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McLeod syndrome: Five new pedigrees with novel mutations

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ABSTRACT

Objective: To present five new McLeod Syndrome (MLS) pedigrees with novel *XK* gene mutations, review the literature of this disorder, and discuss the typical and atypical clinical features noted with these new mutations.
Methods: This is a multi-center retrospective review of five MLS cases with novel gene mutations. Genotypic and phenotypic information has been obtained from each center.
Results: Five novel mutations are reported in this Case series. New clinical findings include prolonged asymptomatic elevated creatine kinase (CK) levels, vocal tics, presence of obstructive sleep apnea (OSA), and one patient of Vietnamese ethnicity.
Conclusions: We expand on the clinical and genetic spectrum of MLS demonstrating the clinical variability of MLS.

1. Introduction

McLeod Syndrome, one of two neuroacanthocytosis syndromes along with chorea-acanthocytosis (ChAc), is a rare X-linked disorder caused by mutations in the *XK* gene. This gene encodes for the XK protein expressed in liver, skeletal muscle, brain, pancreas, heart, kidney, spleen, and erythroid tissues. The chromosomal region associated with MLS spans a region between two loci, mutations of which are associated with Duchenne muscular dystrophy and chronic granulomatous disease [1]. XK protein is a 10-span multi-pass transmembrane protein in the red blood cell (RBC) membrane that forms a heterodimer with the single-pass Kell glycoprotein. This dimer is part of a multi-protein complex cytoskeleton network that includes glycoprotein B/C, Rh protein/Rh-associated glycoprotein, and Duffy glycoprotein [1]. This complex controls the discocyte shape of RBCs. The function of XK protein is unknown but may be an important mediator of cation exchange and maintaining homeostasis. Lipid imbalance between RBC membrane leaflets may lead to acanthocyte formation [1]. In the brain, XK is thought to have a pivotal role in organogenesis, cellular structure, and subcellular electrolyte and nutrient exchange, thus accounting for various neurological manifestations [1].

Males with this progressive neurodegenerative disorder are typically asymptomatic until adulthood. Wide clinical variability may include movement disorders, neuropsychiatric symptoms, seizures, neuromuscular symptoms, and cardiomyopathy [2]. Deep tendon reflexes are reduced or absent, and hepatosplenomegaly may be present [3]. Clinical variability likely results from the type of mutation: missense mutations causing milder neurological symptoms; mutations leading to truncation or loss of expression of XK protein causing severe neurological disability [1].

Movement disorders are almost always present in MLS and can encompass hyperkinetic (chorea and tics) and hypokinetic (parkinsonism) features [4]. Choreiform movements are the presenting symptom in 30% of cases and develop in over 90% of individuals during the disease course [2]. Although more typically associated with ChAc, orofacial dyskinesia including feeding dystonia can occur [2]. Dysarthria and dysphagia are common. Brain imaging often shows striatal atrophy and hypometabolism [5]. Neuropsychiatric symptoms include

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depression, anxiety, psychosis, irritability, obsessive-compulsive features, and cognitive dysfunction [6]. Twenty percent of patients present with generalized tonic-clonic (GTC) seizures and 40% develop seizures during the disease course [7]. Neuromuscular symptoms include asymptomatic hyperCKemia, sensorimotor axonal neuropathy, myopathy, muscle fatigue, and atrophy. Laboratory workup shows elevated CK, RBC acanthocytosis, and may show elevated aspartate transaminase (AST) and alanine transaminase (ALT) levels [3]. One report of 22 males with MLS showed 33% had elevated AST/ALT levels that often increased in parallel [3]. Muscle biopsy usually shows nonspecific myopathic and/or neuropathic changes with an absence of inflammatory cell infiltrates [8], although two cases report muscle cell inflammation, further emphasizing the variability in clinicopathological features of MLS [9,10].

