Facioscapulohumeral Dystrophy

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Facioscapulohumeral dystrophy (FSHD) is the third most common inherited muscular dystrophy after Duchenne dystrophy and myotonic dystrophy. Over the last decade, major advances have occurred in the understanding of the genetics of this disorder. Despite these advances, the exact mechanisms that lead to atrophy and weakness secondary to the genetic defect are still not understood. The purposes of this article are to increase awareness of FSHD among clinicians; to provide an update regarding the genetics, clinical features, natural history, and current management of FSHD; and to discuss opportunities for research.

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Facioscapulohumeral dystrophy (FSHD) is the third most common inherited muscular dystrophy after Duchenne dystrophy and myotonic dystrophy.[1] Facioscapulohumeral dystrophy, as the name implies, is characterized initially by weakness and atrophy of the facial, scapular, and humeral muscles. It is inherited as an autosomal dominant trait. Over the last decade, major advances have occurred in the understanding of the genetics of this disorder.[2–4] These advances have led to molecular diagnostic tests and improved genetic counseling and have allowed prenatal testing.[5–10] Despite these advances, the exact mechanisms that lead to atrophy and weakness secondary to the genetic defect are still not understood. Currently, there is no genetic or pharmaceutical[11] curative treatment for this condition. The mainstay of management is treatment of symptomatic impairments, prevention of secondary problems, and improvement of functional abilities and quality of life within the constraints imposed by this progressive condition.[12–14]

Physical therapists are appropriately trained to play a major role in the management of FSHD. The purposes of this article are: (1) to increase awareness of FSHD among clinicians, (2) to provide an update regarding the genetics, clinical features, natural history, and current management of FSHD, and (3) to discuss opportunities for research.

Historical Developments

Facioscapulohumeral dystrophy was first described by 2 French physicians, Louis Landouzy and Joseph Dejerine, in the late 1800s; their description was based on a family that they had monitored for 11 years.[15] Their publications described all the main elements of FSHD, including early involvement of the face, progressive weakness and atrophy of the scapular and humeral muscles, the hereditary nature of the disorder, and clinical variability among affected members of the same family. In 1950, Tyler and Stephens[16] described a kindred from Utah that included 1,249 people spanning 6 generations. All were descendants of an affected individual who had migrated to Utah in 1840. The authors were able to examine 240 members of this family, 58 of whom were affected. Their report provided detailed inheritance and clinical information. Their findings confirmed the autosomal dominant inheritance pattern and the clinical heterogeneity of the disorder, as described by Landouzy and Dejerine. In 1982, on the basis of a retrospective review of 107 patients, Padberg[17] provided detailed information regarding the presenting complaints, clinical progression, and laboratory findings in patients with FSHD.

Clinical criteria for the diagnosis of FSHD were established by an international consortium in 1991[18] and are as follows:

- onset of the disease in the facial or shoulder girdle muscles and sparing of the extraocular, pharyngeal, and lingual muscles and the myocardium
- facial muscle weakness in more than 50% of affected family members
- autosomal dominant inheritance in familial cases
- evidence of myopathic disease from electromyography and muscle biopsy in at least one affected member, without biopsy features specific for alternative diagnoses

Since the publication of these criteria, myocardial involvement has been documented.[19,20]

Since the establishment of these clinical diagnostic criteria, major advances have occurred in the area of genetics related to FSHD. These advances have provided molecular tests for the diagnosis of FSHD and improved genetic counseling for family members. The availability of molecular tests has also expanded the spectrum of presenting complaints and clinical phenotypes.

