Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy


ABSTRACT

Objective: To develop recommendations for the evaluation, diagnosis, prognostication, and treatment of facioscapulohumeral muscular dystrophy (FSHD) from a systematic review and analysis of the evidence.

Methods: Relevant articles were analyzed in accordance with the American Academy of Neurology classification of evidence schemes for diagnostic, prognostic, and treatment studies. Recommendations were linked to the strength of the evidence and other factors.

Results and recommendations: Available genetic testing for FSHD type 1 is highly sensitive and specific. Although respiratory insufficiency occurs rarely in FSHD, patients with severe FSHD should have routine pulmonary function testing. Routine cardiac screening is not necessary in patients with FSHD without cardiac symptoms. Symptomatic retinal vascular disease is very rare in FSHD. Exudative retinopathy, however, is potentially preventable, and patients with large deletions should be screened through dilated indirect ophthalmoscopy. The prevalence of clinically relevant hearing loss is not clear. In clinical practice, patients with childhood-onset FSHD may have significant hearing loss. Because undetected hearing loss may impair language development, screening through audiometry is recommended for such patients. Musculoskeletal pain is common in FSHD and treating physicians should routinely inquire about pain. Aerobic exercise in FSHD appears to be safe and potentially beneficial. On the basis of the evidence, patients with FSHD might be encouraged to engage in low-intensity aerobic exercises.

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GLOSSARY

AAN = American Academy of Neurology; CI = confidence interval; FSHD = facioscapulohumeral muscular dystrophy; FSHD2 = facioscapulohumeral muscular dystrophy type 2; MD = muscular dystrophy; poly-A = polyadenylation; QOL = quality of life.

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common form of muscular dystrophy (MD), with a prevalence of approximately 1:15,000–1:20,000.1,2 It is an autosomal dominant disorder; however, up to 30% of cases are sporadic, arising from de novo mutations.

FSHD symptoms typically develop in the second decade of life but can begin at any age from infancy to late adulthood.1 FSHD is characterized by a distinctive, initially regional distribution of muscle involvement. Facial, periscapular, and humeral muscles typically are involved early in the disease course, although the deltoids are spared.3 FSHD typically progresses slowly but variably.4,5 About 20% of individuals with FSHD become wheelchair dependent after age 50.1

Extramuscular manifestations occur in FSHD and can include respiratory compromise; retinal vascular...
The molecular genetic basis of FSHD is complex. At the tip of chromosome 4q35 lies a repetitive 3.3 kilobase (kb) DNA sequence known as D4Z4 repeats.6,7 Moreover, there are 2 different DNA variants distal to the D4Z4 repeats, called the A and B allelic variants.8 FSHD type 1 (FSHD1), accounting for 95% of FSHD cases, results from deletion of a critical number of D4Z4 repeats, but only when this occurs on the A allele. The biological basis for this dual requirement is becoming increasingly understood. Contraction of the D4Z4 repeat results in a more open chromatin structure, allowing the potential expression of gene sequences within the repeats. One such gene, double homeobox 4 (DUX4), lacks the polyadenylation (poly-A) sequence required to produce stable messenger RNA.9,10 Because only the A (not the B) allele variant contains a poly-A sequence, stable DUX4 expression can occur only in the presence of the A allelic variant.11,12

Complicating matters is the existence of a genetically distinct but clinically identical FSHD type—FSHD type 2 (FSHD2)—now known to account for approximately 5% of patients with clinically defined FSHD.13,14 Unlike the majority of patients with FSHD (i.e., FSHD1), patients with FSHD2 do not have contractions in the 4q35 D4Z4. As with FSHD1, and despite a normal number of repeats, the chromatin structure at the D4Z4 repeats is more open, and at least one 4q35 allele is an A variant.13 Recent studies have implicated mutations in SMCHD1, a gene on chromosome 18 that functions as a chromatin modifier, as the cause of the D4Z4 chromatin changes observed in about 85% of patients with FSHD2.15 Comprehensive molecular genetic testing for FSHD2 is complex and not readily available currently, and thus is not addressed herein.

