

Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2

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Due primarily to a significant lack of studies and data, no evidence-based guidelines exist to inform the clinical care of people living with myotonic dystrophy type 2 (DM2). In order to improve and standardize care for this disease now, 15 leading myotonic dystrophy (DM) clinicians from western Europe, Canada and the United States have created the Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2. A complete list of authors and an overview of the process is available in Addendum 1. A complete reading list for each of the study area sections is available in Addendum 2.

The Board of Directors of the American Academy of Neurology formally affirmed the value of the Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2 as an educational tool for neurologists.

An update policy has been adopted for this document and will direct a systemic review of literature and appropriate follow up every three years. Myotonic staff will provide logistical and staff support for the update process.

A Quick Reference Guide extrapolated from the Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2 is available here <http://www.myotonic.org/clinical-resources>

For more information, visit [myotonic.org](http://www.myotonic.org)

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Life-threatening symptoms

Cardiovascular management

Background

DM2-related cardiac pathophysiology, although affecting all myocardial tissue, preferentially targets the cardiac conduction system. Conduction system defects are progressive and, while initially asymptomatic, increase the risk for symptomatic arrhythmias.

Clinical presentations include pre-syncope, syncope, palpitations, dyspnea, chest pain or sudden death from cardiac arrest.

Evaluation of the severity of cardiac conduction involvement is done by cardiac testing, including the 12-lead electrocardiogram (ECG), long-term ambulatory Holter-ECG monitoring and, for patients at increased risk, an invasive electrophysiological study.

Patients with DM2 are at risk of both bradyarrhythmias and tachyarrhythmias. Pacemakers can be implanted in DM2 patients, either to treat symptomatic bradyarrhythmias or prophylactically in those at high risk for complete heart block.

The most common tachyarrhythmias are atrial fibrillation and atrial flutter, which pose a risk of cardiogenic embolism and stroke. DM2 patients are also at an increased risk of ventricular tachyarrhythmias (tachycardia or fibrillation), a mechanism responsible for cardiac arrest. Implantable cardioverter-defibrillators (ICDs) can be installed in DM2 patients who have survived an episode of a ventricular tachyarrhythmia, or prophylactically in those at high risk for a ventricular tachyarrhythmia.

Sudden cardiac death has been observed in a small cohort of DM2 patients with pacemakers or ICDs, raising the question of a non-arrhythmia mechanism for this phenomenon.

Imaging studies, including echocardiography, magnetic resonance (MR), and nuclear imaging can be used to assess the heart's mechanical status, including left ventricular function. Asymptomatic abnormalities are observed in a moderate number of adults with DM2 and are more common in those with conduction system disease.

The development of dilated, non-ischemic cardiomyopathy is an infrequent but recognized occurrence in adults with DM2. Once a symptomatic dilated cardiomyopathy is present, progression is typically rapid, with congestive heart failure leading to death.

Recommendations

General:

- a. Encourage use of emergency medical alert devices

Look for:

- a. Palpitations, pre-syncope, syncope, dyspnea and chest pain; if observed, direct patient to seek prompt attention

- b. Arrhythmias including sinus bradycardia, heart block, atrial fibrillation and flutter, and ventricular tachycardia. Evaluate and treat using ACC (American College of Cardiology)/AHA (American Heart Association)/ESC (European Society of Cardiology) Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (see <http://www.ncbi.nlm.nih.gov/pubmed/16949478>)
- c. Symptom change, abnormal cardiac imaging (MRI or echocardiogram), abnormal ECG in all DM2 patients; exam should be conducted by cardiologist or clinician who is knowledgeable about cardiac manifestations in DM

Test for:

- a. Signs via a 12-lead ECG and/or a 24-hour Holter-ECG at DM2 diagnosis based on clinical judgement; conduct at diagnosis and approximately annually thereafter
- b. Impulse or conduction abnormalities on a standard 12-lead ECG including sinus rate < 50 BPM, PR interval > 200 ms, QRS duration > 100 ms including left or right bundle branch block, left anterior or posterior fascicular block, 2nd or 3rd degree AV block, abnormal Q-waves, atrial tachycardia, fibrillation, or flutter, and ventricular arrhythmias - indicate cardiac involvement
- c. Heart failure if abnormal ECG indicative of conduction disease or if other symptoms suggestive of heart failure are present; conduct echocardiography, and consider cardiac MRI

Treat with:

