [66, 67]. For the latter cases one could argue that clinical follow-up was not sufficiently long to witness symptom development, yet both types of observations, if confirmed, would provide valuable insights into MLS disease mechanisms at the molecular level.

Diagnosis and Management

In adults presenting with the clinical triad of progressive disorders of movement, cognition, and behavior (huntingtonism), genetic testing for mutations in the Huntington´s disease gene is mandatory. If negative, further differential diagnosis is complex [68]. Low erythrocyte sedimentation rate, elevated levels of CK, ALT, AST, and LDH, as well as red cell acanthocytosis – that, however is difficult to determine and not even an obligatory finding under routine clinical conditions [69, 70] – may lead one to consider the two related conditions of MLS and VPS13A disease. While male sex, older age, and affection also of a brother or maternal uncle support an assumption of MLS, the two conditions cannot, however, be sufficiently distinguished on the basis of clinical phenotype alone. Several cases are on record where the diagnosis had to be changed to MLS after more extensive testing (cases of, e.g., Gandhi et al. [71] and the case of Faillace et al. [72] and Marsh [73]).

For an elderly male patient (>40 years of age) with clinical and laboratory features as detailed above, we thus first recommend an immunohematological search for the "McLeod blood group phenotype" and/or genetic testing to identify a pathogenic variant or a deletion involving the *XK* gene. Patient blood samples are first evaluated serologically for KEL and Kx antigen reactivity which is expected to be either negative or weakened (further details and flowchart in Frey et al. [74]). At the level of genetic analysis, a specific approach to overcome diagnostic difficulties with *XK* gene deletions has been proposed [75].

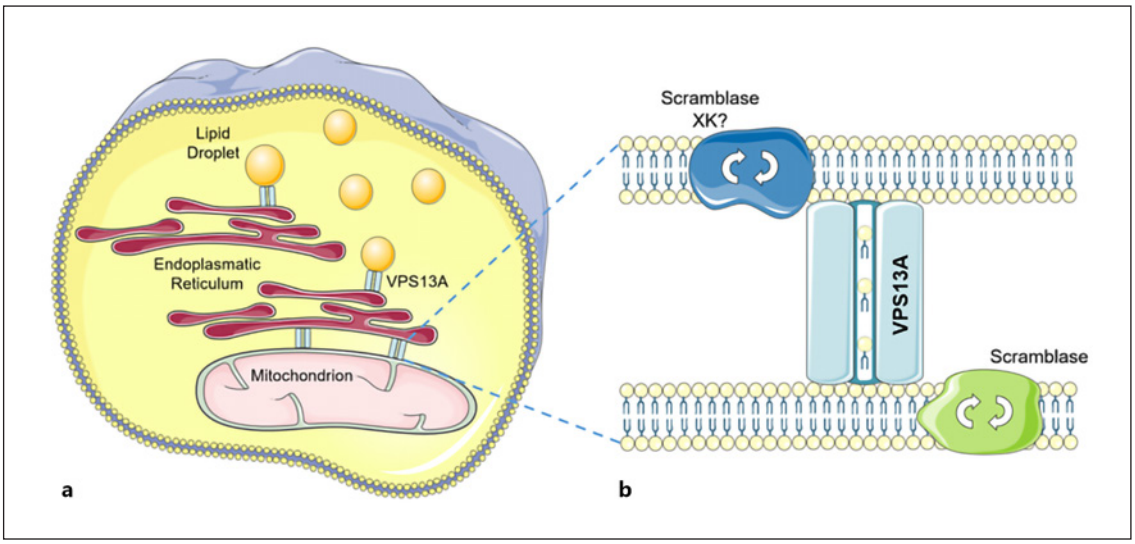

Fig. 2. Subcellular localization and putative functions of VPS13A and XK. **a** The VPS13A protein (chorein) localizes at membrane contact sites between the endoplasmic reticulum and mitochondria or lipid droplets, respectively. **b** VPS13A seems to function as bulk lipid transporter between membranes. Putative partner proteins include scramblases (possibly XK among them) that translocate phospholipids between the two sheets of the membranes tethered by VPS13A. Contains modified images from Servier Medical Art (https://smart.servier.com) licensed by a Creative Commons Attribution 3.0 Unported License.

Similar to the diagnosis of MLS that is based on the absence of the XK protein (carrier of the Kx antigen) and/or presence of *XK* gene mutations, diagnosis of VPS13A disease should be based upon the absence of the chorein protein in erythrocyte membrane Western blot [76] and/or the identification of mutations in the *VPS13A* gene. VPS13A disease is clinically more suspicious in younger patients of both sexes, in particular in siblings without cases in the parents´ generation who might, nevertheless, share a common family or regional background. Based on the literature [65–67] and on our own experience [77], we propose that only analyses on both the gene and the protein levels should be considered as sufficient for full diagnosis of the two clinical conditions of MLS and of VPS13A disease.

Treatment of both diseases is currently purely symptomatic: a detailed review for the resultant manifestation-specific approach is available, but treatment decisions are highly individual [8]. Chorea, for example, may be addressed by dopamine-depleting drugs such as tetrabenazine. For seizures, conventional anticonvulsants are usually effective, yet there is no evidence for superiority of any particular drug. Most important in the management of every single MLS patient, because of the risk of sudden cardiac death [37], is cardiological surveillance on a regular (yearly) basis with subsequent individual treatment decisions that may even include implantation of a cardioverter-defibrillator [61] or a heart transplant [63].