Genetic Developments

A glossary of genetic terms is provided in the Appendix.[21] The FSHD locus was mapped to the subtelomeric portion of chromosome 4 (4q35) in 1990.[2] This subtelomeric region is composed mainly of a polymorphic repeat structure consisting of 3.3-kilobase repeat elements designated D4Z4. The number of repeat units varies from 11 to more than 100 in the general population. In patients with FSHD, there is a deletion of an integral number of these units, and they exhibit an allele of 1 to 10 residual units.[3] With the mapping of the FSHD locus, molecular diagnostic tests with a specificity and a sensitivity of 95% have become available.[6,7,9,22] The tests are performed on DNA isolated from peripheral blood leukocytes and are available commercially. Facioscapulohumeral dystrophy has a high rate (10%–30%) of sporadic cases[23]; therefore, there may not be a family history of people who were affected. Ten percent of these sporadic cases are attributed to new mutations, and 20% are attributed to mosaicism.[24]

The genetic diagnostic tests do not allow precise prediction of the course of the disease in an individual, but an approximate and inverse relationship among the residual repeat size, the age at onset, and the severity of the disease has been described. Patients carrying 1 to 3 units are usually severely affected and often represent new mutations, whereas patients carrying 4 to 10 units are typically familial cases.[25] However, because of the high degree of interfamilial and intrafamilial variability of disease expression in family members even with fragments

of the same size, it is impossible to predict the disease severity and progression in a given individual. Despite all of the advances in the understanding of the genetics of the disease, the exact mechanisms responsible for the clinical features are still not known.[26]

Prevalence

On the basis of the studies of Padberg and colleagues,[17,27] the prevalence of FSHD in the Dutch population in the Netherlands is estimated to be 1 in 21,000. For the United States, Flanigan et al[28] reported a prevalence of 1 in 15,000 in the Utah-southern Idaho region, on the basis of their follow-up of and findings for 971 additional members of the family first described by Tyler and Stephens.[16]

Clinical Features

The clinical presentation of FSHD is usually quite characteristic, with a majority of patients in the second or third decade having complaints related to difficulty with overhead activities. On the basis of a retrospective review of 107 patients, Padberg[17] reported that 82% of patients noticed shoulder girdle weakness as the first symptom, 10% reported facial muscle weakness, and 8% reported ankle dorsiflexor muscle weakness. On examination, however, he found that 94% had facial muscle weakness, 93% had shoulder girdle weakness, 67% had ankle dorsiflexor muscle weakness, and 50% had pelvic girdle weakness. Recently, Padberg[29] reported that 5% of patients report symptoms related to pelvic girdle weakness as their initial symptoms. This information is important because symptoms or signs of pelvic girdle weakness may confuse the clinical diagnosis of FSHD with limb girdle dystrophies, especially in the absence of facial muscle weakness.

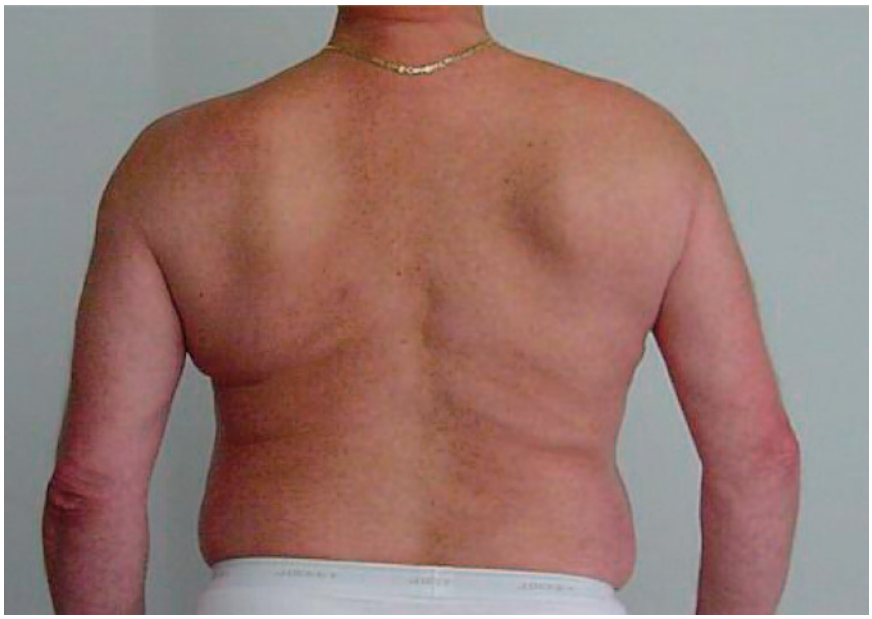

Figure 1.
Elevated position of the scapulae and internal rotation of the arms are characteristic of facioscapulohumeral dystrophy.

