Myotonic Dystrophy (DM): Overview of Screening and Management

A Resource for Clinicians

Background

- As a multisystem disease, DM can present with a variety of symptoms best evaluated by multidisciplinary screening. Subtypes (DM1, DM2) are confirmed via genetic testing, and additional subtypes are defined based on symptom onset and severity
- Current treatment is based on a multidisciplinary approach (including small molecule therapies) to reduce symptoms. Additional therapeutic strategies are being evaluated through preclinical and clinical research

Screening: Multidisciplinary Approach[1,2]

NEUROLOGY: Muscle weakness; need for AFOs or mobility devices like PWCs

PULMONOLOGY: Respiratory insufficiency (PFT); central/obstructive sleep apnea (sleep study)

CARDIOLOGY: Conduction abnormalities and need for pacemaker

OPHTHALMOLOGY: Early cataracts

PRIMARY CARE/ENDOCRINOLOGY: Diabetes and thyroid abnormalities; painful lumps on skin (pilomatrixomas, basal cell carcinoma)

GASTROENTEROLOGY: Dysphagia and need for PEG/feeding tube placement

AFOs, ankle-foot orthoses; PEG, percutaneous endoscopic gastrostomy; PFT, pulmonary function test; PWCs, power wheelchairs.

Treatment Approach[3–8]

Symptomatic

Myotonia/pain
- Mexiletine (caution for cardiac side effects)[a]

Insulin resistance
- Metformin

CNS related
- Modafinil and/or behavioral therapy

Muscle weakness
- Aerobic exercise

Excessive daytime somnolence
- Sleep study; use of NIV

Dysphagia
- Nutritional supplement to prevent weight loss; PEG tube discussion

Pregnancy
- Genetic counselor and high-risk OB-GYN visit

Therapeutic Strategies

Small molecule drugs[b]
- Mexiletine[a]
- Metformin[c]
- Pitolisant[d]
- Tideglusib[e]

Oligonucleotide based
- AOC
- ASO
- microRNA

Gene therapy
- CRISPR/Cas9

[a]Under investigation for efficacy and safety in a phase 3 trial for myotonia in patients with DM1 and DM2 (NCT04700046) by reducing DMPK mRNA levels.[4] [b]These repurposed drugs, which were initially developed to treat a different condition, are being investigated in clinical trials for their possible therapeutic use in DM1, and not yet approved for this condition. [c]Under phase 3 investigation for efficacy and safety, to improve muscle function by correcting splicing defects, in patients with DM1 (NCT05532813). [d]Under phase 2 investigation for efficacy and safety, for excessive daytime sleepiness in patients with DM1 (NCT04886518). [e]Under phase 2/3 investigation for efficacy and safety in congenital DM (NCT03692312) by reducing expression of DMPK RNA.[4]

AOC, antibody oligonucleotide conjugate; ASO, antisense oligonucleotide; CNS, central nervous system; CRISPR, clustered regularly interspaced short palindromic repeats; DM, myotonic dystrophy; DMPK, dystrophia myotonica protein kinase; NIV, noninvasive ventilation; OB-GYN, obstetrician-gynecologist; PEG, percutaneous endoscopic gastrostomy.

Additional observational and biomarker studies are ongoing to help inform clinical phenotype/genotype, less invasive assessment methods (vs muscle biopsy), and clinical endpoints[9]

1. Gutiérrez Gutiérrez G, et al. *Neurologia (Engl Ed)*. 2020;35(3):185-206. **2.** Bird TD. GeneReviews® [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1165/. Accessed November 21, 2022. **3.** Ashizawa T, et al. *Neurol Clin Pract*. 2018;8(6):507-520. **4.** Pascual-Gilabert M, et al. *Drug Discov Today*. 2021;26(7):1765-1772. **5.** ClinicalTrials.gov. NCT04700046. https://clinicaltrials.gov/ct2/show/NCT04700046. Accessed December 22, 2022. **6.** ClinicalTrials.gov. NCT05532813. https://clinicaltrials.gov/ct2/show/NCT05532813. Accessed December 22, 2022. **7.** ClinicalTrials.gov NCT04886518. https://clinicaltrials.gov/ct2/show/NCT04886518. Accessed December 22, 2022. **8.** ClinicalTrials.gov. NCT03692312. https://clinicaltrials.gov/ct2/show/NCT03692312. Accessed December 22, 2022. **9.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/results?cond=myotonic+dystrophy&term=biomarker&cntry=&state=&city=&dist=. Accessed December 22, 2022.

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