Diagnosis of MLS is made by serological testing of RBCs demonstrating weakened expression of Kell system antigens (K/k, Kpa/b) and by DNA analysis showing mutation in the XK gene [11]. Management of MLS remains symptomatic: annual cardiac monitoring with echocardiography is recommended as is raising awareness of blood transfusion complications due to patients being at risk of sensitization to XK protein present on donor RBCs [12].

Huntington's disease (HD) is much more common and should be tested for initially in patients with undiagnosed chorea. Chorea-acanthocytosis typically presents at a younger age and affects both sexes equally. The diagnosis can be made genetically or by Western blot showing absence of chorein.

2. Methods

This is a retrospective review of five new pedigrees with novel mutations from centers across the United States. These mutations were not reported in the recent review paper by Roulis et al. [1]. Patients were followed by their neurologists and had genetic testing after obtaining informed consent. When possible, the closest living relatives were also tested. Clinical features of the cases are summarized in Table 1. Patients and families gave permission for their clinical details to be published.

3. Results

Case 1. Case 1 (III-3 in Fig. 1a) is of Northern European ancestry (German on father's side; Irish on mother's side). Though asymptomatic, he was found incidentally at age 34 to have hyperCKemia, elevated aldolase, and elevated AST/ALT. Neurologic examination showed areflexia and diffuse fasciculations. Nerve conduction studies (NCS) were normal and electromyography (EMG) showed active denervation in the legs and right arm. At age 57, he developed atrial fibrillation and underwent cardiac ablation. At age 63 he developed painless proximal right arm weakness. He noted fatigue and memory loss that did not interfere with daily functioning. He developed restlessness and agitation after knee arthroplasty and had severe bradycardia and heart block, necessitating pacemaker placement. Three months later, he had two GTC seizures. Since then, he noted progressively worsening anxiety, restlessness, compulsiveness, and unsteady gait. Polysomnography showed severe OSA with an apnea-hypopnea index of 49.

Examination showed 4-/5 weakness and atrophy of the right deltoid and biceps. There were no fasciculations. Sensory exam was normal. Reflexes were absent. Cognitive examination showed reduced language fluency (Mini Mental State Examination 28/30). Mild opisthotonic posturing of his trunk and mild postural instability were noted. He had slight gait unsteadiness and difficulty with tandem.

Laboratory testing revealed persistent hyperCKemia and elevated AST/ALT levels (Table 1). NCS/EMG showed mild neurogenic changes consistent with multilevel cervical and lumbosacral radiculopathies, carpal tunnel syndrome, and ulnar neuropathy. Right deltoid muscle biopsy demonstrated myopathic changes including necrotizing fibers and inflammation. Echocardiogram showed a dilated left ventricle with eccentric hypertrophy and ejection fraction of 57%. His baseline electrocardiogram (EKG) showed sinus rhythm with premature atrial complexes, premature ventricular complexes, and a right bundle branch block with left anterior fascicular block (QRS 132 ms). Non-contrast brain magnetic resonance imaging (MRI) revealed mild diffuse atrophy and mild white matter T2 hyperintense signal changes. No striatal atrophy was present. Electroencephalogram (EEG) showed rare independent bitemporal epileptiform discharges and left frontotemporal theta/delta slowing. Genetic analysis showed XK gene mutation c.1015A > T (K339*).

Case 1's family is notable for an asymptomatic younger brother (aged 59; III-4 in Fig. 1a) with hyperCKemia (600–700) and a maternal aunt who has two children with unknown psychiatric conditions. One sister (III-2 in Fig. 1a) is an asymptomatic carrier of the mutation. His other sister and parents have not pursued molecular testing and are asymptomatic.