With the availability of molecular diagnostic tests, a broader spectrum of clinical presentations is being reported. Bushby et al[30] described 4 patients in whom muscle pain was a prominent complaint. Van der Kooi et al[31] described 6 cases in which 3 patients had foot drop, 2 had walking difficulty, and 1 had shoulder pain. On examination, 1 of the 2 patients with walking difficulty had calf muscle weakness, and the other patient had quadriceps femoris and hamstring muscle weakness. Felice and Moore[32] described 4 patients with atypical presentations: 1 with facial muscle sparing and scapular myopathy, 1 with limb girdle involvement, 1 with distal myopathy, and 1 with asymmetric brachial weakness. Even though the most common presenting complaints of FSHD are related to scapular muscle and shoulder girdle involvement, symptoms or signs of weakness of facial muscles, the pelvic girdle, or lower-extremity muscles or all of these in a patient in the presence or absence of a family history of similar problems require a thorough examination and, if necessary, a medical referral to rule out FSHD.

Facial Muscle Weakness

The most commonly affected facial muscles are the orbicularis oculi and the orbicularis oris. Often the involvement around the lips is asymmetric. Recently, Wohlgemuth et al[33] documented swallowing difficulties in 10 of 87 adult patients. Videofluoroscopic and magnetic resonance imaging examinations revealed atrophy or weakness or both of the tongue in 6 of these patients. The authors did not find any evidence of atrophy or deterioration of the pharyngeal or laryngeal muscles and concluded that the swallowing problems were secondary to the weakness of the orofacial muscles only.

Shoulder Girdle Weakness

On examination of the shoulder girdle, a striking feature is the elevated position of the scapulae because of weakness of the middle and lower trapezius muscles[16] and internal rotation of the arms (Fig. 1). There is a

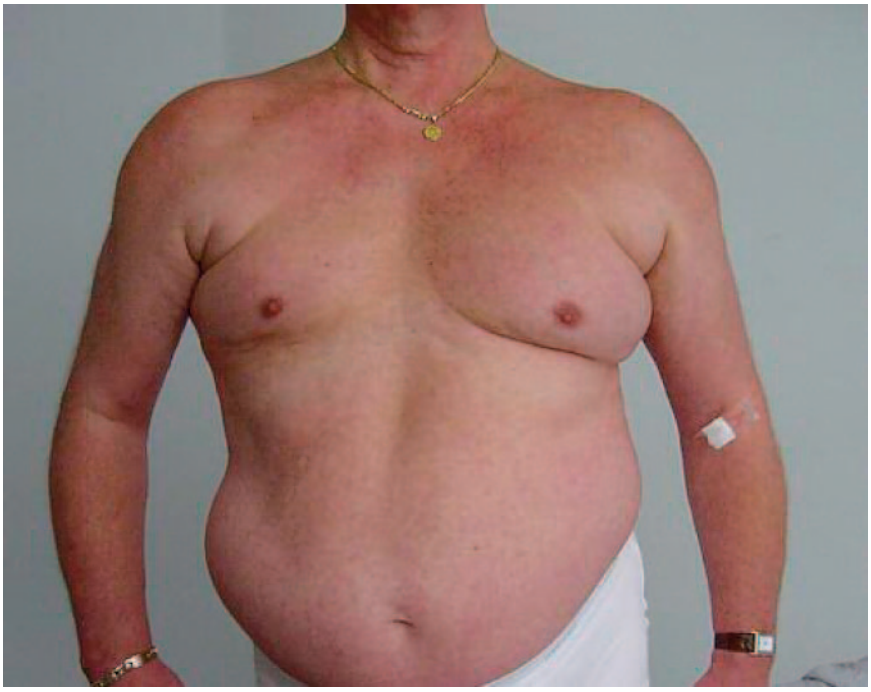

Figure 2.
Atrophy of the pectoralis major muscle, especially the sternal head, and involvement of the clavicular portion of the sternocleidomastoid muscle—early features of the disease.

flattening of the anterior chest wall, and 5% of patients have pectus excavatum.[17] Atrophy of the pectoralis major muscle, especially the sternal head, and involvement of the clavicular portion of the sternocleidomastoid muscle also are early features of the disease[16] (Fig. 2). On active shoulder flexion or abduction, there is marked winging of the scapula (Fig. 3). The weakness often is asymmetric, and this feature distinguishes FSHD from limb girdle dystrophies.

