McLeod Syndrome in a Commercial Airline Pilot

Christopher Haas; Dana Levin; Margherita Milone; Johnené Vardiman-Ditmanson; Charles Mathers

BACKGROUND: The following case report describes the first known case of McLeod Syndrome in a commercial airline pilot. The case describes a 56-yr-old experienced pilot who showed a slow and subtle decline in cognitive function and muscle control in the cockpit. On further examination, the pilot's erratic behavior and movement along with lab abnormalities pointed toward McLeod Syndrome.

CASE REPORT: The pilot was recommended for evaluation by his fellow crewmembers due to his fidgetiness, clumsiness, and lack of focus during critical portions of flight. The pilot reported having a long-standing history of elevated CK levels. Further lab investigations revealed acanthocytes on blood smear while neurological evaluation detected chorea. The combination of clinical and laboratory features along with genetic test results were all consistent with McLeod Syndrome.

DISCUSSION: The case highlights how subtle behavioral and motor coordination changes can be a warning sign for an underlying progressive neurological disorder that requires further workup and referral.

KEYWORDS: neuroacanthocytoses, pilot, myopathy, axonal neuropathy, chorea.

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McLeod Syndrome (MLS) is a slowly progressive disease characterized by a spectrum of neurological manifestations, cardiac involvement in the form of cardiomyopathy or cardiac arrhythmias, and acanthocytosis.[3] The spectrum of clinical features is the result of deletions that affect the XK gene and adjacent genes located on the p21.1 region of the X chromosome.[5] Common manifestations of the disease include: elevated creatine kinase (CK) with or without muscle weakness, peripheral neuropathy, chorea, cognitive impairment, and psychiatric symptoms. The laboratory hallmark of MLS is the peripheral acanthocytosis, featured by irregular horn-like projections on the surface of red blood cells. As seen in **Table I**, the neuroacanthocytoses vary in pathogenesis and clinical presentation. These syndromes are rare, with a prevalence ranging from approximately 1000 cases worldwide for chorea acanthocytosis to an estimated 150 to 300 cases worldwide for MLS.

The main neuroacanthocytoses are MLS and chorea acanthocytoses. Both diseases affect the central and peripheral nervous system, resulting in cognitive deficits, behavioral changes, involuntary movements, myopathy, and peripheral neuropathy. The second grouping of neuroacanthocytoses include abetalipoproteinemia and other low lipoprotein diseases. This group can similarly have a peripheral neuropathy, but distinctively these conditions also cause degeneration of the dorsal column, which contributes to the ataxia.[4] Huntington-like 2 disease and pantothenate kinase 2 disease are sometimes considered part of the neuroacanthocytoses, but these conditions are extremely rare and are distinct from MLS and chorea acanthocytoses.[5,8]

MLS is named for Hugh McLeod who, at age 25, was noted to have a distinctive pattern on a blood survey taken during initial enrollment to Harvard Dental School.[1] Despite progressive symptoms, he maintained a practice in dentistry until age 64 and he died 5 yr later.[8] Although antigens specific for McLeod's can be detected incidentally during blood screens of healthy individuals, it is difficult to define with certainty when symptoms will arise given the variation in symptom

From the University of Texas Medical Branch, Galveston, TX, USA.

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Address correspondence to: Christopher Haas, University of Texas Medical Branch, Preventive Medicine and Population Health, 301 University Boulevard, Galveston, TX 77555-1110; cthaas@utmb.edu.

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Table I. Neuroacanthocytoses Disease Summary.

	PATHOGENESIS	GLOBAL PREVALENCE	AGE OF ONSET	AGE OF DEATH
McLeod Syndrome	X-linked, XK Protein	~150–300 cases	20–60 yr	30–70 yr
Manifestations	Dystonia/chorea, (cardio)myopathy, seizures, peripheral neuropathy (axonal), behavioral / cognitive deficiencies			
Study Findings	Acanthocytosis, ↑ CK protein, abnormal brain MRI, abnormal nerve conduction studies, abnormal muscle biopsy			
Chorea-Acanthocytosis	Autosomal recessive, Chorein Protein	<1000 cases	<35 yr	28–65 yr
Manifestations	Dystonia/chorea, bradykinesia, vocal tic, frontal lobe syndrome, seizure, peripheral neuropathy, impaired memory			
Study Findings	Acanthocytosis, ↑ CK protein, abnormal brain MRI, abnormal nerve conduction studies, abnormal muscle biopsy			
Abetalipoproteinemia	Autosomal recessive, MTP Protein*	~100 cases	12–18 yr	Normal lifespan
Manifestations	Vision problems, steatorrhea, dyscoordination, truncal ataxia, sensory and motor loss			
Study Findings	Retinitis pigmentosa, fat-soluble vitamin deficiency, anemia, spinocerebellar & posterior column degeneration			

*MTP = microsomal triglyceride transfer protein (builds chylomicrons, VLDL, LDL).