Despite having distinct genotypes, FSHD1 and FSHD2 have an identical molecular basis that results from the aberrant expression of the DUX4 gene in skeletal muscle.11,15 DUX4 protein is a transcription factor normally expressed only in the germline, but little is known about its function.16 Preliminary evidence suggests that inappropriate expression of DUX4 and its transcriptional targets in skeletal muscle can result in apoptosis, impaired muscle regeneration, and induction of an immune response.16

Previous FSHD practice guidelines have been based on expert opinion.17,18 The present guideline, based on systematic review of the evidence, focuses exclusively on FSHD. Duchenne MD and myotonic dystrophy will be discussed in forthcoming guidelines; limb-girdle MD and congenital MD are addressed in separate guidelines.19,20 The present guideline addresses the following practical issues related to FSHD (reflective only of evidence relevant to FSHD1; no large FSHD2 clinical studies exist):

1. For patients with clinically defined FSHD (as determined by explicitly stated clinical criteria substantially similar to the consortium criteria),21 how often does D4Z4 contraction on 4q35 confirm diagnosis of FSHD (irrespective of presence of allele A)? For individuals who do not have FSHD, how often is a D4Z4 contraction on 4q35 found, and how often is a D4Z4 contraction on 4q35 on allele A found?
2. Which factors are associated with or predict loss of clinically meaningful milestones (e.g., loss of independent ambulation)?
3. How frequent are respiratory abnormalities, cardiac abnormalities, retinal disease, hearing loss, and pain?
4. Do interventions (as compared with no intervention) improve patient-relevant outcomes? Are there features that identify patients who are more or less likely to improve with a specific intervention?

DESCRIPTION OF THE ANALYTIC PROCESS

The methods used to develop this guideline are detailed in the complete guideline (see data supplement on the Neurology® Web site at Neurology.org). In brief, the American Academy of Neurology (AAN) convened an author panel of clinicians with FSHD expertise. The panel systematically reviewed the evidence relevant to the posed questions according to the processes described in the 2004 and 2011 AAN process manuals.22,23 The panel formulated practice recommendations based on the evidence systematically reviewed, stipulated axiomatic principles of care, strong evidence from closely related conditions, and judgments regarding risk–benefit and patient preferences.

ANALYSIS OF EVIDENCE FSHD genetic testing.

Understanding the molecular genetics of FSHD1 is critical to molecular diagnosis of this disorder. Healthy individuals possess at least 11 D4Z4 repeats, yielding a DNA fragment >38 kb on standard genetic testing. Affected individuals, in contrast, possess 1–10 repeats, yielding DNA fragments 10–38 kb in size.7 Measurement of the size of the residual D4Z4 sequence on 4q35 forms the basis for genetic testing in FSHD. As previously discussed, FSHD identification also requires that the contraction occur on the A allelic variant. Routine first-pass commercial genetic testing in the United States measures the residual D4Z4 repeat sizes without determining the A or B allelic variants. The prevalence of D4Z4 repeat sizes ranging from 1 to 10 alleles is low in the general
population. This low prevalence raises questions about the clinical utility of routine determination of the A/B variant in molecular confirmation of FSHD.

Our systematic review identified 9 Class III studies\textsuperscript{24–32} from specialty clinics that, together, demonstrate that the finding of a D4Z4 contraction on chromosome 4q35 likely has a sensitivity of 93% and a specificity of 98% for diagnosis of clinically defined FSHD. In a patient population with clinically defined FSHD, the degree of specificity is unlikely to be further enhanced by testing for presence of the A variant.

Risk factors for disease severity. In any neuromuscular disorder, a critical aspect of patient management lies in identifying clinical, biochemical, or genetic aspects of the illness associated with prognosis. It is indispensable to identify such risk factors that might be linked to a severe (or more benign) course when discussing prognosis with patients, designing therapy programs and other meaningful interventions, and helping patients make important medical, financial, and other life decisions. This is true particularly in a disease such as FSHD where extent and severity of involvement vary tremendously.