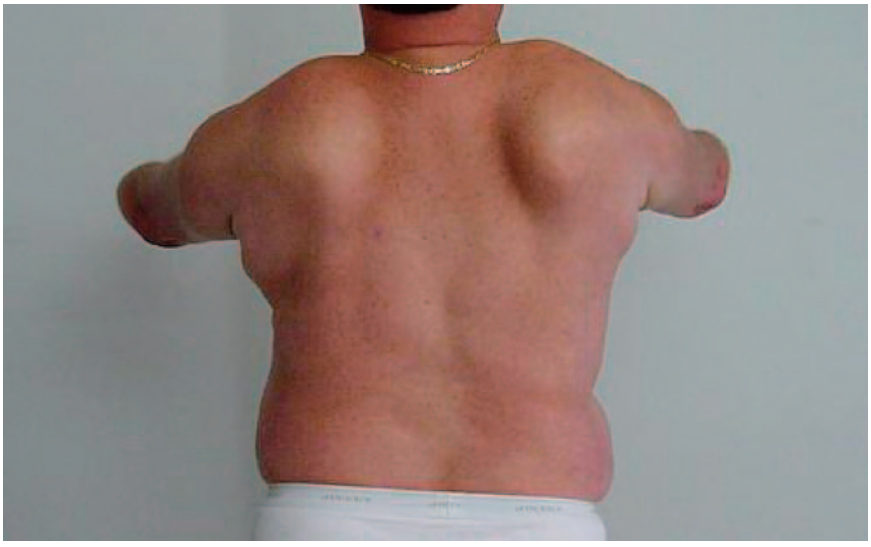

Figure 3.
Marked winging of the scapula on active shoulder flexion or abduction.

Abdominal Muscle Weakness

Abdominal muscle weakness is another early feature of the disease. The weakness results in a lordotic posture with a protuberant abdomen. The weakness is prominent in the lower abdominal muscles, and a positive Beevor sign (upward movement of the umbilicus on an attempt to sit up) has been reported in a majority of patients with FSHD.[34,35] On the basis of their findings, the authors of those studies recommended considering a positive Beevor sign as an additional clinical criterion in confirming the diagnosis of FSHD.

Lower-Extremity Muscle Weakness

For the lower extremities, weakness has been reported in the ankle dorsiflexor muscles as well as the pelvic girdle.[17,29] In a prospective natural history study in which 81 patients were monitored for 3 years, the investigators[36] documented weakness in muscles usually considered to be spared in FSHD, such as the hamstring and quadriceps femoris muscles, in addition to marked weakness in the ankle dorsiflexor muscles. Olsen et al[37] described findings from magnetic resonance imaging of lower-extremity muscles in 18 patients with FSHD. The most marked involvement was seen in the hamstring muscles, followed by the tibialis anterior and medial gastrocnemius muscles.

Progression of Weakness

According to Padberg,[17] 30% of all familial cases never progress beyond shoulder weakness. In the remaining cases, the next stage involves foot dorsiflexor muscle weakness in 80% or pelvic girdle weakness in 20%. These patterns are not restricted to certain families, and both patterns have been observed within the same family. At the same time, in the up-

per extremities, there is progression to the "humeral component"; the biceps and triceps muscles become weak and wasted. Eventually, the wrist extensor muscles are involved, resulting in a weak grip and functional limitations in activities of the hand. Approximately 10% of all patients and 20% of those more than 50 years of age will eventually become wheelchair dependent in outdoor activities. Patients usually live a normal life span, although about 20% are severely disabled because of weakness. The progression of weakness is very slow and occurs over decades, thus allowing patients to adapt and compensate for their weakness and continue to function.