The syndromes can be divided into those that impart neurological effects as a result of degeneration of the basal ganglia, such as MLS and chorea acanthocytosis, and syndromes that have low lipoprotein levels, such as abetaliprotenemia, that cause ataxia due to degeneration of the dorsal columns. Prevalence, age of onset, and age of death provided are estimates.[6]

progression seen in patients. Symptoms more often start later in life. The natural history of MLS often begins with mood disorders, memory problems, disinhibited behavior, and personality changes in mid-adulthood. The behavioral changes appear to plateau in most patients, but involuntary movements, such as dystonia and chorea, and the myopathy and neuropathy are progressive.[2] Seizures, life threatening arrhythmias, and cardiomyopathies are also common in McLeod patients, with most patients dying 5 to 10 yr after onset of symptoms.[6] Some reports have suggested that the disease duration is inversely related to the volume of the basal ganglia upon diagnosis.[4] To our knowledge, this is the first described case of a neuroacanthocytosis in a professional aviator.

CASE REPORT

A 56-yr-old male commercial airline pilot with over 25,000 h of flying time presented to the clinic for a fitness-for-duty evaluation after peers noted a decrease in the pilot's concentration as well as behavioral changes in the cockpit. The pilot's peers reported that he was devoting increasing amounts of time to noncritical tasks such as repeatedly cleaning knobs and switches. Additionally, the pilot was reportedly not following instructions from the captain during critical phases of flight such as failing to make an ascent between clouds as directed. The pilot reported that his actions were not an issue with cognition; he reported that when he needed to be focused such as during checkrides, he had no issues staying focused. Crewmembers also noted that the pilot was clumsy and was dropping items with increasing frequency. According to the pilot, he stated his clumsiness had always been present and he attributed this characteristic to his high energy level. The pilot reported that with additional concentration, the behaviors noted above could be controlled and avoided, but at the same time, his peers reported concerns about the pilot's ability to manage the aircraft on his own for any duration of time. The pilot reported that he did not have any involuntary movements and he remained active in outdoor sports.

The pilot's prior medical history was noncontributory, although both the pilot and his mother had significantly elevated blood creatinine kinase levels for many years. The pilot reported that he initially underwent muscle biopsies and an EMG study, which were reported as being normal. He denied any history of traumatic brain injury or seizure. He also reported no family history of any movement disorders or dementia.

Upon examination, the pilot was noted to be average in height with a thin build. He had an appropriate demeanor throughout the exam. He had a quick speech pattern with occasional slurring from one word to the next. The pilot appeared to have a difficult time staying still and he had occasional mild twitches of his eyelid, tongue, and legs (while lying flat). The pilot's cardiac exam did not reveal any arrhythmias, murmurs, or evidence of enlargement, and the remainder of the lung and abdominal exam was unremarkable. There was no muscle asymmetry. The neurological exam did not reveal any cranial deficits. The pilot's reflexes were 1+ throughout. The pilot displayed a mild degree of imbalance standing on one leg with his eyes closed, but proprioception was overall within normal limits. The pilot did not have any decrement in light touch sensation.

The pilot's lab work was within normal limits except for an elevated CK (7930) and mild elevations in ALT and AST (175 and 282, respectively). GGT was within normal limits, suggesting that the AST and ALT elevation was of muscle origin.

The pilot was referred to psychiatry and was not found to have any mood disorder. He next underwent a battery of neurocognitive tests with a Federal Aviation Administration Human Intervention Motivation Study trained neuropsychologist. This battery contains the following exams: Wechsler Adult Intelligence Scale-Fourth Edition, Wechsler Memory Scale-Fourth Edition, Trail Making Tests, Rey-Osterrieth Complex Figure, Wisconsin Card Sorting Task, Achievement, Verbal, Sensory, Motor, Connors' Continuous Performance Test-II, Paced Auditory Serial Addition Test, COGSCREEN-Aeromedical Edition, and the Minnesota Multiphasic Personality Inventory-2.

