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Short communication

Life expectancy and mortality in chorea-acanthocytosis and McLeod syndrome

Ruth H. Walker[a,b,*], Marcelo Miranda[c], Hans H. Jung[d], Adrian Danek[e]

[a] Department of Neurology, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA
[b] Department of Neurology, Mount Sinai School of Medicine, New York, NY, USA
[c] Department of Neurology, Clinica Las Condes, Santiago, Chile
[d] Department of Neurology, University and University Hospital Zurich, Zurich, Switzerland
[e] Department of Neurology, Ludwig-Maximilians-Universität München, Munich, Germany

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ABSTRACT

Objective: To document life expectancy and causes of death in chorea-acanthocytosis (ChAc) and McLeod syndrome (MLS).
Methods: We reviewed our personal databases and the published literature to identify cases of ChAc and MLS for whom adequate information was available regarding ages of disease onset and death, cause of death, and other clinical information.
Results: Adequate information was obtained on 52 patients with ChAc and 34 with MLS. Causes of death included pneumonia, cardiac disease, seizure, suicide, and sepsis. Mean disease duration from diagnosis was 11 years for ChAc, while for MLS it was 21 years.
Conclusions: Given the current data, causes of death in ChAc and MLS are similar to those for the phenotypically similar Huntington's disease, with additional risks due to the presence of seizures and cardiac disease. Suicidality was seen in 10% of patients with ChAc. Identifying causes of mortality is valuable for disease management and ultimately for clinical trials. In the absence of disease-modifying agents, disease management should focus upon treating symptoms which may contribute to morbidity.

1. Introduction

The core neuroacanthocytosis syndromes, ChAc and McLeod syndrome (MLS), are progressive neurodegenerative conditions which have many phenotypic similarities Huntington's disease (HD) [1]. Management of these disorders is at present purely symptomatic.

ChAc is an autosomal recessive disease with typical onset in young adulthood while MLS is X-linked with a typical onset in middle age. While these are genetically distinct disorders, with distinct underlying (albeit current unknown) mechanisms of neurodegeneration, historically they have often been confused, thus it is important to highlight potential differences in causes of mortality.

The typical clinical course is one of slow progression over 1-2 decades, similar to that seen in other neurodegenerative disorders, with patients ultimately succumbing to pneumonia or sepsis of other etiologies. However, sudden death may also be seen due to other factors which are specific features of neuroacanthocytosis syndromes, such as seizures, cardiac dysfunction, or autonomic nervous system involvement. The presence of significant psychiatric morbidity in some patients may raise the concern of suicide.

While the typical presentations of ChAc and MLS are at this point fairly well documented, predominantly from reports of single cases, families, or small case series, disease progression and causes of morbidity and mortality have not been systematically studied, limiting our ability to prognosticate. Identification of the most common causes of death will provide important information regarding potential treatment goals in this group of rare, progressive neurodegenerative diseases.

2. Methods

We reviewed our personal databases and the published literature to generate the information regarding age of onset, age at death, cause of death, and pertinent clinical factors, such as the presence of seizures, and whether these were well-controlled. Institutional Review Board approval was not required from any institution as all reported subjects are deceased. For cases to be included at least 2 of the following were

* Corresponding author. Department of Neurology (127), James J. Peters Veterans Affairs Medical Center, Bronx, NY, 10468, USA.
E-mail address: ruth.walker@mssm.edu (R.H. Walker).

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required; age of onset, age of death, and cause of death. The presence and nature of seizures and cardiac disease was noted when documented. In some cases autopsy had been performed which provided specific information about cause of death.

2.1. Data availability statement

Study data for the primary analyses presented in this report are available upon reasonable request from the corresponding and senior author.

3. Results

Pertinent information was available for 52 patients with ChAc (e-table 1) and 34 with MLS (e-table 2). In many cases information was incomplete, thus our conclusions here are based upon the best available information.

For ChAc, mean age of reported disease onset was 29 years (range of 18–48 years). Mean (and median) life expectancy following diagnosis was 11 years (e-table 1). Cause of death was documented for 32 patients. Reported causes included; aspiration pneumonia (n = 7), sudden unexplained death (n = 6), cardiac (or likely cardiac) (n = 5), suicide (or injuries related to a suicide attempt) (n = 4), seizure (n = 4), aspiration/asphyxia (n = 3), renal failure (1), sepsis (n = 1) and injuries from a motor vehicle accidents (n = 1) (Fig. 1a).