Asymmetry of Weakness

Asymmetric weakness is characteristic of FSHD, but the reason underlying the sometimes extraordinary asymmetry is unknown. Various hypotheses have been proposed for the observation, including overwork weakness[38] and handedness,[39] whereas other authors have ascribed the asymmetry to an intrinsic disease process[40] or to an intrinsic genetic mechanism.[29] Despite the asymmetric weakness, the incidence of contractures or scoliosis is low. About 10% of patients with FSHD have ankle contractures, and 30% develop scoliosis.[29]

Cardiac and Pulmonary Features

In addition to the facial, abdominal, and extremity muscle weakness, pulmonary and cardiac involvement also has been documented. Wohlgemuth et al[41] conducted a nationwide study in the Netherlands to investigate the prevalence of respiratory insufficiency in FSHD. They identified 10 patients who had FSHD and who were on nocturnal ventilatory support at home, representing approximately 1% of the Dutch population with FSHD. The risk factors that they identified included severe involvement with wheelchair confinement, moderate to severe kyphoscoliosis, and the presence of pectus excavatum. Galetta et al[20] compared 24 patients with FSHD with 24 age-matched controls who were healthy and reported subclinical cardiac involvement in the patients with FSHD. Their findings suggested a preclinical reduction of left ventricular function and abnormal myocardial activity. Trevisan et al[19] described findings from a multicenter study aimed at investigating cardiac involvement in patients with FSHD. Ten of the 83 patients (12%) demonstrated symptoms or signs of heart involvement, mainly arrhythmic in origin, in the absence of cardiovascular risk factors.

Extramuscular Features

In addition to the muscular involvement, retinal abnormalities[42,43] and hearing loss also are associated with FSHD. Visual loss occurs in only a small minority of patients, but high-tone hearing loss[29,43] has been described in 25% to 65% of patients.

Pain

Even though pain is not a symptom commonly mentioned in textbooks, pain is a symptom often reported by patients and described in recent case reports. A survey conducted in France[44] showed that, out of 270 patients who responded (approximately 10% of the patients with FSHD in France), only 5% did not complain of pain and 32% reported pain as a daily problem. The exact nature and cause of the pain were not specified. A similar survey conducted in the Netherlands[45] revealed that, out of 109 people who responded (approximately 18% of the patients with FSHD in the country), 74% experienced pain for more than 4 days per month and 58% did so for 4 or more days per week. The percentage of people who experienced daily pain was similar to that reported in the French survey, namely, 32%. The majority of the respondents attributed the pain to exertion (91%) or faulty posture (74%) because of weakness. Environmental temperature (48%) and humidity (27%) also had significant influences on the complaints related to pain. The various pain management techniques used by the respondents, including analgesics, hot baths or showers, and massage, provided only temporary relief. The respondents also reported that pain had a substantial effect on their well-being and functioning.

Fatigue

Kalkman et al[46] surveyed the prevalence of severe fatigue and its relationship to functional impairments in daily life in 598 patients with a neuromuscular disease (139 with FSHD). Sixty-one percent of the patients with FSHD reported severe fatigue. These patients also reported reduced levels of physical activity and reduced motivation. The causes and mechanisms underlying the complaint of fatigue in FSHD are not well understood.

Infantile and Early-Onset Presentation

Although most patients with FSHD report having signs or symptoms in the second or third decade, infantile and early-onset presentations had been described since the late 1970s.[47,48] Most early-onset cases are sporadic, with large deletions resulting in fragments with only 1 to 3 D4Z4 repeats. Some cases are occasionally diagnosed as Möbius syndrome. These patients often have normal motor milestones and develop signs of muscle weakness several years later.[49,50] A report from Japan has indicated an association with mental retardation and epilepsy in people with an early onset who are severely affected.[51]

Management

Currently, there are no curative genetic or pharmaceutical treatments[11] for this disease. The mainstay of

management is care directed at the symptomatic impairments in order to maximize functional abilities and improve the quality of life of patients. Recommendations are usually based on expert opinion because there are very few studies, except in the areas of exercise and scapular surgery; even in those 2 areas, the majority of the studies are cohort studies or pilot open trials with inadequate numbers.

