



EVALUATION, DIAGNOSIS, AND MANAGEMENT OF FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

This is a summary of the American Academy of Neurology (AAN) guideline on the evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy (FSHD).

Please refer to the full guideline at AAN.com/guidelines for more information, including the complete clinical context and definitions of the classifications of evidence and recommendations.

Diagnosis of FSHD

Clinical Context

When clinical presentation of FSHD is typical and the inheritance pattern is consistent with autosomal dominant inheritance, clinical diagnosis is usually straightforward. If, in such circumstances, the diagnosis is genetically confirmed in a first-degree relative, genetic testing is not necessary for each affected individual. However, atypical presentations are not uncommon. In the setting of atypical or sporadic cases, genetic confirmation is important for genetic counseling, especially with the recent discovery of two genetically distinct forms of FSHD (PRIN).

In the most common FSHD type, FSHD type 1 (FSHD1), disease results from contraction of a DNA repeat sequence, termed *D4Z4 repeat*, on one copy of 4q35 from >10 repeats to 1–10 repeats. In addition, the contraction must occur in the presence of one particular (A variant) of two (A/B) sequence variants distal to the repeats (PRIN). Available molecular testing for FSHD1, which measures only the presence of a repeat contraction on initial testing, is highly sensitive and specific (EVID). In studies that utilized strict diagnostic criteria for FSHD, determining whether a contraction occurs on an A variant genetic background does not appear to improve diagnostic specificity (EVID). However, in clinical practice, strict clinical diagnostic criteria might not be adhered to, increasing the chances of a false-positive result (INFER). In consequence, determining that a D4Z4 contraction is occurring on an A variant is warranted when the clinical presentation is atypical for FSHD. At present, commercial genetic testing in FSHD is limited to FSHD1 testing.

Level B

Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of the disease.

Predictors of Severity in FSHD

Clinical Context

Factors that predict disease severity in FSHD are important for counseling patients and for screening for and managing potential complications (PRIN). The D4Z4 deletion size appears to be somewhat predictive of the overall rate of disease progression (EVID). D4Z4 deletion size should be used cautiously for predicting disease progression rate in any particular individual due to other sources of variation affecting disease severity, including intrafamilial factors (INFER). Clinical experience suggests that patients with severe childhood-onset disease almost invariably have very large deletions (i.e., contracted D4Z4 allele of 10–20 kb or 1–4 repeats), suggesting a much more robust correlation between disease severity and large deletions (EVID).

Level B

Large D4Z4 deletion sizes (contracted D4Z4 allele of 10–20 kb) should alert the clinician that the patient is more likely to develop more significant disability and at an earlier age. Patients with large deletions are also more likely to develop symptomatic extramuscular manifestations.

Monitoring for Complications of FSHD

Pulmonary Complications

Clinical Context

Our systematic review revealed that some patients with FSHD develop respiratory muscle weakness that can result in respiratory failure and need for mechanical ventilator assistance (e.g., nocturnal bilevel positive airway pressure), although this complication is uncommon (EVID). Patients with chronic respiratory failure from neuromuscular-related weakness often do not have classic symptoms of ventilatory failure (i.e., overt dyspnea). Impending respiratory failure, therefore, may begin with respiratory insufficiency mainly during sleep, resulting in excessive daytime somnolence or nonrestorative sleep. Respiratory insufficiency in patients with FSHD, therefore, may be evident only through pulmonary function testing (PRIN). Respiratory failure constitutes a major source of morbidity in patients with most muscular dystrophy types and can severely disrupt sleeping, daily activities, and quality of life (QOL) (PRIN). Early intervention with noninvasive mechanical ventilation leads to improved survival and QOL (RELA).

Level B	Clinicians should obtain baseline pulmonary function tests on all patients with FSHD. Patients should be monitored regularly if they have abnormal baseline pulmonary function test results or any combination of severe proximal weakness, kyphoscoliosis, wheelchair dependence, or comorbid conditions that may affect ventilation (e.g., chronic obstructive pulmonary disease, cardiac disease).
Level B	In patients who have FSHD and either 1) compromised pulmonary function studies (e.g., forced vital capacity <60%) or 2) symptoms of excessive daytime somnolence or nonrestorative sleep (e.g., frequent nocturnal arousals, morning headaches), clinicians should refer patients for pulmonary or sleep medicine consultation for consideration of nocturnal sleep monitoring or nocturnal noninvasive ventilation in order to improve QOL.
Level B	Patients with FSHD who do not get regular pulmonary function testing should be tested prior to surgical procedures requiring general anesthesia, as such testing may uncover asymptomatic respiratory compromise.

Cardiac Abnormalities

Clinical Context

Our systematic review revealed very little evidence for structural cardiac abnormalities in FSHD. Also, data are insufficient to suggest that patients with FSHD are susceptible to cardiac arrhythmias (EVID). Routine electrocardiographic/echocardiographic testing is therefore unnecessary in patients with FSHD who are asymptomatic (INFER).