Case 2. Case 2 is of French ancestry. No relevant family history was identified. He developed focal seizures with impaired awareness described as “flashbacks” at age 37; he subsequently had focal seizures with bilateral tonic-clonic spread. He is currently stable on levetiracetam. He noted forgetfulness with names by age 60. Head CT at this time showed caudate atrophy. At age 63, he was evaluated for continued memory loss and increased irritability, and was noted to be “restless” with possible myoclonus. Examination noted decreased reflexes and diminished distal sensation. EEG was normal. Brain MRI was notable for persistent caudate atrophy, diffuse parenchymal volume loss, and white matter T2 hyperintense signal changes. Neuropsychological testing at age 64 documented severe impairment in learning, memory, and tasks of verbal and visuospatial abstract reasoning. He was diagnosed with “dementia not otherwise specified.”

At age 66, Case 2 developed chorea. HD genetic testing was negative. Peripheral blood smear showed 1 + (5–10%) acanthocytes. Video-EEG showed no epileptiform discharges. NCS/EMG testing demonstrated “electrophysiological evidence of a chronic, length-dependent axonal sensorimotor polyneuropathy, and a right ulnar neuropathy at the elbow.”

Laboratory testing revealed hyperCKemia and elevated AST/ALT levels (Table 1). Immunohematologic characterization of RBCs revealed weakened expression of Kell blood group system antigens and Kx negative. Sequencing of the *XK* gene identified a deletion of a single nucleotide in exon 2 (del A) at position c.475 in the cDNA, predicted to result in a frameshift and premature stop codon in the protein, designated p. Ser159ValfsTer15 by HGVS nomenclature. MLS was diagnosed at age 67.

Repeat neuropsychological testing showed progression of cognitive decline with worsening in learning, memory, psychomotor skills, and executive functioning. Cardiac workup demonstrated atrial fibrillation, and an echocardiogram revealed left ventricular hypertrophy, mildly reduced left ventricular systolic function, and a mildly thickened aortic valve with a fibroelastoma. Other medical history is notable for OSA, benign prostatic hypertrophy, post-traumatic stress disorder, and hypothyroidism.

Case 3. Case 3 (III-1 in Fig. 1b) is of English/Welsh/Scottish/Irish ancestry on his mother's side. In his 30s he developed episodes of fatigue and nausea, and evaluation at age 40 showed elevated AST/ALT levels and hyperCKemia (Table 1). He was diagnosed at age 44 with MLS when sequencing of the *XK* gene showed a c.300T > G (p.Y100*) mutation. Peripheral blood smear confirmed acanthocytes, and blood group testing showed reduced Kell and absence of Kx antigen expression. Neurological examination showed fidgeting movements described as choreiform as well as occasional throat-clearing attributed to his history of Tourette's syndrome since age 7 with frequent head-shaking. Motor strength and gait were normal. Reflexes

Table 1
Clinical and genetic features of the five cases.