The battery data indicated the pilot had a significant number of deficits, especially with short-term memory, focus, and his ability to understand instructions. The COGSCREEN-Aeromedical Edition results were considered very impaired, particularly involving problems with working memory and dual tasking, as well as motor speed. Further problems with motor speed were evident on the Connors' Continuous Performance Test-II, and his inability to grasp instructions quickly was evident on some of the verbal memory tests. It was recommended that the pilot receive a complete neurological workup to determine whether the motor and cognitive deficits could be explained by a neurological disorder.

The pilot was next referred to a neuromuscular specialist for the persistent hyperCKemia, which was first documented in 1985. The pilot described no neuromuscular symptoms. His neurological examination showed normal muscle strength, size, and tone, but revealed features of a mild length-dependent sensorimotor peripheral neuropathy and chorea. Electromyography/nerve conduction studies confirmed the presence of an axonal peripheral neuropathy and showed no myopathic changes. Peripheral smear revealed acanthocytes. Thyroid function, HIV antibodies, and several tests performed to search for acquired etiologies of peripheral neuropathy and alternative etiologies of the movement disorder (including measurement of ceruloplasmin and copper) were normal or negative. Two previously performed muscle biopsies showed slight increase in internalized nuclei and rare necrotic fibers, respectively. No dystrophin immunostaining was performed, which can rule out a muscular dystrophy. Cardiac evaluation by EKG, 24-h Holter monitoring, and echocardiogram were significant only for premature ventricular complexes and borderline right ventricular enlargement with reserved function. The combination of hyperCKemia, peripheral neuropathy, chorea, peripheral acanthocytes, and male sex suggested MLS. *XK* gene sequencing revealed a hemizygous deletion c.192_245 + 16del453 encompassing the 5′ untranslated region of exon 1 of the *XK* gene, confirming the clinical suspicion of MLS. Additional next generation sequencing searching for mutation in other genes possibly causative of hyperCKemia, including ryanodine receptor 1 (*RYR1*) and alpha-1 subunit of the skeletal muscle calcium channel (*CACNA1S*) genes, showed no mutations.

Of interest, the pilot's mother had elevated CK, but was reportedly asymptomatic. MLS is an X-linked recessive disorder and, therefore, primarily affects men. However, women can manifest symptoms as carriers of the MLS mutation if genes on the paternal X chromosome are not properly silenced. The pilot's mother was not available for a neurological examination and did not undergo genetic testing.

As no cure is available for MLS, the patient was recommended supportive and symptomatic care. Monitoring of cardiac function is crucial throughout life, as cardiac arrhythmias and cardiomyopathy can occur. Tetrabenazine can ameliorate the chorea.[8] Psychotropic drugs can help control the psychiatric symptoms, should these present.

DISCUSSION

MLS is caused by mutations in the *XK* gene. This gene encodes instructions for producing the XK protein, which carries the blood antigen Kx. XK protein is found particularly in the brain, heart, and muscles.[6] The exact function of the XK protein and its relation to the presenting features of McLeod's has not been clearly defined, but different mechanisms have been proposed. Absence of the XK protein from red blood cells is itself thought to cause deformation of red blood cells and alter membrane transportability.[5,8] The XK protein forms a complex with Kell proteins, and Kell proteins either are reduced or absent in McLeod's syndrome. Kell proteins are thought to serve as neurotransmitters in the basal ganglia and the reduction in Kell protein could contribute to the neurological changes seen in McLeod's.[3]

MLS presenting features are often subtle. In addition, there is intrafamilial phenotypic variability. As an example of the subtle findings, Chen et al. described a patient whose initial abnormal movements consisted of general restlessness and flicking motions of the fingers while reading.[2] Outward findings seen in patients can include facial grimacing and excessive eyewinks. Involuntary facial movements may occur in over 85% of individuals with McLeod's Syndrome.[4] These descriptions are similar to the patient seen in our clinic, who in general seemed restless and appeared to have a slight increase in eye winking. Tongue and lip biting can also occur.[7] Muscle weakness and atrophy increases over time and can preferentially affect the lower extremity muscles in McLeod's.[3] A majority of patients will develop areflexia due to the peripheral neuropathy. Cognitive deficits may not appear until later in the course of the disease. Cognitive findings may also be subtle, as once again demonstrated by the pilot in our case—his peers noticed that he had a lack of focus compared to prior years and he was cleaning the cockpit at inappropriate times. Of note, obsessive-compulsive disorder can be a psychiatric manifestation of McLeod's,[4] but this was ultimately ruled out in our patient.