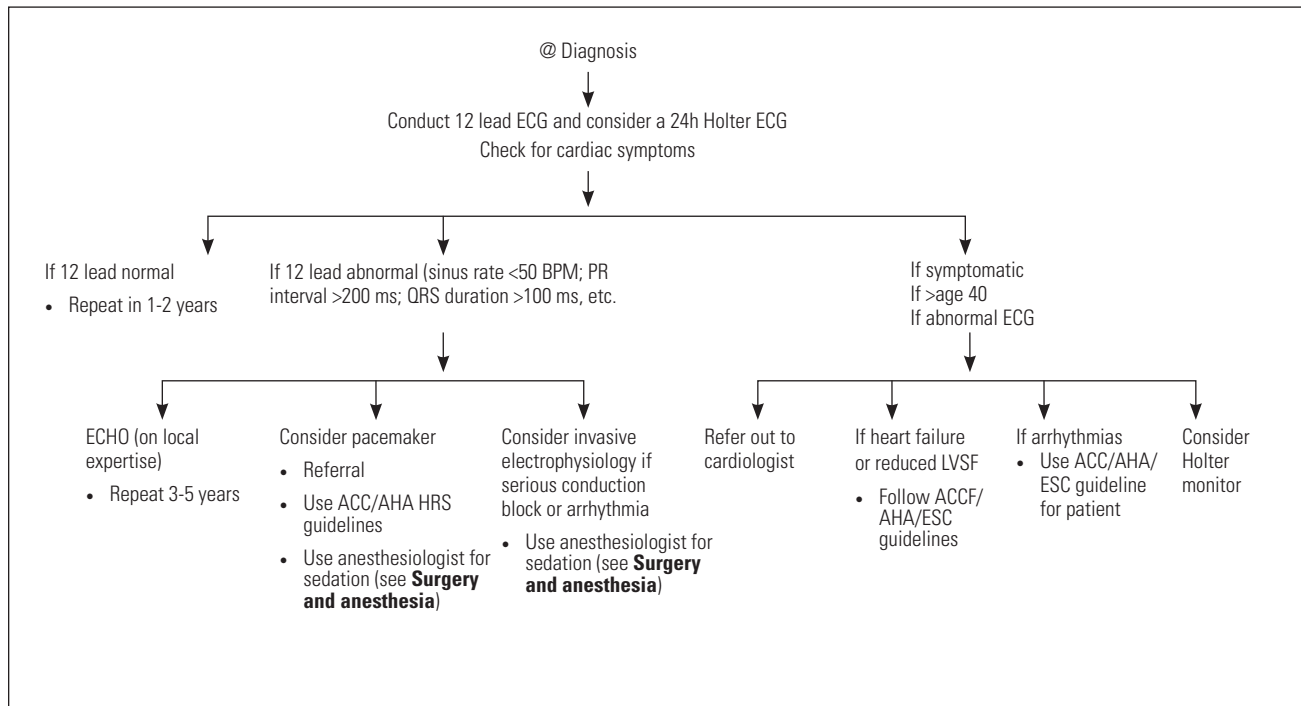
- a. Serial periodic clinical cardiology evaluations; cardiology consultations are recommended in patients with abnormal electrocardiograms and/or cardiac symptoms
- b. A primary prevention pacemaker or ICD may be considered in a DM2 patient found to be at risk of cardiac arrest or sudden cardiac death from abnormalities detected via noninvasive or invasive cardiac testing
- c. Cardiac imaging in DM2 patients may be considered at diagnosis and every three to five years thereafter. Cardiac imaging modalities other than echocardiography are reasonable alternatives for testing if symptoms being assessed and local expertise warrant intervention
- d. Invasive electrophysiology when there is concern about a serious conduction block or arrhythmia because of abnormalities detected via noninvasive cardiac testing
- e. Appropriate pharmacological and device therapies based on the ACCF (American College of Cardiology Foundation)/AHA (American Heart Association) Guideline for the Management of Heart Failure (see <http://www.ncbi.nlm.nih.gov/pubmed/23747642>) if heart failure or reduced left ventricular systolic function is present
- f. A primary (prophylactic) or secondary (symptomatic) prevention pacemaker or ICD based on the ACC (American College of Cardiology)/AHA (American Heart Association)/HRS (Heart Rhythm Society) Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (see <http://www.ncbi.nlm.nih.gov/pubmed/18498951>). This care needs to be delivered under the management of a cardiologist and coordinated with the patient's primary care provider and other consultants as necessary

- i. Patient and family preference and the assessment of other risk factors affecting morbidity and mortality should be considered in the decision to implant a pacemaker or ICD in a patient with DM2
- g. Ambulatory Holter ECG monitoring – either short-term (24-48 hours) or long-term (30 days or more) may be considered to detect mechanisms of arrhythmias in patients with cardiac symptoms. Test at baseline and periodically repeat such monitoring every 3-5 years if indicated by symptomatic status or if change observed on serial 12-lead ECG

Refer to:

- a. A cardiology center experienced in care of DM2 patients with cardiac symptoms if patient exhibits new abnormal annual or biennial ECG indicative of cardiac involvement, as well as DM2 patients without previous cardiac involvement. However, cardiology referral for all DM2 patients is reasonable if part of a multidisciplinary program or if the practitioners providing primary care are unfamiliar with cardiac history, exam, and ECG assessment
- b. An anesthesia practitioner, separate from the operating physician, to provide procedural sedation and monitoring for electrophysiology studies and pacemaker or ICD implantation. Perform these cardiology studies and associated anesthesia/sedation in a clinical environment that allows immediate endotracheal intubation and ventilation to be fully prepared to care for those patients who develop post-sedation respiratory insufficiency or respiratory failure (see **Surgery and anesthesia**)

Fig. 1 DM2 Cardiac Care Recommendations Flowchart



Life-threatening symptoms

Respiratory management

Background

Some DM2 patients have significant breathing problems that can result from muscle weakness of the diaphragm, abdominal and intercostal muscles and myotonia of these muscles, leading to poor ventilatory force and resulting in low blood oxygen and elevated blood carbon dioxide levels.

Fatigue, excessive daytime sleepiness (EDS) and respiratory failure can occur in DM2, significantly reducing quality of life. Their causes may overlap, but some sources believe that fatigue and EDS in DM2 are mostly due to primary central nervous system involvement and that respiratory insufficiency or failure is mostly due to respiratory muscle weakness. That said, insufficient air flow during sleep may contribute to disrupted sleep and excessive daytime fatigue.

Weakness of the inspiratory and expiratory muscles reduces cough effectiveness and impairs clearing of secretions, leading to an increased risk of pulmonary infections and to aspiration of material into the lungs. Weakness of the swallowing muscles can add to the risk of aspiration of food and drink, saliva, nasal secretions and stomach fluids.

General anesthesia and intravenous pain medications, especially opiates, can cause respiratory failure in patients who were previously clinically stable, highlighting the need for careful perioperative management of patients with DM2. (see **Surgery and anesthesia**)

Recommendations

Monitor at baseline and every 2 years thereafter.

