Reviews

Management of Neuroacanthocytosis Syndromes

Ruth H. Walker[1,2*]

[1] Department of Neurology, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA, [2] Department of Neurology, Mount Sinai School of Medicine, New York City, NY, USA

Abstract

Background: The two core neuroacanthocytosis (NA) syndromes, chorea-acanthocytosis (ChAc) and McLeod syndrome, are progressive neurodegenerative disorders that primarily affect the basal ganglia. The characteristic phenotype comprises a variety of movement disorders including chorea, dystonia, and parkinsonism, as well as psychiatric and cognitive symptoms attributable to basal ganglia dysfunction. These disorders are symptomatically managed on a case-by-case basis, with very few practitioners seeing more than a single case in their careers.

Methods: A literature search was performed on PubMed utilizing the terms neuroacanthocytosis, chorea-acanthocytosis, and McLeod syndrome, and articles were reviewed for mentions of therapies, successful or otherwise.

Results: There have been no blinded, controlled trials and only one retrospective case series describing ChAc. The various therapies that have been used in patients with NA syndromes are summarized.

Discussion: Management remains at present purely symptomatic, which is similar in principle to other more common basal ganglia neurodegenerative disorders such as Huntington's disease (HD) and Parkinson's disease (PD). However, there are some specific issues particular to NA syndromes that merit attention. An integrated multidisciplinary approach is the ideal management strategy for these complex and multifaceted neurodegenerative disorders.

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*To whom correspondence should be addressed. E-mail: ruth.walker@mssm.edu

Introduction

The two core neuroacanthocytosis (NA) syndromes are chorea-acanthocytosis (ChAc), which is autosomal recessive, and McLeod syndrome, which is inherited in an X-linked manner. These disorders share a number of similar features including chorea, dystonia, peripheral neuropathy, myopathy, seizures, and psychiatric symptoms, and there can be a striking phenotypic overlap.[1–3]

Due to the rarity of these conditions, all reports of therapies are anecdotal, and no controlled clinical trials have been performed. The only significant case series that has been published is a retrospective survey of 15 patients with ChAc who underwent deep brain stimulation (DBS) at 11 centers internationally,[4] which constitutes level 4 evidence.

Treatment for most of the symptoms of NA syndromes is based upon empiric evidence from patients with other conditions. For example, the effects of botulinum toxin injections for dystonia have been systematically studied in a controlled, blinded manner primarily in patients with isolated cervical dystonia and occasionally with isolated dystonia affecting other regions. More complex dystonia such as that involving the lower facial area and tongue is challenging to study in a systematic manner due to the variability of affected muscle groups. In McLeod syndrome, it is possible to anticipate and prepare for cardiac and hematological complications.

The ideal approach to these complex neurodegenerative disorders, as in Parkinson's disease (PD),[5,6] is a multi-disciplinary, holistic approach employing physical, occupational, and speech therapists, in addition to nurses, social workers, and neurologists with expertise in movement disorders.[7] While the availability of particular therapies may be limited, especially when there is no clear potential for improvement, it is essential to recognize that functions can be

maintained with appropriate, ongoing activities. In the face of apparently relentless disease progression and ongoing deterioration of motor and cognitive functions, it can be helpful to identify specific and realistic goals. For example, it is beneficial to coordinate injections of botulinum toxin for focal dystonia with therapies aimed at maximizing specific functions such as speech and swallowing.[7]

In an attempt to synthesize the current available knowledge, here I review the data, primarily in the form of single case reports, small series, and personal and anecdotal evidence, for the management of ChAc and McLeod syndrome. In addition, I discuss the issue of performing clinical trials in very rare disorders, and the role of online patient-oriented resources for patients, caregivers, and clinicians.

Methods

A literature search was performed on PubMed utilizing the terms neuroacanthocytosis (n=191, excluding review articles), chorea-acanthocytosis (n=314, excluding review articles), and McLeod syndrome (n=124, excluding review articles). All articles in English were reviewed for their mention of therapies, successful or otherwise. All reports were from university clinics, as far as could be ascertained. The majority of reports were of single cases, except as noted. Where available the dosages used are given. Suggested doses are provided where appropriate.