Level C	Patients with FSHD should be referred for cardiac evaluation if they develop overt signs or symptoms of cardiac disease (e.g., shortness of breath, chest pain, palpitations). However, routine cardiac screening is not essential in the absence of cardiac signs or symptoms.
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Retinal Vascular Disease

Clinical Context

Our systematic review suggests that symptomatic retinal vascular disease in the form of an exudative retinopathy (Coats disease) is very rare in FSHD but tends to affect patients with large deletions almost exclusively (EVID). Untreated exudative retinopathy can lead to significant visual loss, which may be prevented by early intervention (INFER).

Level B	Clinicians should refer patients with FSHD and large deletions (contracted D4Z4 allele of 10–20 kb) to an experienced ophthalmologist (e.g., retina specialist) for dilated indirect ophthalmoscopy (Level B). The presence and severity of retinal vascular disease at initial screening should be used to determine the frequency of subsequent monitoring.
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Hearing Loss

Clinical Context

Our systematic review shows that the available studies fail to capture the prevalence and clinical relevance of hearing loss in FSHD (EVID). In clinical practice, most patients with FSHD and hearing loss requiring the use of a hearing aid have childhood-onset FSHD with large D4Z4 deletions. Two recent studies support this clinical impression (EVID). Moreover, one of the studies suggests that hearing loss is progressive in some patients. Adults and older children are cognizant of the hearing loss onset, and therefore intervention can occur early when required. However, failure to detect hearing loss in infants and younger children may significantly delay or impair language development (PRIN).

Level B	Clinicians should screen all young children with FSHD at diagnosis and yearly thereafter until these children start school, as hearing loss may not be present at diagnosis and can be progressive.
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Pain

Clinical Context

Pain is a common complaint in FSHD and appears to be mostly musculoskeletal in origin (EVID). Pain compounding muscle weakness can have a significant impact on QOL (INFER). Physical therapists often can provide insight into the mechanism of pain in patients with weakness (PRIN). Nonsteroidal anti-inflammatory medications are useful for acute pain, and antidepressants or antiepileptics for chronic musculoskeletal pain (PRIN).

Level B	Treating physicians should routinely inquire about pain in patients with FSHD. Referral for a physical therapy evaluation may prove helpful as an initial nonpharmacologic intervention. In patients with persistent pain and no contraindications, a trial of nonsteroidal anti-inflammatory medications is appropriate for acute pain and antidepressants or antiepileptics for chronic pain.
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Treatment of FSHD

Pharmacologic Interventions

Clinical Context

As of this writing, no evidence exists for any effective pharmacologic interventions that improve strength or slow disease progression in FSHD. Randomized, controlled trials of albuterol were negative (EVID). Uncontrolled, open-label trials of corticosteroid and diltiazem showed no benefit. A controlled early phase II study of MYO-029, a myostatin inhibitor, also failed to show benefit.

Level B	In patients with FSHD, clinicians should not prescribe albuterol, corticosteroid, or diltiazem for improving strength.
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Surgical Scapular Fixation

Clinical Context

In patients with FSHD, limited shoulder range of motion due to periscapular muscle weakness is a major source of functional limitation (PRIN). Moreover, in many patients, bedside manual scapular fixation can result in significant improvement in shoulder range of motion (PRIN). Postoperative complications are infrequent but include hemo- or pneumothorax, pain, infection, non-union, and reduced lung capacity. Scapular fixation appears to be generally safe and may be effective for improving shoulder range of motion (EVID).

Level C	Surgical scapular fixation might be offered cautiously to selected patients after careful consideration of the overall muscle impairment in the involved arm, assessment of potential gain in range of motion by manual fixation of the scapula, the patient's rate of disease progression, and the potential adverse consequences of surgery and prolonged postsurgical bracing.
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Aerobic Exercise

Clinical Context

Aerobic exercise in FSHD appears to be safe and potentially beneficial (EVID), as has been shown in many other muscle diseases (RELA). Aerobic fitness is important for overall health (PRIN). To minimize injury from falls or overuse, the type of aerobic exercise should be tailored to the patient's particular distribution of weakness. For example, a stationary bicycle rather than a treadmill should be recommended for patients with leg weakness (PRIN). Although no data exist to suggest that strength training is detrimental in FSHD (EVID), further research is needed to determine whether such strength training will result in clinically meaningful long-term functional improvement (INFER).

Level C	Clinicians might encourage patients with FSHD to engage in low-intensity aerobic exercise. An experienced physical therapist can help guide development of individualized exercise programs. Clinicians might also use the practical physical activities guidelines for individuals with disabilities, provided by the US Department of Health and Human Services, when counseling patients about aerobic exercise. ¹
Level C	In patients interested in strength training, clinicians may refer patients to physical therapists to establish a safe exercise program using appropriate low/medium weights/resistance that takes into consideration the patients' physical limitations.

¹US Department of Health and Human Services Office of Disease Prevention and Health Promotion. Additional Considerations for Some Adults. In: Physical Activity Guidelines for Americans; chap 7. <http://www.health.gov/paguidelines/guidelines/chapter7.aspx>. Published September 2008. Accessed October 1, 2012.

This guideline was endorsed by the FSH Society and the MDA.

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Definition of Clinical Context Terms

EVID = Evidence-based conclusions for the systematic review

PRIN = (Stipulated axiomatic) principles of care

RELA = (Strong evidence from) related conditions not systematically reviewed

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Copies of this summary and additional companion tools are available at AAN.com or through AAN Member Services at (800) 879-1960.

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