Look for:

- a. Ineffective cough, recurrent pulmonary infections, a Forced Vital Capacity (FVC) value of less than 50% of predicted normal values or an MIP of less than 60; if present evaluate every 6 months or more frequently for:
 - i. History and frequency of chest infections
 - ii. Respiratory rate, auscultation, assessment of chest wall motion and recruitment of abdominal muscles (as minimum components of a pulmonary exam)
 - iii. Orthopnea, dyspnea, poor sleep, morning headaches, apnea, fatigue and snoring
- b. Symptoms of nocturnal hypercapnia (daytime sleepiness, morning headache, concentration/attention difficulties). Respiratory difficulties when lying down flat

Test for:

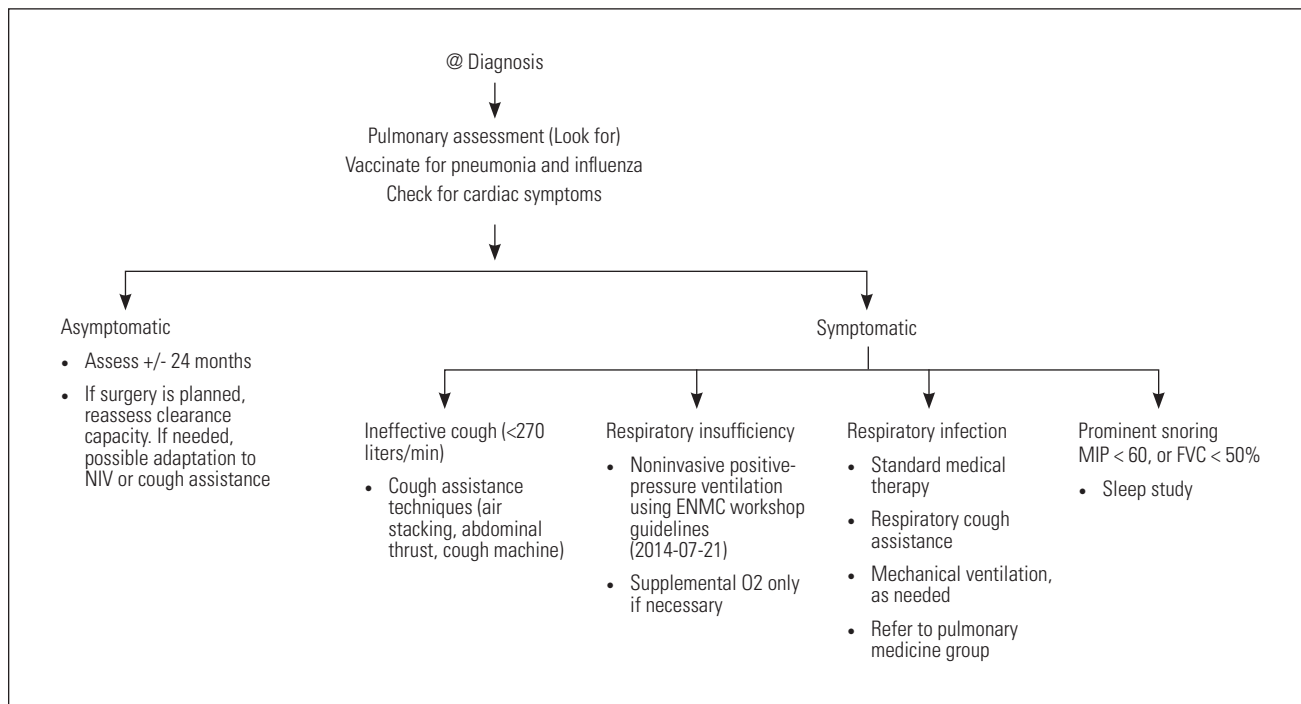
- a. Prominent snoring, nightly interrupted sleep, MIP value and FVC in upright and lying position
- b. Sleep behavior via a sleep study or other respiratory tests. In general, the threshold for obtaining a sleep study in DM2 patients should be low

- c. Clearance capacity and other respiratory assessments prior to surgery; if needed, adaptation to nocturnal noninvasive ventilation or to cough-assist devices should also occur prior to surgery (see **Surgery and anesthesia**)

Treat with:

- a. Vaccinations for influenza and pneumonia if no contraindications. Patients with respiratory infections should be treated as soon as possible using standard medical therapy, as well as respiratory cough assistance and mechanical ventilation (as needed). Obtain consultations from respiratory therapy and pulmonary medicine groups as needed
- b. Airway clearance and lung volume recruitment techniques (e.g., breath stacking, abdominal thrust, the vest and the mechanical insufflator/exsufflator) for DM2 patients with ineffective cough (cough peak flow of less than 270 liters/minute), and during chest infections and perioperative periods (see **Surgery and anesthesia**)
- c. Some patients will progress to requiring nighttime ventilatory support and full-time ventilation. Information regarding noninvasive positive-pressure ventilation criteria has been previously published at an ENMC (European Neuromuscular Centre) Workshop (2014-07-21)
- d. Supplemental oxygen *with caution* in conjunction with noninvasive ventilation (see **Surgery and anesthesia**)
- e. Emergency medical alert devices prophylactically

Fig. 2 DM2 Pulmonary Care Recommendations Flowchart



Severe symptoms

Pain control

Background

Myotonic dystrophy type 2 is often associated with pain. In some cases, the pain originates inside the muscles. In other cases, the pain originates in the joints, ligaments, or spine. Muscle weakness may predispose individuals to arthritic changes or strain in these areas. Common symptoms are difficulty standing up from a low chair, rising from the ground or a squatting position, or climbing stairs. Reaching up or working with the arms overhead also may be difficult. People with DM2 often experience unusual fatigue with exercise, which can lead to additional connective tissue or joint pains. Muscle pain in the neck, back, shoulders, hip flexors, and upper legs may be a prominent symptom, and the severity of pain can fluctuate from day to day.