Results

ChAc

Orolingual dystonia. ChAc can present with a wide spectrum of symptoms that may vary over time. When present, a characteristic movement disorder of ChAc is dystonia involving the lower face and tongue,[8] precipitated specifically by eating. While a similar phenomenon may be occasionally seen in other disorders including tardive dyskinesia, McLeod syndrome, and pantothenate kinase-associated neurodegeneration (PKAN),[9] the severity of this symptom, disproportionate to other involuntary movements, strongly suggests ChAc. In addition, the self-mutilating tongue and lip biting that are often present[10] are not yet reported in the other conditions. These movements can be very painful and damaging, in addition to interfering with feeding and speech and being socially embarrassing.

Management of this symptom can be very challenging. Some patients have all of their teeth removed to reduce cheek, lip, and tongue biting. Others use a mechanical device such as a stick to reduce biting and tooth-grinding. These objects may also reduce dystonia by functioning as a sensory trick. Bite guards can be helpful but are often expensive, wear out, and interfere with eating. Some patients will use an absorbent item like a towel, which also absorbs saliva.

Botulinum toxin injected into the genioglossus may reduce tongue protrusion (two patients, dose not available: one patient—125 units of abobotulinum toxin into the genioglossus).[7,9] Alternatively, 10 units of onabotulinum toxin to each muscle under ultrasound guidance can be successful in improving eating and speech.[11] As this muscle protrudes the tongue, weakening it should not theoretically result in airway obstruction; however, most physicians are cautious about such injections, especially with the potential of spread to other muscles involved in swallowing. Electromyogram-targeted injections of 35 units of onabotulinum toxin into the inferior head of the lateral pterygoid muscles bilaterally, in addition to 15 units into each masseter, were reported to be helpful in reducing bruxism and tongue biting.[12]

Tetrabenazine may reduce dystonia including tongue protrusion for sustained periods of time (Brandon Barton, MD, personal communication). It should be started at 12.5 mg/day, increasing weekly as tolerated to a total of 50 mg/day in divided doses, with close monitoring for parkinsonism and depression. Other authors have reported worsening of dysphagia with this medication.[13]

Truncal and limb chorea and dystonia. Severe neck ("head drops") and truncal flexion/extension movements are often seen and are likely to be choreic in nature rather than being due to motor impersistence or dystonia. The gait can appear quite bizarre and "rubbery," with buckling at the knees and hips, a feature which otherwise raises suspicion of a psychogenic gait disorder. Despite a severely abnormal gait, balance can be remarkably preserved with relatively few falls. The feet are often plantar-flexed and inverted due to dystonia, sometimes in combination with a peripheral neuropathy. This lower leg dystonia may respond to botulinum toxin injections.

Dystonia was reported to respond to levodopa in two patients (benserazide/levodopa 25/100/three times daily [t.i.d]),[14] although this medication is not typically helpful. Typical anti-dystonia medications, including anticholinergics (e.g., trihexiphenidyl 1 mg per oral [p.o.] daily, increasing to 2 mg t.i.d and higher if tolerated), benzodiazepines (e.g., clonazepam 0.25 mg daily, increasing to 0.5 mg t.i.d and higher if tolerated), and baclofen (5 mg t.i.d, increasing as tolerated) may be tried. Tetrabenazine can be considered, although it is not always beneficial.[13] Amantadine (200 mg/day) has been reported to reduce chorea.[15] Doses of 100 mg t.i.d. or four times daily (q.i.d.) may also be tried.

In selected patients, DBS of the ventro-postero-lateral region of the globus pallidus pars interna (GPi) may result in a sustained reduction in chorea and dystonia including feeding dystonia, trunk movements, and head banging.[4,16] Positive effects were also seen for self-mutilation and tongue biting. In two cases, additional stimulation of the thalamic ventralis oralis region was required for adequate control of the involuntary movements.[17]

Worsening of chorea during pregnancy has been noted (Pietro Mazzoni, MD, PhD, personal communication), with improvement following delivery.[18]

One case was reported of a young female with ChAc who suffered from severe knee pain due to joint destruction as a consequence of leg hypotonia and involuntary movements.[19] She underwent joint replacement with marked improvements in pain and functioning, illustrating that the presence of a progressive neurodegenerative condition should not preclude orthopedic intervention.