For McLeod syndrome, mean age of onset was 38 years (range of 11–76 years) (e-table 2). (The reported age of onset of 11 years [2] is intriguing, and it is impossible to know definitively whether this reflected clinical onset of MLS or not. The patient was reported to be "fidgety" from approximately this age, and the "fidgetiness" spread to other parts of his body in adulthood, which sounds consistent with chorea.) One patient was diagnosed age 18, and several were diagnosed in their early 20s. It should also be noted that the erythrocyte McLeod phenotype is sometimes detected by blood type screening prior to the onset of neurological symptoms, thus the implications of the "diagnosis" of MLS likely reflected quite a different disease stage that the "onset" of ChAc. For this article we have in general attempted to identify the onset of neurological symptoms in MLS.

Mean life expectancy of MLS following diagnosis was 21 years (median of 16 years; range 5–51 years). Reported causes of death (n = 22) included; cardiac (or "likely cardiac") (n = 9), pneumonia (n = 6), seizure (n = 2), sudden unexplained death (n = 2), aspiration (n = 1), and hepatic failure (n = 1) (Fig. 1b). There was one case of pancreatic cancer, which was likely unrelated to MLS.

4. Discussion

The conclusions presented here are limited by the fact that clinical information regarding these very rare disorders is limited and is not currently collected in any systematic manner.

Factors determining the age of onset of neuroacanthocytosis syndromes are not yet known. ChAc typically presents in young adulthood, while MLS presents in middle age. The ages of reported onset of ChAc (29 years) and MLS (38 years) were lower than the average age of diagnosis of HD (40 years), although of course for HD this figure varies inversely with the size of the trinucleotide repeat expansion and can range from infancy to old age. In HD, subtle preclinical signs are detected before the appearance of unequivocal motor signs, and there is currently much debate regarding how and when to make the diagnosis in a person carrying the causative mutation. As in HD, the age of clinical disease onset of ChAc and MLS is often hard to define; presentations are often subtle, with changes in behavior or cognition, or occasionally can be dramatic, with the development of seizures. The symptoms may be psychiatric or cognitive, and are often initially attributed to other causes. Involuntary movements may be attributed to medications given for symptoms initially attributed to be a primary psychiatric illness.

The ages of onset reported in publications or by clinical history are likely those at which either a dramatic event occurred, e.g. seizure, or when signs or symptoms became severe enough to require medical attention. It should also be noted that in a number of affected families, the diagnosis was made by genetic or protein-based methodology in a sibling with relatively subtle symptoms following the presentation of an affected family member.

Life expectancy following diagnosis with ChAc was 11 years, while for MLS it was 21 years. These figures are indicative of the fact that MLS can have a much more variable presentation and course, with some patients reported to have a remarkably mild neurologic phenotype. This mild phenotype appears to be related to missense mutations of the *XK* gene but can also be present in loss-of-function mutations. It should also be noted that other causes of cardiac illness may well be contributing factors in this population of middle-aged and older males. To date there appears to be no genotype-phenotype correlation in ChAc.

Definitive genetic diagnosis of NA syndromes has only been available since the early 2000s, thus it is likely that we are underestimating life expectancy; we are aware of patients who have been living with these diseases for several decades whose information has not been included here. These patients may have less severe symptoms (e.g. may not have seizures or significant psychiatric morbidity), or may be receiving optimal disease management to reduce the risk of aspiration or seizures.

Survival following diagnosis with ChAc and McLeod was similar to that of HD, where survival is reported as 15–20 years, with significantly shorter disease duration for those at the extremes of younger or older ages. In HD, the size of the trinucleotide repeat expansion determines age at death [3]. Causes of death in HD [4] are similar to those noted here, and include pneumonia, choking, nutritional deficiency, and chronic skin ulcers. Similarly, suicide rates are recognized to be increased in HD [5].