\textbf{D4Z4 repeat size.} The systematic review identified one Class I study\textsuperscript{35} demonstrating that in patients with FSHD, smaller D4Z4 repeat size is probably associated with more severe disease as measured by age at diagnosis and age at wheelchair dependence. Class II and Class III studies\textsuperscript{29,34–36} provided evidence that smaller fragment size is possibly associated with other measures of disease severity, including early age at onset, quantitative computerized muscle testing, severity of leg weakness, global severity scores, and earlier loss of ambulation.

\textbf{Age at onset.} One Class III study\textsuperscript{34} demonstrated that earlier age at onset appears to be associated with earlier loss of ambulation (as well as smaller fragment size).

\textbf{Complications.} Although the cardinal features of FSHD involve limb weakness that starts with focal weakness of the shoulders, face, and humeral muscles, additional systemic features may occur. These extra-muscular features may have significant and, at times, life-threatening consequences.

\textbf{Respiratory abnormalities.} Evidence from one Class II study\textsuperscript{37} and one Class III study\textsuperscript{38} suggests that respiratory insufficiency and reduced pulmonary function may occur, with estimated frequencies varying from 1.25% (95% confidence interval [CI] 0.5%–2%) to 13% (95% CI 0.7%–27%).

\textbf{Cardiac abnormalities.} Four Class III electrocardiographic/echocardiographic studies found no structural abnormalities in 80 patients with FSHD (95% CI 0%–4.6%)\textsuperscript{39,40,e1,e2} indicating that the frequency of structural cardiac abnormalities on electrocardiography/echocardiography may be low. Six Class III studies examining the frequency of symptomatic or inducible supraventricular arrhythmias in patients with FSHD\textsuperscript{36–38} found these arrhythmias in 9.7% (95% CI 6.5%–14.2%). Because of risk of referral bias in these studies, data are insufficient to reliably determine the frequency of clinically relevant cardiac abnormalities.

\textbf{Retinal vascular disease.} The combined results from 4 Class III studies\textsuperscript{e14,e15} demonstrated that up to 25% (95% CI 20.9%–30.8%) of patients with FSHD had abnormalities on retinal examination and 0.6% (95% CI 0.2%–1.5%) had symptomatic retinal disease.

\textbf{Hearing loss.} Eight Class III studies using audiometry to examine hearing demonstrated that 15.5% (95% CI 12.1%–19.4%) had audiometric abnormalities.\textsuperscript{25,32,e3–e5} In addition, hearing loss occurs only in patients with large deletions (≤20 kb); 32% (95% CI 16.7%–51.4%) of patients in this group have hearing loss.\textsuperscript{40} Confidence in the evidence for prevalence of audiometric abnormalities is very low due to the wide range of frequencies.

\textbf{Pain.} One Class II study and 2 Class III studies\textsuperscript{e11–e15} observed that up to 79% (95% CI 74.6%–82.8%) of patients with FSHD complained of pain. The most common sites of pain are, in descending order, the lower back, legs, shoulders, and neck.\textsuperscript{e12} A single Class III study assessing pain severity noted that 10.8% (95% CI 3.2%–18.3%) of patients had clinically significant pain.\textsuperscript{e11}

\textbf{Treatment.} The goal of therapy in FSHD is to improve muscle strength or function, or both. Until recently the underlying pathophysiology of FSHD was unknown, and thus pharmacologic trials have focused on improving muscle mass and strength, whereas surgical studies of scapular fixation have been motivated by efforts to improve function notwithstanding the presence of weakness.

\textbf{Pharmacologic interventions.} Based on 2 Class I studies examining the effect of oral albuterol on strength in FSHD,\textsuperscript{41,e14,e15} it is highly likely that albuterol is ineffective for improving muscle strength. Data are insufficient to judge the efficacy of albuterol for muscle pain and fatigue.\textsuperscript{e16}

A Class I study of the effect of an IV myostatin inhibitor (MYO-029) demonstrated no significant improvement in muscle strength. Data are insufficient to support or refute the effects of prednisone (1 Class IV study\textsuperscript{e17} or diltiazem (1 Class IV study)\textsuperscript{e18} on muscle strength.
**Surgical scapular fixation.** One Class III study and 10 Class IV uncontrolled case series used different surgical approaches and demonstrated consistent responses on measures of shoulder function to scapular fixation. These studies indicated that scapular fixation is possibly effective for improving shoulder abduction and anterior flexion.