Parkinsonism. Parkinsonism can be a presenting sign[20] or the primary movement disorder present.[21] However, bradykinesia usually develops later,[22] which may suggest a similar progression of neurodegeneration

to that seen in Huntington's disease (HD), with a "burnout" of the hyperkinetic movements. Amantadine (200 mg/day) was reported to improve gait.[21] Levodopa (1,000 mg/day) may have a weak effect[20,22] or be ineffective,[22,23] consistent with evidence that there may be degeneration of both pre-[22] and post-synaptic neurons,[24] which would limit the effectiveness of these medications. Doses of levodopa up to 2,000 mg/day in divided doses with a peripheral dopa-decarboxylase inhibitor may be tried as tolerated. DBS of the GPi did not improve parkinsonism.[4]

Tics. Tics, both motor and vocal, can suggest a diagnosis of Tourette syndrome prior to emergence of the full neurologic syndrome of ChAc.[25] Self-mutilation seems to be due to behavioral compulsion[26] and may include severe tongue, lip, cheek, or finger biting or throwing the body to the floor. It has been observed that a mouth guard also reduced obsessive-compulsive behaviors and tics,[27] suggesting that the neuronal circuits controlling these behaviors may be closely linked.[28]

Levetiracetam (250 mg twice daily [b.i.d.])[29] or benztropine, quetiapine, and lorazepam in combination[30] have been reported to reduce tics. The effects of traditional medications for tics in ChAc have not yet been described.

Speech and swallowing issues. Impairment of speech and swallowing are early features of ChAc. Dysarthria due to dystonia affecting the tongue and jaw is an invariable feature. In later stages, patients may become completely anarthric. The use of communication devices such as communication boards, keyboards, and computer-assisted speech are often critical to maintain communication.

Dysphagia can be due to tongue dystonia with eating and also to impaired coordination of the oropharyngeal musculature. Aspiration is a major risk, as patients adopt dramatic maneuvers to swallow food, such as extending the head and throwing food into the back of the throat. As in HD, weight loss is common, possibly for metabolic reasons, and nutrition should be closely monitored. It is often necessary to consider a percutaneous endoscopic gastrostomy (PEG) at relatively early disease stages to safely maintain adequate nutrition. DBS of the GPi did not significantly improve speech and swallowing.[4]

Psychiatric symptoms. Psychiatric symptoms can often be the initial signs of basal ganglia dysfunction in ChAc, similar to other basal ganglia neurodegenerative disorders. As in HD, the psychiatric features can be more disabling than the motor symptoms, and treatment of these symptoms may play a large role in improving quality of life.

Obsessive-compulsive behavior is not uncommon in ChAc, as is depression.[31] These symptoms should be aggressively treated, for example using selective serotonin re-uptake inhibitors such as citalopram (40 mg/day).[32] High doses of quetiapine (600 mg/day) are also reported to be effective.[33]

Frontal disinhibition can result in apparently criminal behaviors and can be very challenging to manage.

Seizures. Unlike most other choreiform disorders, seizures are seen in approximately 40% of patients with ChAc (but also McLeod syndrome).[34,35] These are often an early or presenting sign and typically originate in the temporal lobe.[29,36,37] Conventional anti-convulsant agents are usually effective, although, rarely, seizures are refractory to multiple drugs.[29] Lamotrigine may worsen tics.[29] Bilateral seizure origin was recognized using intracranial electroencephalography in a patient who was being evaluated for epilepsy surgery.[36] In general, patients with ChAc are poor candidates for this neurosurgical intervention.

Cardiac and other autonomic nervous system manifestations. Cardiac involvement, specifically cardiomyopathy, has been rarely reported in ChAc. Dilated cardiomyopathy was reported in a 40-year-old male in whom McLeod syndrome had been excluded, although genetic confirmation of ChAc was not performed.[38] Left ventricular hypertrophy was reported in a 34-year-old patient with genetically confirmed ChAc who also had tobacco-related pulmonary disease.[39] He died suddenly 4 years later, which was presumed by the authors to be due to cardiac causes. Another patient in this report carried an identical mutation but did not develop cardiac disease; thus, the significance of these findings is unclear.