Case#	1	2	3	4	5
Age of onset	34	37	44	48	45
Gender	M	M	M	M	M
Initial Symptom	Asymptomatic HyperCKemia	seizures	Fatigue	Generalized chorea	Head nodding chorea
Chorea y/n (age of onset)	N	Y (63)	Y (46)	Y (48)	Y (45)
Parkinsonism y/n (age of onset)	N	N	N	N	N
Other Abnormal Movements	Mild truncal opisthotonic posturing	N	Vocal tics	N	Vocal tics
Cognitive impairment y/n (age of onset)	Y (Post-op delirium at 63 followed by slowly progressive cognitive issues) MMSE: 28/30	Y (Memory loss at age 60, irritability at 63, deficits in memory, language, visuospatial functioning at 64)	N	Y (late 40s)	Y (52) MMSE: 22/30 SAGE: 12/22
Seizures (age of onset)	Y (64)	Y (37)	N	N	N
Generalized Peripheral Neuropathy (age of onset)	N (has compressive neuropathies in arm only)	Y (63)	Y (44)	Y (diagnosed on EMG at age 48)	N
Myopathy (age of onset)	Y (biopsy proven myopathy and limb weakness at 63)	N	N	N	N
Cardiomyopathy y/n, details	Y, Cardiomegaly but normal LV EF, ablation for arrhythmia in 2012; pacemaker in 2017	Y mild to mod LVH, mildly reduced LV systolic function, mildly thickened aortic valve	N	N/A	N
CK levels Normal range[a]: 32–267 U/L	894–2125	1147	1000–4000	1019	1162
Liver Function Test levels Normal ranges[a]: ALT 0–35 U/L AST 0–35 U/L	ALT 83-120 AST 57-89	ALT 82-90 AST 70	AST 44-152 ALT 55-176	ALT 98 AST 77, 89	ALT 21–72 AST 17-59
Deep Tendon Reflexes	Absent	Reduced	Absent	Absent	Absent to minimal
MRI findings	Mild diffuse atrophy. No striatal atrophy. Mild small vessel white matter disease.	Caudate atrophy on superimposed diffuse atrophy.	N/A	Marked bilateral caudate/putamen atrophy	Minimal small vessel white matter disease. No atrophy.
Mutation	pathogenic variant in *XK* (p.K339*),	Sequencing of the XK gene identified a deletion of a single nucleotide in exon 2 (del A) at position c.475 in the cDNA	Pathogenic XK variant c.300T > G(p.Y100*)	contiguous 1.1 MB deletion of CYBB and XK genes, encompassing Xp21.1 – Xp11.4.	missense variant c.452A > C, p.Gln151Pro

[a] Normal laboratory ranges obtained from [27].

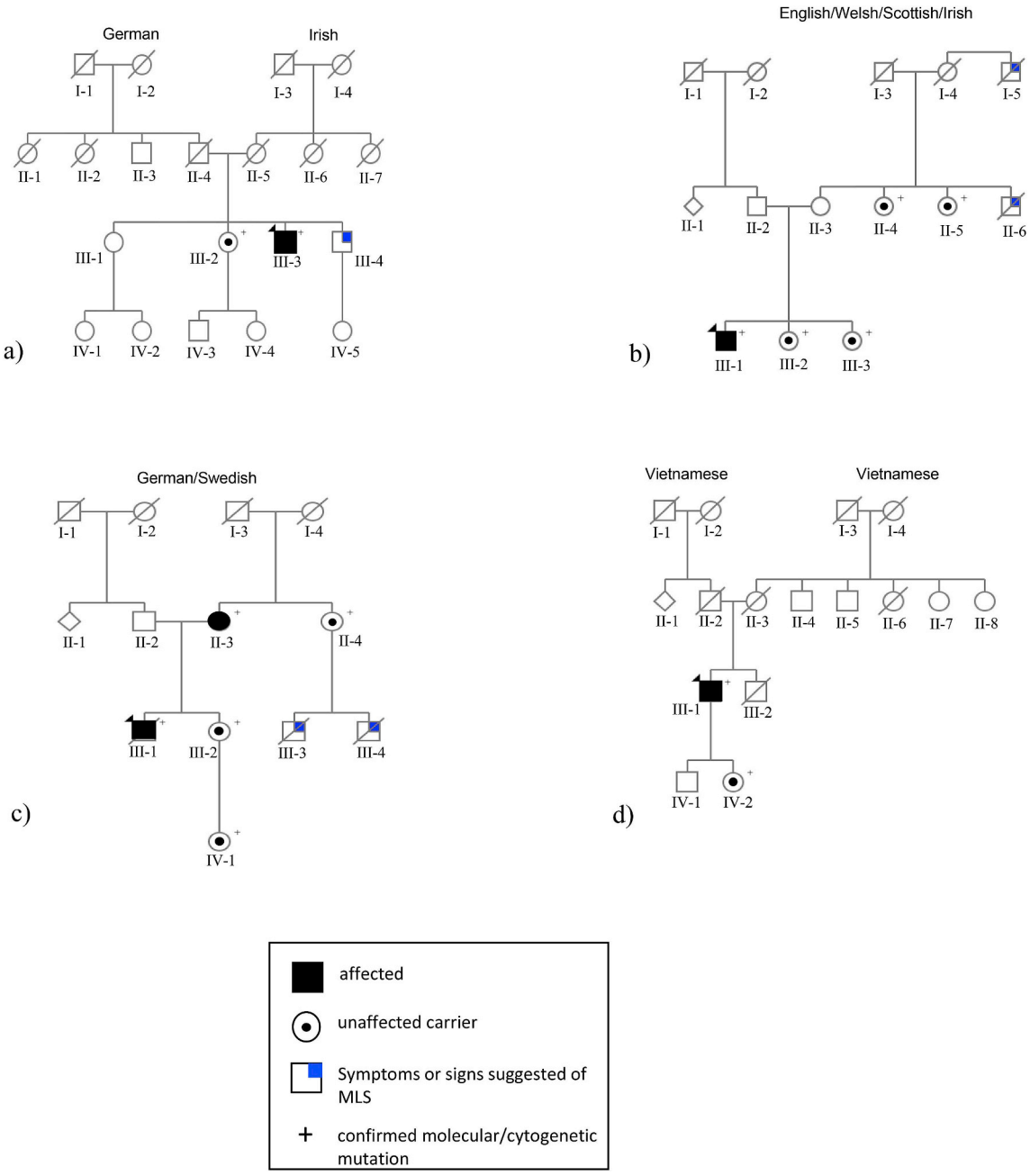
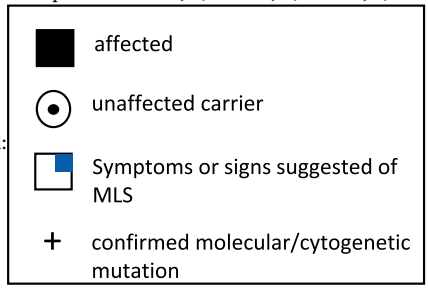