The other highly relevant management topic relates to the rarity of compatible blood units worldwide and the question of their availability in cases of urgent need. In spite of regional and national differences with respect to the procedures involved, the banking of autologous blood units in specialized transfusion institutions is highly recommended.

Family studies are helpful to detect additional, perhaps subclinically affected members (patients´ brothers and maternal uncles, but in particular their mothers and sisters) and to offer genetic counseling [36] about risks for individuals (and their precautions, see above) and for family offspring (possibly including discussion of preimplantation genetic testing).

At the present date, no disease-modifying approach is known for MLS, even if first exploratory results are available for VPS13A disease [78–80]. There, inhibition of hyperactive Lyn kinase may have addressed a relevant disease mechanism, but so far this approach has not been extended to MLS where Lyn kinase may not even be a potential drug target.

XK and VPS13A Proteins, Localization and Interaction

XK and VPS13A are ubiquitously expressed proteins that interact with each other (as recently demonstrated by Park and Neiman [81]). Prior to this, the intriguing clinical similarities of MLS and VPS13A disease had already suggested some sharing of pathways [82].

XK protein is an integral membrane protein [17] and in red blood cells forms a heterodimer with the Kell glycoprotein [83], as part of a larger membrane multiprotein complex important for red cell membrane cytoskeleton stability [84]. The exact localization of XK in nonerythroid tissues remains elusive, but it was shown that it is not coexpressed with the Kell protein in brain tissue [85] and probably not in skeletal muscle either [86, 87].

As shown early in red blood cells, XK absence leads to a reduction of phosphatidylserine in the inner leaflet of the cell membrane [88]. In line with this, XK-related (Xkr) proteins were later found to translocate phosphatidylserine between the two membrane leaflets [89, 90]. This specific activity of a molecule is summarized by its designation as a "scramblase." The structure of two human XKrs (Xkr8 and Xkr9) – with Xkr8 working in a complex with the chaperone basigin – was just successfully elucidated [91, 92]. For XK, foremost member of the Xkr family, however, the putative scramblase function remains to be proven.

VPS13 proteins localize to membrane contact sites and, according to a rapidly growing body of evidence, seem responsible for bulk lipid transport between the membranes of various organelle types [for reviews, see 93, 94]. Impaired interorganellar mobility of lipids impresses as the common denominator of this novel group of neurodegenerative/neurodevelopmental VPS13 diseases. As illustrated here (Fig. 2a), VPS13A/chorein localizes to membrane contact sites of the endoplasmic reticulum and mitochondria and, respectively, lipid droplets in human cells [95, 96]. Tethering of mitochondria and endosomes was also described [97]. In yeast, organelle-specific adaptor proteins recruit Vps13 to the various interorganellar contact sites that each mediates a distinct function [98].

Recent studies suggest that *XK and VPS13A are partner proteins*: their coimmunoprecipitation was shown in HEK293 cells [99], and they form complexes in human cells [81]. It was also shown that XK is involved in the relocalization of VPS13A from lipid droplets to endoplasmic reticulum subdomains when overexpressed [81]: XK seems to recruit VPS13A to probably the endoplasmic reticulum. Thus, at the beginning or the end of a VPS13 bulk lipid transport chain, Xkr family proteins may act as scramblases that exchange lipids between the leaflets of the membrane of origin or, respectively, destiny. This process would allow lipid equilibration within the membranes that were temporarily tethered for the purpose of bulk lipid transport [81, 93, 94] (Fig. 2b).

Overall, conditions caused by dysfunction of VPS13 proteins and of partners such as the McLeod protein XK might be lumped together under the common concept of "bulk lipid transport diseases." This label stresses the presence of shared pathways, and, if investigated from such a more general point of view, therapeutic options that are focused on the commonalities of these diseases might become available faster than approaches that result from studying the single conditions in isolation.

A pressing question among the many that are still open is the question whether proteins of the VPS13 and of the Xkr families might, at least partially, compensate for deficiency of a member within the specific protein family or even across protein families. Such mechanisms would provide an explanation for both the clinical heterogeneity as well as the late onset observed in MLS patients and in individuals affected by VPS13 disease. For VPS13A disease and MLS it is of particular interest whether the presence of both chorein and XK in membranes of mature red blood cells (that lack subcellular organelles and thus contact sites) indicates interaction that is still ongoing or is just a trace of a pathway once shared, e.g., in erythropoiesis.

Conclusion

In this review, we focused on nonhematological manifestations of the rare neurohematological disorder MLS. Because of the multisystemic nature of their condition, MLS patients necessarily deserve interdisciplinary collaboration, with participation of transfusion medicine specialists, neurologists, and cardiologists.

MLS strongly resembles VPS13A disease. The basis for the phenotypical commonalities most likely is the interaction of the two proteins affected, XK and VPS13A/chorein. We propose the term "bulk lipid transport diseases" to place special emphasis on the putative main function of VPS13 proteins that unfolds in interaction with a number of partner proteins.

Bulk lipid transport is essential for the rapid availability of membrane constituents necessary for shrinkage or growth of organelles. Fission and fusion of mitochondria as well as the formation of autophagosomes are pertinent examples. XK appears to work as scramblase, equilibrating lipids within the bilayers tethered by the VPS13A molecular machinery. Consideration of this function and its involvement in a variety of processes at the subcellular level might be particularly relevant for a deeper understanding of McLeod syndrome pathophysiology.

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Conflict of Interest Statement

The authors declare that they have no competing interest related to the paper.

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