Autonomic nervous system dysfunction with orthostatic hypotension and bradycardia has been described[40,41] and is attributed to peripheral post-ganglionic sympathetic denervation. These authors hypothesize that denervation hypersensitivity to norepinephrine may cause fatal arrhythmias and may account for reports of sudden death.[42] Pacemaker implantation has been useful in the treatment of sustained bradycardia (Barbara Karp, MD, personal communication).

McLeod syndrome

Chorea and dystonia. When movement disorder aspects are more prominent, the phenotype of McLeod syndrome can be very similar to that of ChAc. However, the presentation of McLeod syndrome may vary considerably, and the movement disorders may be minimal. As McLeod syndrome is an X-linked recessive disorder, it typically presents in males; however, female carriers may develop the condition.[43,44] The onset is usually in middle age in contrast to the young-adult onset of ChAc.

Treatment of movement disorders is symptomatic but is often not required. When present these can include chorea, dystonia, and parkinsonism. The latter symptom can be a presenting sign or emerge as the disease evolves from hyper- to hypo-kinetic movements.[45] Head drops[46] and orolingual dystonia with feeding, otherwise suggestive of ChAc, are rare,[47] and self-mutilating lip biting has not been reported. Positive results have been reported with DBS of the GPi.[48]

Neuropathy and myopathy. The myopathy of McLeod syndrome is due to axonal neuropathy. It is typically mild and subclinical but occasionally may be very debilitating,[49–51] contrary to what was originally hypothesized.[52] Rhabdomyolysis has occasionally been reported.[53]

Psychiatric symptoms. A variety of psychiatric or cognitive issues may be seen, often as presenting symptoms,[54] although they are not always present. These should be treated using conventional methods.

Cardiac disease. Cardiac disease is one of the most important aspects in McLeod syndrome, and presents a valuable opportunity for active disease management.[55,56] Annual echocardiography is recommended for early detection of potentially treatable cardiomyopathy or arrhythmias.[56,57] Heart transplantation may be an option, as it is in other genetic cardiomyopathic conditions.

Hematologic issues. The X-linked "McLeod phenotype" was first identified in 1961 by the erythrocyte phenotype of reduced Kell and absent Kx antigen cell-surface expression.[58,59] The causative mutations of the *XK* gene on the X chromosome result in absent or dysfunctional XK protein.[60] XK is linked to Kell by a disulfide bond;[61] thus, when XK is absent or not present on the membrane, there is reduced expression of the 23 antigens normally expressed by Kell. Some patients are identified prior to the development of neurological symptoms if they undergo blood typing.

The Kell antigen system is the third most important erythrocyte antigen system after ABO and Rh. When individuals with the McLeod red cell phenotype are transfused with Kell-positive blood, there is also a risk of developing anti-Kell antibodies. If they require subsequent transfusions, there is a risk of transfusion reactions with donor cell hemolysis.[62] Thus, it is recommended that people with McLeod syndrome bank their own blood for autologous donation in case of future need or for donation to others.

In addition to the presence of acanthocytosis, the membrane abnormalities due to the absence of normal XK usually result in a mild, compensated hemolytic anemia. However, there are no particular issues with respect to freezing or thawing McLeod erythrocytes, despite the apparent increase in red cell membrane fragility (Connie Westhoff, PhD, personal communication). Subjects may donate blood every 8 weeks, as long as their hemoglobin level is above 12.5 g/dL.

As XK is contiguous with the gene for chronic granulomatous disease,[63] there are a number of individuals with both conditions. Due to their medical vulnerability, these patients often need blood transfusions.

Causes of morbidity in NA

The natural history of these disorders, similar to other neurodegenerative conditions such as PD and HD, is one of progressive motor debility. Dysphagia tends to occur relatively earlier in ChAc than in these other conditions, and PEG placement should not necessarily be regarded as a pre-terminal event as it may be critical for maintaining adequate nutrition and preventing further weight loss. Even though patients often develop tricks for eating to overcome tongue dystonia, these often put them at risk of pneumonia, and safety in swallowing must be emphasized.