The X-linked recessive inheritance pattern, hyperkinetic movements, and cognitive changes are important clues for leading the clinician to a McLeod's diagnosis. Laboratory findings also help lead the clinician to the diagnosis and ultimately confirm the presence of the disease. In this case, the pilot had noticeably elevated CK levels more than a decade prior to his diagnosis. CK level increases are seen in most patients and are the result of muscle involvement. Analysis of skeletal muscle may show muscle degeneration by muscle biopsy. Muscle CT and MRI scans may show selective fat infiltration in McLeod and chorea acanthocytosis,[9] and nerve conduction studies can demonstrate the presence of an axonal peripheral neuropathy.[7] Liver enzymes are often mildly elevated. A blood smear may be helpful since acanthocytosis is often present to varying degrees.[4,8] The combination of acanthocytosis and elevated liver enzymes may lead the clinician to misdiagnose a primary hepatic disease, but neurocognitive findings and neuropathy suggest a different process. Thus, with such findings, it is important to perform blood typing and genetic testing. In

McLeod's, the Kx antigen will be absent and the Kell proteins will either be reduced or absent altogether—this finding confirms the presence of McLeod's.[5] The diagnosis is further confirmed by the presence of a McLeod gene mutation. There are multiple variations of the XK gene mutation.

Brain MRI abnormalities are observed within the basal ganglia. The key finding is atrophy of the caudate nucleus and lentiform nucleus. Although not specific to MLS, the basal ganglia in MLS patients also typically demonstrate early accumulation of iron deposits. This can result in an increase in ventricular size of the frontal horns and lateral ventricles. McLeod's syndrome does not appear to cause significant atrophy in the cerebellum.[9]

There is no definitive cure for MLS at present, but there are key components of providing care for MLS patients. Extraneous movements are often treated with the dopamine antagonist tetrabenazine. However, in a case series by Danek et al., patients on tetrabenazine (or buspirone) did not show an improvement in abnormal movements, but there was some success using tialipride and sulpiride.[3] Antiepileptic agents may be necessary as up to half of McLeod's patients develop seizures.[6] EKG and echocardiogram to detect signs of arrhythmia or cardiomyopathy should be done on a frequent basis or based on any signs of heart decompensation or arrhythmias. As the McLeod's blood phenotype is distinct from the general population, it is also important to search for the development of antigens against the Kx and Kell proteins and include this information when selecting future transfusion of blood products.[6] Treatment of McLeod's patients with stem cell transplantation has been described, but evidence regarding the efficacy of this approach remains limited.[8]

There are several important aeromedical implications in this case. Observations of the pilot frequently dropping items and occasional mild slurring of speech was likely due to hyperkinetic movements, as he had no objective muscle weakness. A captain also described how the pilot would become fixated on tasks in the cockpit. It is possible this was a manifestation of trying to overcome early motor difficulties or decrements in neurocognitive function. A psychiatric consultation did not find any evidence of obsessive-compulsive disorder at the time of the evaluation. The anticipated progressive decline in both motor and cognitive functions, elevated risk of seizure, potential for cardiac complications, and possibility of psychiatric disorders make this rare condition incompatible with the safe operation of an aircraft. The neurological findings present in this pilot emphasize the importance of an aviation medical examiner performing a thorough physical examination on every pilot. If presented with historical or examination findings similar to those in this case, the aviation medical examiner should defer the pilot's application to the Federal Aviation Administration.

In this case, the pilot's employer sent him for an aeromedical fitness for duty evaluation due to observations made by his coworkers. The pilot complied with our recommendation for evaluation and accepted our determination of unfit for duty. This case demonstrates that a culture of safety among commercial airlines and pilots' union is paramount for the safety of passengers and the airspace system. The pilot and individuals involved in this case demonstrated an exemplary commitment to safety in the face of a difficult diagnosis.

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Authors and Affiliations: Christopher Haas, M.D., M.P.H., and Johnené Vardiman-Ditmanson, M.S., University of Texas Medical Branch, Galveston, TX, USA; Dana Levin, M.D., M.P.H., Columbia University, New York, NY, USA; Margherita Milone, M.D., Ph.D., Mayo Clinic, Rochester, MN, USA; and Charles Mathers, M.D., M.P.H., Fedeal Aviation Administration, Oklahoma City, OK.

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