Pain negatively affects the psychosocial life of DM2 patients, and focusing on pain can make the negative effects worse. Coping strategies are important and support groups can help.

Recommendations

Look for:

- a. Muscle pain in the neck, back, shoulders, hip flexors, and upper legs
- b. Statin-induced pain, which can occur in DM2

Treat with:

- a. Conventional pain medications (Ibuprofen, etc.)
- b. Opioids – avoid if possible. If implemented, low doses should be used with close monitoring for side-effects (See **Surgery and anesthesia**)
- c. Other remedies, such as massage, nerve blocks, heat/ice, or chiropractic care. Some patients have reported that cannabinoids help ease pain as well, however more research needs to be conducted (Jensen et al, 2008)

Refer to:

- a. Physical therapy or occupational therapy if conventional treatment is not successful

Severe symptoms

Skeletal muscle weakness and rehabilitation

Background

Skeletal muscle weakness and myalgia are major features of DM2. The weakness, which is associated with a dystrophic process, is bilateral and progresses at the relatively slow rate of 1 to 3 percent per year. Involvement of distal and facial muscles is usually absent. Initial weakness is in proximal hip girdle and neck (flexors > extensors) muscles. Axial muscle weakness is frequent in DM2 and may result in lower back pain.

Mild ptosis may occasionally be present. Calf hypertrophy may occur.

Typical effects of adult-onset DM2 on skeletal muscle include the following:

- Myalgic pains, which can be the most prominent clinical feature in the early stages and may severely affect occupational performance
- Neck flexor weakness, causing difficulty raising the head from a surface
- Impacts to employment and activities of daily living due to proximal and axial muscle weakness (e.g. climbing stairs, standing up from the floor, etc.)

Recommendations

Look for:

- a. Difficulty with myalgia, mobility, balance and falls
- b. The effect on activities of daily living
- c. The effect on activities at home, school, work and in the community
- d. Need for assistive devices or modifications in the home, school or workplace

Evaluate annually through the primary care provider or by appropriate specialists, including physical therapists/physiotherapists, occupational therapists, speech/language pathologists, dietitians/nutritionists, social workers, nurses/nurse practitioners, psychiatrists and orthopedists, to monitor the above.

Treat with:

- a. Moderate- or low-intensity aerobic and resistance exercise, minimizing sedentary activities, if possible. Obtain a cardiac evaluation prior to starting a new exercise routine
- b. Orthoses, braces
- c. Walking aids such as a walking cane or walker
- d. Home modifications as necessary

Refer to:

- a. Appropriate rehabilitation specialist for individual recommendations

Severe symptoms

Skeletal muscle myotonia

Background

Myotonia – sustained muscle contraction and difficulty relaxing muscles may be absent in some patients. Even if it is not the most disabling aspect of the disease, myotonia can contribute to muscle stiffness, pain, prolonged hand grip, speech and swallowing difficulties, and GI issues, and may be associated with hand tremor.

Clinical examination for myotonia may be limited mainly to percussion of wrist extensor muscles or proximal limb muscles. Electrical myotonia can also be demonstrated by abnormal, spontaneous muscle fiber discharges seen on a needle electromyogram (EMG) in proximal muscles.

DM2-associated myotonia is commonly worse in cold weather and is more pronounced after rest. Its improvement with muscle activity is known as the “warm-up” phenomenon. Myotonia in adult-onset DM2 generally declines as weakness increases.

Drugs affecting ion channels can improve myotonia, although their potential for causing cardiac arrhythmias must be weighed against their possible benefits.

Look for:

- a. Delayed relaxation after grip or percussion and difficulty with activities of daily life

Treat with:

- a. Mexiletine as an option for myotonia, if myotonia is present and is distressing to the patient
 - i. As mexiletine is an antiarrhythmic, obtain a electrocardiogram (ECG) prior to use, and then at serial intervals (see **Cardiovascular management**)
 - ii. Instruct the patient to take mexiletine with food to avoid dyspepsia and transient ‘dizzy feelings’. Food extends absorption and lowers the peak level in blood, and lessens the gastrointestinal side effects that can potentially occur with mexiletine

Severe symptoms

Ocular management

Background

Major and clinically relevant eye manifestations in DM2 can include the following: cataracts, eyelid ptosis and incomplete eyelid closure, retinal changes and changes in intraocular pressure.

Visual impairments in patients with DM2 are most often caused by cataracts. Posterior subcapsular iridescent lens opacities are highly suggestive of DM2, although they are not diagnostic. Cataracts in DM2 may progress faster than usual cataracts, and thus patients with DM2 may present with early-onset cataracts. Cataracts before the age of 55 or a family history of premature cataracts suggest a diagnosis of DM or DM in patients with muscle symptoms.

By direct ophthalmoscopy, the cataracts associated with DM are nonspecific and appear as punctate (dotlike) opacities. By slit-lamp examination, they have a multicolored, iridescent appearance and are located in the posterior lens capsule. Posterior subcapsular iridescent lens opacities represent an initial phase of cataract formation in DM. They are detectable only with slit-lamp examination and are usually found in patients who have not developed visual symptoms.

Glare and blurriness of vision develop as lens opacities progress to stellate (starlike) cataracts and eventually to mature cataracts, which may be indistinguishable from more common types of cataracts. Surgery to remove cataracts in DM2 patients can be performed, but local anesthesia is preferred so that complications associated with general anesthesia in these patients can be avoided (see **Surgery and anesthesia**).

Bilateral eyelid ptosis is not a frequent feature of DM2.