**Exercise.** One Class I study examining the effect of strength training on muscle strength demonstrated no evidence of improved isometric strength testing; however, it reported improvement of significant but questionable importance in dynamic strength in 1 of 2 muscle groups tested. This study supported the conclusion that strength-training exercise is probably ineffective for improving muscle strength meaningfully.

A single Class III study provided very weak evidence that low-intensity aerobic exercise improved both workload (by 17%; standard deviation 4, \( p < 0.002 \)) and self-reported levels of activity, without evidence of muscle damage.

**PRACTICE RECOMMENDATIONS** The recommendations below encompass 4 major areas: diagnosis, predictors of severity, surveillance for complications, and treatment. A clinical context section precedes each recommendation, and outlines the evidence, general principles of care, and evidence from related disorders that inform the recommendations.

**Diagnosis of FSHD.** See also the algorithm in the figure.

**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 2 genetically distinct forms of FSHD.

In the most common FSHD type, FSHD1, disease results from contraction of a DNA repeat sequence, termed D4Z4 repeat, on 1 copy of 4q35 from \( >10 \) repeats to 1–10 repeats. In addition, the contraction must occur in the presence of 1 particular (A variant) of 2 (A/B) sequence variants distal to the repeats. Available molecular testing for FSHD1, which measures only the presence of a repeat contraction on initial testing, is highly sensitive and specific. 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. However, in clinical practice, strict clinical diagnostic criteria might not be adhered to, increasing the chances of a false-positive result. 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.

**Recommendation.** Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of FSHD1 (Level B). The figure shows the recommended FSHD molecular diagnosis decision tree.

**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. The D4Z4 deletion size appears to be somewhat predictive of the overall rate of disease progression. 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 intrainfamilial factors. 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.

**Recommendation.** 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 (Level B) (see next section on Monitoring for complications of FSHD).

**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. 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. Respiratory failure constitutes a major source of morbidity in patients with most MD types and can severely disrupt sleeping, daily activities, and...
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. Routine electrocardiographic/echocardiographic testing is therefore unnecessary in patients with FSHD who are asymptomatic.

Recommendation. 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 (Level C).

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. Untreated exudative retinopathy can lead to significant visual loss, which may be prevented by early intervention.

Recommendation. 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 (Level B).

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. In clinical practice, most patients with FSHD and hearing loss requiring the use of a hearing aid have childhood-onset FSHD with large deletions. Two recent studies support this clinical impression. 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.

Recommendation. 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 (Level B).

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

**Recommendation.** 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 antiepiletics for chronic pain (Level B).

**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. 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.

**Recommendation.** In patients with FSHD, clinicians should not prescribe albuterol, corticosteroid, or diltiazem for improving strength (Level B).

**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. Moreover, in many patients, bedside manual scapular fixation can result in significant improvement in shoulder range of motion. Postoperative complications are infrequent but include hemothorax or pneumothorax, pain, infection, nonunion, and reduced lung capacity. Scapular fixation appears to be generally safe and may be effective for improving shoulder range of motion.

**Recommendation.** 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 (Level C).

**Aerobic exercise. Clinical context.** Aerobic exercise in FSHD appears to be safe and potentially beneficial, as has been shown in many other muscle diseases. Aerobic fitness is important for overall health. 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. Although no data exist to suggest that strength training is detrimental in FSHD, further research is needed to determine whether such strength training will result in clinically meaningful long-term functional improvement.

**Recommendations.** 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 (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 (Level C).

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REFERENCES


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This Week’s Neurology® Podcast

Evidence-based guideline: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy (see p. 357)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the July 28, 2015, issue of Neurology. In the second segment, Dr. Ted Burns talks with Dr. Rabi Tawil about the AAN guideline on the evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy. Dr. Sarah Wesley reads the e-Pearl of the week about vertical nystagmus. In the next part of the podcast, Dr. Alberto Espay focuses his interview with Dr. Helen Mayberg on her Robert Wartenberg Lecture at the AAN Annual Meeting on the topic of what deep brain stimulation has taught us about the neurology of depression.

Disclosures can be found at Neurology.org.

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