Fig. 1. Pedigrees of reported families, a) Case 1; b) Case 3; c) Case 4; d) Case 5. No family history available for case 2.

Pedigree Legend:



were absent. NCS/EMG in 2014 showed diffuse chronic mild denervation consistent with motor neuronopathy and mild superimposed sensorimotor peripheral neuropathy. EKG was normal. He had a history of OSA.

Case 3's maternal great uncle (I-5 in Fig. 1b) was diagnosed clinically with "neuroacanthocytosis" in his late 60s (by author JJ); unfortunately, laboratory details are no longer available, and the case was never published. He had abnormal movements including gait abnormality, facial chorea, and vocal tics in addition to seizures (Video 1). His maternal uncle (II-6 in Fig. 1b) died at age 57 from infection and had gait abnormalities and anxiety though was never diagnosed with neuroacanthocytosis. His two sisters (III-2 and III-3 in Fig. 1b) and two maternal aunts (II-4 and II-5 in Fig. 1b) are asymptomatic carriers.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.04.022

Case 4. Case 4 (III-1 in Fig. 1c) was of German and Swedish ancestry. He was diagnosed with chronic granulomatous disease (CGD) as an infant, with a contiguous 1.1 MB deletion of *CYBB* and *XK* genes, encompassing Xp21.1 – Xp11.4. He had frequent infections including lung and liver abscesses and took prophylactic long-term antibiotics and gamma interferon.

At age 48 he had mild generalized chorea. Strength was normal though generalized muscle atrophy and gastrocnemius fasciculations were noted. Gait was wide-based and unsteady. Reflexes were absent. NCS/EMG showed generalized chronic denervation and mild sensorimotor peripheral neuropathy. Brain MRI demonstrated marked atrophy of bilateral caudate nucleus and putamen. Laboratory testing showed hyperCKemia and elevated AST/ALT levels (Table 1).