Recommendations

Look for:

- a. Symptoms of cataracts and other eye manifestations in DM2. Advise patients about safety measures for adjusting to changes in light levels, precautions for driving in the sun and at night related to the effects of the cataracts, and how to protect the cornea, especially if they sleep with the eyes partially open because of weak eyelid closure muscles, blepharitis, eyelid problems/infections and conjunctivitis

Test for:

- a. DM2 ocular manifestations via a slit-lamp examination as part of an annual eye exam even in asymptomatic patients. Perform regular ophthalmological examinations AFTER the cataract surgery as well, as cataracts may recur
- b. Eyelid ptosis; if ptosis becomes severe and interferes with vision, intervention, such as eyelid "crutches" that can be inserted into glasses, may be warranted. Try crutches as a remedy for ptosis before eyelid surgery is considered, due to anesthesia risks and concomitant eye closure weakness

Refer to:

- a. Surgical ophthalmologist when cataracts interfere with the ability to meet the needs of daily living, and surgical removal of the opaque lens with intraocular lens implantation is indicated. Ensure anesthesia risks are clear to the DM2 patient and surgical team, and the long-term efficacy as well as side effects of the surgery are thoroughly vetted with the patient, his/her family, and other care providers (see **Surgery and anesthesia**)
- b. Ophthalmologist for regular follow-up to evaluate weakness of eyelid closure. Ophthalmic lubricants for dry eye can be considered

Severe Symptoms

Gastrointestinal management

Background

Among the common problems are dysphagia, aspiration, abdominal pain and bloating, especially after eating, slow gastric emptying, gastroesophageal reflux, constipation, diarrhea and “irritable bowel” symptoms, gallstones, dilated colon which can result in fecal impaction, megacolon and even perforation of the bowel; and anal incontinence.

Elevated GGT, which is usually NOT an expression of a liver disease, is a common and early finding. However, liver steatosis and cholelithiasis are also common findings in DM2 and should be carefully monitored.

Recommendations

Look for:

- a. Problems with chewing or swallowing, drooling, gastroesophageal reflux, bloating, abdominal pain, frequency and characteristics of bowel movements, diarrhea and fecal incontinence. Careful history should be taken to differentiate oropharyngeal dysphagia from esophageal dysphagia. Esophageal dysphagia sometimes causes chest pain due to acid reflux from the stomach
- b. Involuntary weight loss or weight gain; dysphonia or dysphagia that may indicate pharyngeal muscle weakness; frequent cough and recurrent broncho-pneumopathies that may indicate aspiration; abdominal pain on palpation (generally in, or in the area of, the gall bladder); and abdominal bloating during routine physical exams

If symptoms persist, refer to gastroenterologist for proper examinations which can include among others: ALT, AST, GGT, abdomen ultrasound and in some cases endoscopic evaluations

Treat with:

Non-pharmacologic treatments for gastrointestinal symptoms:

- a. High-fiber diet (15-20 grams per day), for patients with diarrhea or constipation as first response. Increased fiber intake should be undertaken with increased water intake, with the exception of drinks that are high in caffeine and fructose
- b. Nutrition consultation for patients with dysphagia, weight loss or weight gain, to assess nutritional adequacy
- c. Dysphagia therapy referral, including compensatory strategies and dietary modifications, for patients with oral pharyngeal dysphagia

Potential pharmacologic treatment for gastrointestinal symptoms:

- d. Loperamide (Imodium), for diarrhea
- e. Gentle laxatives (see below) for constipation. Oils should be avoided. If a patient does not respond to the first- or second-line recommendations below, a referral to a gastrointestinal specialist for anal manometry should be considered:
 - i. First-line therapy recommendations: polyethylene glycol (Miralax), senna (Ex-Lax, Senokot), docusate (Colace) or lactulose (Cholac)
 - ii. Second-line therapy recommendations: bisacodyl (Dulcolax, Correctol), lubiprostone (Amitiza) or linaclotide (Linzess)
 - iii. Metoclopramide (Reglan) may be used to reduce the symptoms of gastroparesis, pseudo-obstruction and gastric reflux. Long-term use is not recommended because this drug can cause tardive dyskinesia
 - iv. If bacterial overgrowth is found on breath testing, treating with antibiotics may reduce diarrhea
- f. Enteral feeding (tube feeding) in patients with severe dysphagia, for example, dysphagia that causes weight loss or recurring pneumonia, if required

DM2 patients should be advised to follow screening guidelines for colon cancer that apply to the general population.

Severe Symptoms

Neuropsychiatric management

Background

Specific cognitive deficits may be seen in DM2, but they are believed to be milder than those seen in all forms of DM1. In addition to the primary alteration in brain function thought to be caused by the DM2 genetic mutation, there may be contributions from the disordered sleep patterns or the hormonal or other systemic abnormalities seen in the disorder. Depressive symptoms may also be present in DM2 and may increase as the disease progresses.

In DM2, cognitive and behavioral abnormalities can involve deficits in intelligence, executive function, visual-spatial construction, arithmetic ability, and attention, although the scope and degree of the involvement vary among patients. Lack of executive function can lead to great difficulty planning and organizing one's life, affecting areas such as paying bills, keeping appointments and arranging schedules.

Reduced blood flow in the frontal and temporal lobes of the brain, reduced cerebral volume compared to age-matched controls, and ubiquitous cerebral white matter changes have been found in patients with DM2, although their relationship to cognitive and behavioral abnormalities is not clear. In addition, studies have shown a unique, abnormal pattern of tau isoform expression in DM2-affected human brains.

The cognitive and personality aspects of DM2 remain relatively uncharacterized, but they can have a significant impact on quality of life for the patient and his or her family.