The majority of patients identified for this report followed the disease course typical of neurodegenerative disorders with progressive debility, decreased muscle mass due to myopathy and neurogenic muscle atrophy, cachexia, impaired motor functions, becoming bedridden, and eventually succumbing to sepsis from pneumonia or other infections. In addition to the features common to diseases characterized by slowly progressive neurodegeneration, ChAc and MLS have several distinctive characteristics that distinguish them from HD. Approximately 50% of patients with ChAc and MLS have seizures. These can be focal or generalized. In general these tend to respond well to conventional anti-convulsants, however, occasional patients have refractory seizures or suffer status epilepticus, and these can be a significant cause of morbidity. Seizures may be related to hippocampal [6] or cortical pathology [7], or be secondary to basal ganglia disease.

Similar to HD, a significant number of our patients died suddenly apparently due to aspiration (although sudden cardiac death or seizure could not always be excluded). This is likely in part due to the dysphagia which is typically present in choreic disorders, but also due to the specific problems related to the tongue protrusion dystonia of ChAc, and occasionally of MLS. Patients often adopt a feeding strategy which involves extending the neck and throwing food into the back of the pharynx in order to bypass the dystonic tongue. If not fatal, this maneuver also predisposes them to aspiration pneumonia.

Annual monitoring is recommended for cardiac disease in MLS, as cardiomyopathy and dysrhythmias are a frequent cause of death. Cardiac disease has been reported rarely in ChAc [6,8,9]. In our review of reports, cardiac causes were a non-infrequent cause of death in ChAc, however, it was not clear in most cases whether this was the primary cause, or thus whether routine cardiac monitoring is indicated in ChAc.

A range of psychiatric issues has been reported in both ChAc and MLS, and may contribute to an increased risk of suicide or suicide attempts. Similar to HD [5], depression, psychosis, anxiety, and impulsivity can all be seen, although a formal comparison of frequency