He developed increased twitching and mannerisms, deteriorating self-care and hygiene, and worsening cognitive changes that caused him to lose his job a few years prior to his death at age 52. Post mortem examination demonstrated pulmonary edema and left ventricular dilatation and hypertrophy. This observation in this subject was also documented in a recent report demonstrating cardiac disease as a major cause of morbidity [13].

Case 4's mother (II-3 Fig. 1c) developed progressive impairment of balance and falls by age 77. She had hypertension, hyperlipidemia, and hypothyroidism. On neurological evaluation at age 83 she had mild generalized chorea and memory loss (mini-mental score 24/30). She had reduced reflexes, distal sensory loss, wide-based gait, and positive pull test. NCS/EMG revealed mild, distal, motor-predominant peripheral neuropathy. Echocardiogram showed mild left ventricular hypertrophy, normal ejection fraction, and moderate left atrial enlargement. Brain MRI showed diffuse atrophy. AST, ALT, and CK were normal. She was noted to have acanthocytosis of undocumented percentage on peripheral blood smear, but MLS testing was not done.

The subject's maternal aunt also was a presumed carrier (II-4 in Fig. 1c). She had two sons with CGD, and presumably MLS, who died at the ages of 1 and 22 years (III-3 and III-4 Fig. 1c). He has one sister who is an asymptomatic carrier of the deletion (III-2 in Fig. 1c). Her daughter, 25, is also an asymptomatic carrier (IV-1 in Fig. 1c) with normal EMG/NCS, echocardiogram, and CK levels.

Case 5. Case 5 (III-1 in Fig. 1d) is of Vietnamese ancestry. He developed head-nodding movements at age 45. By 52, he exhibited frequent orofacial, tongue, and arm choreiform movements, grunting vocalizations, and difficulty holding food in his mouth (not consistent with a classic feeding dystonia but rather orofacial chorea). He displayed progressively worsening cognitive deficits including inattention and short-term memory. Due to this and generalized slowing, he was fired from his factory job at age 54. By 55 he displayed symptoms of mild depression, moderate anxiety, apathy, lethargy, and insomnia.

Neurological examination at age 55 revealed frequent vocalizations, mild paratonia, mild apraxia, face and tongue chorea, minimal dysmetria on finger-to-nose testing, mild sway on Romberg, and abnormal gait related to chorea of trunk and limbs. Sensation was normal. Reflexes were absent. Cognitive evaluations showed: Mini-Mental State Examination (MMSE) 22/30; Self-Administered Gerocognitive Examination (SAGE) 12/22 [14]; Modified Boston Naming Test 14/15; and impairments in delayed recall, calculation, abstraction skills, and constructional abilities. These findings reflected frontal and parietal cortical impairments.

Laboratory evaluations revealed hyperCKemia, 6% acanthocytosis on peripheral smear, and negative HD testing. Echocardiogram was normal. Brain MRI revealed minimal white matter T2 signal increase. Genetic testing revealed lack of erythroid expression of Kx protein and missense variant c.452A > C, p. Gln151Pro.

Family history was negative for movement disorders, psychiatric disorders, seizures, cardiac issues, or dementia (Fig. 1d).

4. Discussion

This Case series of patients with novel mutations in MLS further demonstrates the clinical, electrographic, and radiologic variability of this rare disorder (estimated prevalence 1/10,000,000 [15]). Our subjects developed features in middle age, consistent with previous reports [12]. Four of five had chorea, one as the presenting symptom. None had parkinsonism and one had focal truncal dystonia. One had vocal tics which has not been well-described in MLS. One series of six subjects with neuroacanthocytosis described one subject with ChAc who had simple tics; no tics were described in the MLS subjects [16].