Recommendations

Look for:

- a. Difficulty organizing and planning, apathy, depression

Test for:

- a. Patient's mental health via information from significant others and family members where privacy regulations allow this, as patients with DM2 can have limited insight about their cognition and behavior
- b. Psychiatric or behavioral issues and cognitive changes as part of patient's annual exam. A baseline neuropsychological evaluation is recommended, with additional testing to be dictated by the patient's clinical course

Treat with:

- a. Psychostimulants may be considered if apathy is associated with an impairing level of fatigue or excessive daytime sleepiness (see **Excessive daytime sleepiness**)
- b. Antidepressive medication (cardiac examination before starting treatment, including a 12 lead ECG)

Refer to:

- a. Mental health care professional (psychologist or psychiatrist) when the diagnostic impression includes psychiatric or behavioral abnormalities, when feasible, for possible treatment such as medication, couple or family support, or cognitive behavioral therapy

Severe Symptoms

Excessive daytime sleepiness

Background

Excessive daytime sleepiness (EDS) while common in DM1 is very rare in DM2 but can be a life-altering symptom. General fatigue is relatively common in DM2 and may be seriously disabling. It causes patients to sleep frequently, and often unpredictably, throughout the day, even if sleep duration during the night has been normal or greater than normal.

Fatigue and EDS in DM2 may result from one or more distinct mechanisms, including behavioral abnormalities, with an erratic sleep schedule and poor sleep hygiene; ventilatory muscle weakness resulting in sleep-related hypoventilation and nonrestorative sleep; airway obstruction due to pharyngeal weakness and obstructive sleep apnea; central nervous system (CNS) caused alveolar hypoventilation; and CNS-caused hypersomnia due to disordered arousal mechanisms. Its positive response to the psychostimulant drug modafinil (Provigil) in a few studies suggests to some experts that impaired arousal may be the most common cause of fatigue and EDS in DM2.

Recommendations

Look for:

- a. Alcohol and caffeine consumption, medications and sleep habits for their possible contribution to fatigue and EDS. If poor sleep habits, alcohol or caffeine consumption, or medication side effects are suspected causes of fatigue or EDS, these factors should be addressed if possible

Test for:

- a. EDS via the Epworth Sleepiness Scale or similar scales or sets of questions such as the questions in the Myotonic Toolkit; prescribe polysomnography as needed
- b. Fatigue, via Krupp Fatigue Severity Scale, etc.
- c. Respiratory symptoms, sleep apnea and central hypersomnia during sleep evaluation for fatigue and EDS. Respiratory muscle weakness contributing to EDS in DM2 patients (see **Respiratory management**)

Treat with:

- a. Noninvasive positive-pressure ventilation if a DM2 patient's sleepiness is thought to be related to nocturnal or daytime hypoventilation or sleep apnea. Patients should be referred to pulmonologists who have experience in neuromuscular diseases for consideration of assisted ventilation (see **Respiratory considerations**)
- b. Stimulant therapy with the psychostimulant modafinil can be considered if central hypersomnia is suspected

Refer to:

- a. Cognitive behavioral therapy (CBT) or custom training to reduce daytime fatigue or sleepiness
- b. Sleep specialist and/or pulmonologist for patients who complain of fatigue or EDS or score positively on the ESS or other sleepiness scales

Severe Symptoms

Endocrine and metabolic

Background

Researchers indicate that endocrine and metabolic abnormalities are a feature of DM2, but clinical data are limited to a minimal number of studies with small sample sizes or case reports. For the studies cited below, see Reading List Addendum 2

Insulin resistance. Similar to patients with DM1, investigation of the insulin receptor in skeletal muscle biopsies indicates missplicing of the insulin receptor in patients with DM2. Other studies of clinical data describe insulin resistance in DM2. Patients with DM2 most likely have the same frequency of type 1 or type 2 diabetes compared to age-matched, general population, but more studies are necessary to establish the accuracy of this impression.

Hypothalamic-pituitary axis (thyroid, adrenal, gonadal function). Data evaluating hypothalamic-pituitary axis function are sparse in DM2 patients, but similar to DM1, DM2 may lead to alterations in the regulation of thyroid, adrenal and gonadal hormone levels. Some studies describe hypogonadism in patients with DM2 and data from the National Registry for Myotonic Dystrophy (DM) & Facioscapulohumeral Dystrophy (FSHD) indicates trouble with sexual function in 17.0% of 84 male patients with DM2 and 4.3% of 128 female patients with DM2 and 2.5% of 591 females with DM1 in the National Registry for Myotonic Dystrophy (DM) & Facioscapulohumeral Dystrophy (FSHD).

Hypothyroidism exacerbates DM2. One study indicates that manifestations and diagnosis of DM2 can be masked by hypothyroidism and emphasizes the importance of serial monitoring of thyroid function in patients with established as well as possible DM2. Clinicians should closely monitor patients with DM2 for symptoms suggesting exacerbation of muscle symptoms (i.e., fluctuating levels of pain and fatigue, muscle weakness, and irregular muscle stiffness) and obtain a detailed evaluation of thyroid function. Patients who present with some of the symptoms of hypothyroidism should also be assessed for symptoms and family history of DM2.

Pregnancy can exacerbate DM2. A few reports indicate that pregnancy can exacerbate or unmask the onset of myotonia and cause increased pain in DM2. More research is needed to confirm these observations. It will be helpful to determine if hormonal changes related to pregnancy have an influential role in the regulation of the abnormal splicing in skeletal muscle associated with the development of myotonia and weakness in both DM2 and DM1. In addition, other studies are needed to determine if women with DM2 have more painful or irregular menses similar to DM1 and relatively higher than the general population.

Liver enzyme elevations. Similar to DM1, evidence indicates that elevation of liver enzymes, especially gamma glutamyl transferase, occurs in many patients with DM2. These alterations are generally not progressive. It is not known whether they represent a primary effect of DM2 on liver cells or are consequence of metabolic derangements, biliary stasis or fatty liver. Insulin resistance is likely to be the major contributing factor to observations of fatty liver and hyperlipidemia, although more research is needed. Biliary stasis is not well studied, but it may be related to smooth-muscle myotonia, weakness and/or alterations in enterohepatic circulation.