Facial Muscle Weakness

An inability to smile because of facial muscle weakness remains a major social disability in FSHD. Weakness of the labial muscles can lead to articulation difficulties in the later stages but does not progress to the point at which alternative means of communication become necessary. On the basis of their finding of swallowing difficulties, Wohlgemuth et al[33] recommended that patients be referred to speech therapists for further evaluation of and teaching related to compensatory strategies for swallowing. Weakness of the orbicularis oculi can cause incomplete lid closure (lagophthalmos), which can lead to serious exposure keratitis and corneal scarring, major safety concerns. Eye drops, ointments, taping, or patches have not always been successful in managing these problems.[42]

Scapular Muscle Weakness

Scapular muscle weakness and the resulting difficulties with overhead activities are a major problem for patients. In addition to loss of function, marked winging of the scapula can lead to pain and cosmetic deformity. The force necessary to keep the scapula stabilized while still allowing appropriate mobility have made the use of taping, slings, and spinal orthoses difficult, except in a few cases. There is only one report in the literature describing the benefits of a spinal orthosis.[52]

A Cochrane review[53] on the topic of scapular fixation in muscular dystrophy did not find any randomized or quasi-randomized trials of scapular fixation. Thus, the authors reviewed the case series and case reports related to scapular stabilization surgery in patients with FSHD. The 2 most commonly used procedures were scapulopexy (fascial or synthetic slings were used to improve scapular fixation to the thorax) and scapulodesis (the scapula was fixed to the thoracic wall with screws, wires, or plates, with or without a bone graft to produce a solid fusion). Both procedures resulted in significant improvements, as measured by improvement in shoulder abduction at 1 year and by patient-perceived improvement in the performance of activities of daily living. Some of the complications reported included stretching of the slings, loosening of the screws and wires, and—in some cases—nerve damage. The report recommended that each patient be evaluated thoroughly and that the benefits and complications be weighed carefully prior to making a decision regarding surgical treatment.

Abdominal Muscle Weakness and Lordosis

There are no reports in the literature of specific management techniques shown to be useful for improving posture or decreasing the discomfort secondary to the postural abnormality in patients with FSHD. Clinicians tend to recommend abdominal supports and binders[54] for patients with marked weakness and appropriate postural supports and environmental adaptations when patients are seated.

Ankle Muscle Weakness

Foot drop attributable to ankle dorsiflexor muscle weakness is a common problem in patients with FSHD. There are no reports in the literature of the specific kinetic or kinematic patterns of gait seen in patients with FSHD to guide management. There also are no reports regarding algorithms for the timing or choice of specific types of ankle-foot orthoses and no reports regarding the benefits of these orthoses in patients with FSHD with regard to gait or functional abilities. Decisions regarding the timing and type of orthoses are based on empirical data and vary from clinician to clinician.[12–14] The braces most commonly recommended include fixed or hinged ankle-foot orthoses or floor reaction orthoses.

Role of Exercise

The role of exercise in maintaining or improving strength (force-generating capacity) and function or both in patients with FSHD remains controversial because of concerns about overuse precipitating weakness and the limited number of clinical trials. The paucity of well-designed and appropriately powered studies of exercise in FSHD was highlighted in a recent Cochrane review[55] of strength training and aerobic exercise training for muscle disease. The review identified 36 reports published between 1966 to 2004. Nineteen of these studies examined the effects of strength training, 9 studies examined the effects of aerobic training, and 8 studies examined the effects of a combination of strength training and aerobic training. Unfortunately, most of these studies had small numbers of patients, had a mixture of diagnostic categories, were of short duration, and were nonrandomized (32 of the 36). On the basis of the evidence from the 2 randomized controlled trials that met their criteria for inclusion, the authors concluded that moderate-intensity strength training does not produce any benefit or harm in patients with myotonic dystrophy[56] or FSHD.[57] Since the publication of the Cochrane review,[55] Olsen et al[58] reported the effects of a 12-week home program of aerobic training in 8 patients with FSHD and 7 age- and sex-matched volunteers who were healthy. On the basis of their findings, the authors concluded

that low-intensity aerobic exercise improved fitness safely in patients with FSHD. The 12 weeks of training had positive effects in general on the self-reported measures of strength, endurance, and activity level.