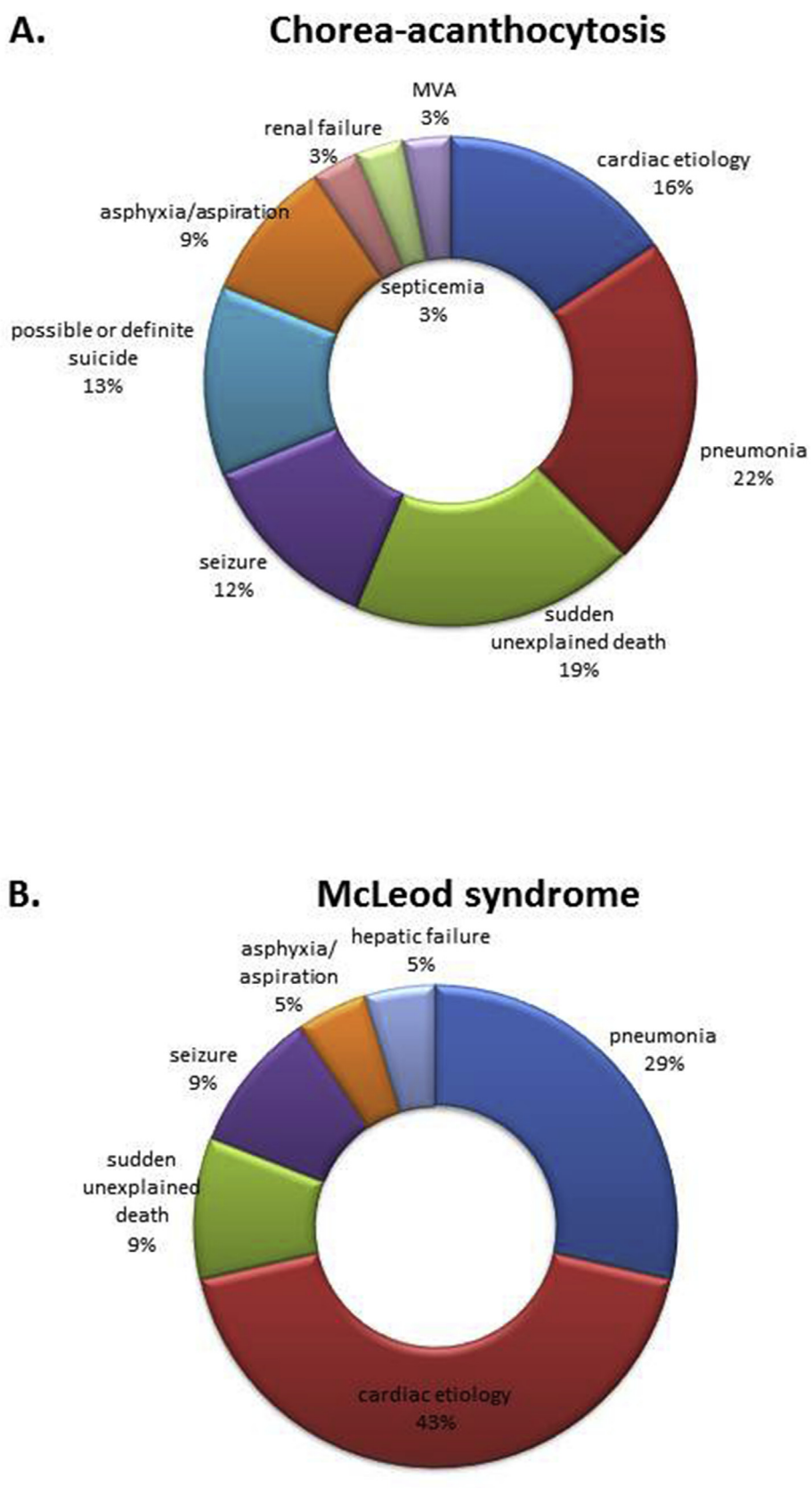

Fig. 1. Causes of death in chorea-acanthocytosis and McLeod syndrome, by percentage for each disease.

has not yet been performed. Suicide was the cause of death in 10% of patients with ChAc, and but none with MLS. The frequency of suicide in ChAc is similar to that in HD, and may be related to the shared psychiatric features. It is possible that suicidality in ChAc is an extreme manifestation of the self-mutilation which appears to be a behavioral compulsion [10], and may also be coupled with aggression towards

others [11]. This latter case responded favorably to cingulotomy. It is of note that atrophy of the head of the caudate nucleus is more severe in ChAc as compared with HD, and may correspond with the obsessive-compulsive traits [12].

Despite the fact that a hematologic abnormality is a diagnostic (although not invariable) feature of these diseases, morbidity due to hematologic factors is relatively rare. Patients with MLS may develop anti-Kell antibodies following transfusion with Kell-positive blood, and are at risk of hemolytic transfusion reaction if they subsequently receive a second transfusion with Kell-positive blood. Patients with MLS should bank their own blood if possible, for autologous transfusion, or for potential use for other McLeod patients. Most patients have a mild compensated hemolytic anemia; the affected sibling of patient ChAc 9 (e-table 1) developed spontaneous hemolysis and secondary splenomegaly at age 19, prior to the appearance of obsessive-compulsive symptoms, tics and chorea. This patient is still alive at the age of 40 with a gastrostomy.

A significant proportion of patients with ChAc and MLS had sudden, unexplained deaths. Sudden unexplained death in epilepsy (SUDEP) is attributed to uncontrolled seizures, however, seizures had not been documented in a number of these patients, and were often reported to be well-controlled. Undetected autonomic nervous system (ANS) instability is a possibility in ChAc; while ANS involvement has been documented only rarely, it is possible that subclinical dysfunction might be more widespread, and might result in fatal cardiac dysrhythmias. Unlike HD, ChAc involves the peripheral nervous system as well as the brain, thus it is reasonable to consider the development of autonomic neuropathy.

In general, there was a paucity of information available regarding causes of death in patients with NA syndromes, indicating the need for further systematic data collection in this area. Our study emphasizes the importance of management of seizures, psychiatric symptoms, cardiac and ANS symptoms, and the reduction of risk of aspiration in the care of patients with NA syndromes.

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Author contributions

AD - acquisition of data, critical revision of the manuscript for important intellectual content.

HHJ - acquisition of data, critical revision of the manuscript for important intellectual content.

MM - acquisition of data, critical revision of the manuscript for important intellectual content.

RHW - Study concept and design, acquisition of data, analysis and interpretation.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.09.003.

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