Skin alterations. Hormonal imbalance or underlying problems with skin and hair follicles may contribute to alopecia and other skin conditions in patients with DM2, such as, dysplastic nevi and seborrheic dermatitis.

Recommendations

Look for:

- a. Painful or irregular menses in female DM2 patients and refer to OB-GYN specialist as appropriate. Assess for the potential exacerbation of symptoms in pregnancy
- b. Reproductive history, fertility/infertility and family planning in male and female DM2 patients; refer to genetic counselor or other specialists as indicated
- c. Signs/symptoms of hypothyroidism/hyperthyroidism

Test for:

- a. Liver enzymes and bilirubin levels at baseline and then annually. Chronic liver enzyme elevation is commonly seen in DM patients and does not necessarily indicate the need for liver biopsy
- b. Thyroid dysfunction in DM2 patients; measure thyroid-stimulating hormone (TSH) and free T4 levels at baseline and every three years. More frequent monitoring is necessary if thyroid dysfunction is suspected. Screen for Thyroid-Antibodies (TPO)
- c. Hyperlipidemia via testing for levels of serum lipids at baseline and then every three years, with more frequent testing if hyperlipidemia develops. As the impact of statins on DM2 patients' health is uncertain, clinicians should monitor patients carefully for muscle-related impacts if these lipid-lowering medications are used, and higher lipid levels can be tolerated without statins if needed
- d. Sex hormones in females, glucose levels, HbA1c, PTH, Vitamin D

Treat with:

- a. Lifestyle changes in diet and exercise and appropriate use of medications to normalize blood glucose and insulin levels for treatment of insulin resistance. Physicians treating DM2 patients should follow criteria from the American Diabetes Association (ADA) at <http://www.diabetes.org> for oral glucose tolerance testing, and request measurements of HbA1c and fasting plasma glucose annually
- b. Statins if needed because of an increased cardiovascular risk. Strict monitoring of clinical symptoms with a CK completed at baseline. Start with a low dose and elevate only if the patient can tolerate

Severe Symptoms

Surgery and anesthesia

Background

Although a higher incidence of adverse reactions to medications used for anesthesia and analgesia has been reported for DM1 (about 8%), it is yet not clear whether similar risks occur also in DM2 patients. However, given this uncertainty and the potentially serious complications reported in some DM2 patients, our advice is to adopt anesthesia guidelines similar to these as suggested for DM1.

See Myotonic's *Practical Suggestions for the Anesthetic Management of a Myotonic Dystrophy Patient* <http://www.myotonic.org/mdf-releases-updated-anesthesia-guidelines> and *Anesthesia Quick Reference Guide* here: <http://myotonic.org/clinical-resources>

Anesthetic risks, as detailed in the Myotonic anesthesia guidelines referenced above, result from DM effects that include the following:

- Cardiac conduction defects and potentially fatal arrhythmias
- Ventilatory insufficiency and poor airway protection
- Gastrointestinal dysmotility that frequently results in pseudo-obstruction and can lead to aspiration
- Erratic responses to succinylcholine (although DM2 does not increase true malignant hyperthermia reactions, this drug should not be used in DM2 patients because of the risk of an increase of myotonia, masseter spasm and hyperkalemia)
- Prolonged and heightened sensitivity to sedatives and analgesics, resulting in serious complications in the post-anesthesia period. After-anesthesia risk of aspiration and other complications, including delayed-onset apnea and respiratory failure, is increased due to the following drug-induced effects:
 - a. Reduction in level of consciousness
 - b. Exaggerated ventilatory weakness
 - c. Pharyngeal dysfunction with reduced airway protection
 - d. Gastrointestinal dysmotility and potential pseudo-obstruction

Recommendations

See Myotonic *Practical Suggestions for the Anesthetic Management of a Myotonic Dystrophy Patient* for anesthesia risks and recommendations before any surgeries or procedures requiring anesthesia and the *Anesthesia Quick Reference Guide* (<http://myotonic.org/clinical-resources>)

1. Monitor during anesthetization for untoward responses and interactions of the cardiac, respiratory, skeletal muscle and central nervous system before, during and after surgery
2. Monitor post-anesthetization for serious adverse events, even if patient's DM2 symptoms are mild (at least 24 hours)
3. Carefully monitor behavioral and cognitive abnormalities preoperatively (if possible); these manifestations, along with hypersomnia and preoperative sleep deprivation, can complicate the patient's immediate postoperative care and longterm recovery
4. Note: most serious complications occur in the post-anesthesia period

Supplemental Considerations

Diagnosis

Background

Making a diagnosis of myotonic dystrophy type 2 (DM2) is not usually difficult, if the disorder is suspected. However, the path to diagnosis is often complicated by the wide range of body systems involved, the number of different practitioners consulted, and the wide variability in severity of the signs and symptoms of disease. It can take many years for a patient to receive a correct diagnosis of DM2.

If DM2 is suspected, a definitive diagnosis can be made via a genetic test using DNA prepared from peripheral blood leukocytes that shows the number of abnormally expanded CCTG repeats in the *CNBP* gene that contains the mutation for DM2. It should be noted that no genotype-phenotype correlations have been established to date. In general, repeat lengths less than 28 are considered normal, while repeats greater than 75 up to 1,000 are associated with clinical symptoms, albeit often highly variable. The impact of repeats in the 28-75 range in leukocyte DNA remains unclear and constitutes a gray zone. Given tissue heterogeneity and somatic instability of mutant repeats, an impact on clinical symptoms and presentation cannot be excluded. DM2 repeat sizing with more accurate methods in the future, including tissues other than blood, and/or segregation studies in the family will be valuable in addressing the role of the grey zone repeat expansions.