Myopathic changes on muscle biopsies in patients with MLS are possibly a consequence of axonal neuropathy; however, while usually asymptomatic or mild, cases of rhabdomyolysis and disabling myopathy have been reported [8]. While four of five of our subjects had neuropathy, one had myopathy only, demonstrating that either can occur separately. Although all had hyperCKemia, similar to other documented cases [17], this was predominantly asymptomatic, and only one developed myopathy. In a retrospective report of 104 subjects with chronic hyperCKemia, 50 were asymptomatic [18], similar to our first Case. Normal or minimally abnormal muscle biopsies were seen in 21 of these cases; the remaining were diagnostic for dystrophinopathies, McArdle disease, and metabolic myopathies. MLS was not considered in this series [18]. Although hyperCKemia is well recognized in MLS, subjects may be asymptomatic for years. MLS should be considered when routine workup is normal to reduce the risk of invasive procedures such as a muscle biopsy. To our knowledge a genotype-phenotype correlation with regard to elevated CK and disease progression has not been well-described, consistent with the significant clinical phenotypic variability seen in MLS.

Four of the five cases had cognitive dysfunction, with three (cases 1, 2, 5) having neuropsychological testing consistent with frontal dysfunction, two (Case 1 and 5) showing subtle language abnormalities, and one (Case 5) with impaired drawing skills. This is consistent with described cases showing deficits in frontotemporal domains [7]. Two cases had seizures, consistent with reports of this occurring in 40% of MLS patients [7]. Although generally well-controlled with antiepileptic medications, refractory seizures and status epilepticus can contribute to mortality [13].

Neuroimaging in cases 2 and 4 showed caudate atrophy, and nonspecific white matter changes were seen in cases 1 and 5, consistent with previously described cases [7]. Cases 1 and 5 did not have caudate atrophy; interestingly, Case 5 presented with chorea, and caudate atrophy is typically present at time of these symptoms [7]). Case 5 also had frontal and parietal atrophy, not previously described in the literature.

Cardiac disease in MLS includes tachyarrhythmias and congestive cardiomyopathy [7]. Two of our subjects had cardiac disease, one requiring pacemaker placement. Cardiac disease is the cause of death in 43% of MLS patients [13]; annual echocardiography is recommended to

identify this potentially treatable cause of mortality.

Case four has four female relatives who are confirmed carriers. His mother has mild chorea and imbalance, and his maternal aunt had cognitive impairment. It is possible that his mother and aunt are manifesting female heterozygotes; this been reported and is likely due to skewed inactivation of the X chromosome carrying the normal XK gene (lyonization) [7,19].

The first three cases had severe OSA confirmed by polysomnography. OSA is not known to be a common comorbid condition in MLS, making this the third ever report of OSA in MLS to our knowledge. While a Case from a 1985 paper demonstrated polysomnographic changes of central etiology, a later paper reported three subjects with comorbid MLS and OSA with polysomnographic features of both peripheral and central causes [3]. We propose a potential role for both peripheral and central causes of OSA in MLS. Peripherally, neuromuscular dysfunction seen in MLS may lead to airway muscle dysfunction during sleep. There may also be a loss of central drive resulting in apneic episodes. This potential facet of MLS deserves further inquiry as the cause has not been well described in the literature. With our three cases, only a total of seven cases of OSA in MLS have been reported to date to our knowledge. Regardless of etiology, OSA should be treated as it is a risk factor for cardiovascular disease [20].

Of interest, although MLS has been reported in Europe [7], North and South America [15], Australia [21], Hong Kong [22], Taiwan [23], and Japan [24], Case 5 is the only reported MLS subject to date with Vietnamese ancestry, thus expanding the geographic distribution of this condition.

In summary, we present five cases of MLS with variable phenotypic presentations and new mutations. This expands on our knowledge of the presentation of this rare neurodegenerative disorder to include asymptomatic hyperCKemia and expands on the geographic distribution of MLS. Serum CK and AST/ALT levels should be performed as part of routine evaluation of patients with unexplained movement disorders or muscle weakness. Treatment remains supportive, although dopamine depleters have been found to be most effective in the treatment of chorea [25,26]. Autologous blood banking is recommended in Case future blood transfusion is needed. Surveillance for cardiac disease may help reduce morbidity and mortality.

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