Loss of insight and behavioral disinhibition are difficult to manage and may put patients at risk for falls other accidents.

Sudden, apparently unexplained death seems to occur quite frequently in ChAc. In some cases it may be due to status epilepticus (personal observation), while in others seizures do not constitute a likely explanation, being either apparently absent or well-controlled. Aspiration may be responsible in some of these cases. Alternatively, it is possible that cardiac arrhythmia may be the cause of sudden death. This latter possibility has not been adequately studied in these patients, although cardiomyopathy and dysrhythmia are well-recognized in McLeod syndrome.

Performing clinical trials in ultra-rare disorders

Carrying out double-blind, placebo-controlled trials in very rare, slowly progressive, neurodegenerative disorders such as those discussed is inevitably challenging. Even the collation of a retrospective series of 15 patients with ChAc who underwent DBS presented many challenges regarding data collection and making the data acceptable for publication.

Single-subject, randomized, double-blind, cross-over studies (n-of-1 trials) may be an option for short evaluations of symptomatic therapies;[64,65] however, these are not ideal for longer studies of disease-modifying therapies as disease progression may not be uniform. Specific symptoms may even become less prominent with disease progression (e.g., chorea may progress to parkinsonism). Intercurrent illness may result in dramatic worsening. Other barriers to trials in rare diseases and potential solutions are discussed in detail elsewhere.[66]

A web-based database has been constructed for NA syndromes; this is piggy-backed onto the European HD database (http://www.euro-hd.net/html/na/registry) with the aim of comprehensively documenting all known cases. This project has been challenging for a number of reasons. One of the major challenges has been the protean manifestations of these disorders, and the use of a number of clinical rating scales to attempt to address all disease features, including the motor scales from the Unified PD and Unified HD Rating Scales; the Burke-Fahn-Marsden Dystonia Rating Scale; a battery of cognitive, psychiatric, and behavioral assessments, details of seizures; and evaluations of functional capacity. The development of a single dedicated rating scale for ChAc and McLeod syndrome may be more appropriate; however, validation may be a challenge for such rare disorders.

Documentation of all known patients and their clinical status is critical in being "trial-ready" in preparation for the launch of a clinical trial as soon as a potential therapeutic agent is identified. An example of this is the Treat Iron-Related Childhood-Onset Neurodegeneration (TIRCON) project for PKAN,[67] which facilitated a clinical trial (still on-going) of the iron chelator deferiprone.[68] Partnership with patient organizations plays an important role in recruitment and investment of patients and families in such trials. Registration of clinical trials in databases such as www.clinicaltrials.gov and the use of social media are important modalities for contacting individuals who might be interested in participating in studies. Coordination over a number of sites, likely internationally, is an additional challenge.

Support groups

Many patients with very rare diseases find that they know more about their disorders than their treating physicians,[69] especially in the current age of the internet. The development of Internet-based support groups (e.g., www.rareconnect.org) and a newsletter (www.naadvocacy.org)[70] have been crucial resources for patients and caregivers, in addition to providing useful forums for researchers seeking clinical trial subjects.

Ongoing psychological support for patients and their caregivers is critical to avoid despair and burnout. Projects such as raising awareness and fund raising fulfill an important role in generating community support and provide rewarding goals.

Discussion

Experience with therapies for ChAc and McLeod syndrome is limited by the rarity of these conditions, with few practitioners seeing more than a single patient in their professional careers. The literature is limited to case reports and small, retrospective, case series. As these disorders are progressive, and manifestations may change over time, periodic tapering of medications is recommended to determine their benefits.

Double-blind, randomized, controlled trials are the research standard for validating new therapies; however, different methodologies, such as n-of-1 trials, may be required for such rare conditions. The availability of a current, comprehensive database enables us to be trial-ready in the event of identification of a potential therapy. In the meantime, a holistic, ongoing, and pro-active multidisciplinary approach with achievable goals and coordination of therapeutic interventions provides the best care for patients with these progressive devastating diseases.

Acknowledgements

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