While many of the following are also true, the diagnosis of DM2 should be suspected in any patient presenting with two of the following criteria:

Highly suggestive:

- Persistent myalgic pains, in particular in case of familial occurrence
- Proximal percussion myotonia at the trapezius during clinical examination
- Proximal hip and neck flexor muscle weakness
- Clinical myotonia or “stiffness” of muscles
- Myotonia or increased insertional activity on EMG
- Pre-senile cataracts, especially the polychromatic type
- First-degree heart block or cardiac arrhythmias

Supportive:

- Irritable bowel syndrome (IBS) or elevated liver enzymes
- Gallstones at a young age
- Increased mean MUP amplitude in RF on EMG
- Laboratory abnormalities: increased level of GGT, decreased level of IgM and IgG, increased level of FSH in males. Mildly elevated CK, elevated cholesterol
- Hypogonadotropic hypogonadism
- Excessive daytime sleepiness (EDS) and/or fatigue
- Brisk reflexes

Look for:

- a. Symptoms as listed above

Test for:

- a. DM2 via DNA-based genetic testing as the first line of investigation for any patient suspected of having DM2. When there is clear clinical suspicion of DM2, muscle biopsy should no longer be performed as a diagnostic test. Patients with more than 75 CCTG in intron 1 of the *CNBP* gene in chromosome 3q21.3 can be considered to have DM2. Patients with repeats in the 28-75 range gray zone are unclear. DM2 repeat sizing in tissues other than blood and/or segregation studies in the family may be valuable in addressing potential pathogenicity. False-negative genetic testing results can occur, even in a family with an established DM2 diagnosis. Expert referral is recommended
- b. Physical findings suspicious for a diagnosis of DM2 via physical examination with particular emphasis on neuromuscular, cardiovascular and respiratory assessments, and obtain a three generation family history
- c. EMG to look for myotonic/pseudomyotonic runs
- d. Muscle biopsy: Differently from DM1, where muscle biopsy is very rarely performed during the diagnostic ascertainment, in DM2 about 40% of patients still undergo a muscle biopsy before the proper diagnosis is reached. The typical histopathological picture of increased centralized nuclei (>5) with pyknotic nuclear clumps, small, angulated fibers and increased fiber caliber variability with a predominance of atrophied type 2 fibers (denervation-like pattern) should also prompt to the DM2 (CCTG) in genetic analysis for diagnostic confirmation. This is not needed if a patient has a genetic diagnosis or clinical symptoms and a first degree relative with genetic confirmation

Refer to:

- a. Genetic counseling (see **Genetic counseling**) for patients who exhibit clinical signs indicative of DM2, and for at-risk family members, in order to enable them to make an informed decision about whether to proceed to genetic testing. Such testing should be done through an accredited laboratory experienced in providing DM2 diagnoses (see <http://myotonic.org/living-dm/testing-and-diagnosis>). Individuals thus identified should be offered genetic counseling (see **Genetic counseling**) to discuss their risk for transmitting DM2
- b. Neuromuscular disease specialist, most likely a neurologist or clinical geneticist with a particular interest in inherited neuromuscular disease, who can facilitate a primary “whole-system” evaluation of the patient, prioritizing additional symptom-specific referrals, and providing ongoing clinical management of the condition

Supplemental Considerations

Genetic counseling

Background

DM2 is caused by the expansion of an unstable CCTG repeat sequence in intron 1 of the *CNBP* gene in chromosome 3q21.3.

The normal number of CCTG repeats in this region is less than 28. Repeat numbers greater than 75 can be considered diagnostic of DM2.

While DNA testing for DM2 is now widely available, there are many potential pitfalls in interpreting the results for the patient and family, making genetic counseling a useful part of the diagnostic process.

A diagnosis of DM2 in one person in a family has implications for other family members, giving rise to questions about whether or not the affected person should tell family members who show no symptoms and then whether or not those family members should be tested. Diagnosis of DM2 in a presymptomatic person can have important implications for health monitoring and family planning, but it can also raise the possibility of difficulty in obtaining certain types of insurance or encountering prejudice in the workplace.

Recommendations

1. Consider a referral of DM2 patients to genetic counseling services or a neurologist with expertise in DM2, even if the patient does not intend to have children
2. Review pedigree annually. Genetic counseling should be repeated when new information or circumstances change the risks for family members
3. Help mutation carriers inform their close relatives of the possibility that they may also have inherited the risks and repercussions of DM2, even if they or their children are currently asymptomatic

Supplemental considerations

Pregnancy and obstetrics management

Background

The effects of DM2 on both smooth and striated muscle can complicate pregnancy, labor and delivery.

Prenatal and preimplantation genetic diagnosis can allow for termination of the pregnancy or selective implantation of unaffected embryos.

Recommendations

Look for:

- a. A patient's reproductive history and DM2-related personal and family history, including current DM2 symptoms

Test for:

- a. Preimplantation genetic diagnosis to determine whether the embryo is affected or prenatal genetic diagnosis to determine if the fetus has the DM2 genetic expansion

Refer to:

- a. Genetic counseling services and family planning services

Addendum I:

Authors and acknowledgments

The Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2 was created by a group of 15 international clinicians experienced in the care and treatment of people living with myotonic dystrophy type 2. They included:

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The following seven primary sources were used to develop this document:

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- Thornton, C. Myotonic dystrophy, *Neurologic Clinics*. Aug 2014 (Thornton, 2014)
- Turner, C., and D. Hilton-Jones. Myotonic dystrophy: diagnosis, management and new therapies (review), *Current Opinion in Neurology*, Oct 2014 (Turner & Hilton-Jones, 2014)
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Myotonic designed and initiated the consensus-based process and provided project management and document preparation services.

Addendum 2:

Reading list

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