Because of the limited literature on the effects of exercise training in patients with FSHD, clinicians have had to depend on consensus or empirical advice for their recommendations regarding exercise and activities for patients with muscle diseases. The current recommendations[59–61] are as follows:

- pursuit of an active lifestyle for its physical and psychological benefits
- flexibility training including stretching and range-of-motion exercises, which may be helpful in decreasing the discomfort attributable to the limited mobility of the joints secondary to muscle weakness
- moderate-intensity resistive strengthening exercise, which may be beneficial in reversing disuse weakness and improving strength during the early stages of the disorder in muscles that have antigravity or greater strength
- moderate-intensity aerobic training programs, which may be beneficial in maintaining or improving aerobic capacity

The authors of these recommendations did not provide an operational definition of "moderate intensity" for either the strengthening or the aerobic fitness training programs. The reports on which they based their recommendations, most of which were cited in the Cochrane review,[55] used a variety of training regimens in their strengthening and fitness programs. The strengthening programs used weights ranging from 20% to 70% of 1 resistance maximum, repetitions ranging from 5 to 12 per set, number of sets ranging from 1 to 4, and frequency ranging from 3 to 7 days per week. A similar diversity of regimens were used in the aerobic fitness training programs. The lack of standardization of the training regimens and the limited number of appropriately designed and powered studies provide immense opportunities for therapists to contribute to this area of care. The most urgent needs include the development of a consensus regarding testing, specifically, submaximal exercise testing,[62] which may be more appropriate in patients with FSHD, and the development of training regimens that incorporate recommendations from the American College of Sports Medicine position stands.[63–65]

Therapists also can contribute to the literature by providing case reports and cohort studies documenting the role of physical therapy and physical therapists in the evaluation and management of FSHD. Specifically, they can report on the role of physical therapy interventions in treatment and management of pain; the role of orthotics in decreasing problems secondary to shoulder girdle, abdominal muscle, and ankle dorsiflexor muscle weakness; and the benefits of exercise in improving strength, aerobic fitness, functional abilities, mood, and quality of life.

Conclusion

Over the last decade, major advances have occurred in the understanding of the genetics and clinical features of FSHD. The exact molecular mechanisms underlying the disease remain elusive, and currently there is no cure for this disorder. Physical therapists can play a major role in the multidisciplinary management of FSHD by providing symptomatic and preventive care to minimize secondary complications and help patients function at their highest level within the constraints imposed by this progressive disorder. Therapists also can help build the evidence to support the efficacies of their interventions through case reports, retrospective and prospective cohort studies, and randomized controlled trials.

Ms Pandya and Ms King provided concept/idea/project design. Ms Pandya provided writing. Dr Tawil provided consultation (including review of manuscript before submission).

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References

1 Emery AEH. Population frequencies of inherited neuromuscular diseases: a world survey. *Neuromuscul Disord.* 1991;1:19–29.

2 Wijmenga C, Frants RR, Brouwer OF, et al. Location of facioscapulohumeral muscular dystrophy gene on chromosome 4. *Lancet.* 1990;336:651–653.

3 Wijmenga C, Hewitt JE, Sandkuijl LA, et al. Chromosome 4q DNA rearrangements associated with facioscapulohumeral dystrophy. *Nat Genet.* 1992;2:26–30.

4 van der Maarel S, Frants R. The D4Z4 repeat mediated pathogenesis of facioscapulohumeral muscular dystrophy. *Am J Hum Genet.* 2005;76:375–386.

5 Bakker E, Van der Weiden MJ, Voorhoeve E, et al. Diagnostic, predictive and prenatal testing for facioscapulohumeral dystrophy: diagnostic approach for sporadic and familial cases. *J Med Genet.* 1996;33:29–35.

6 Upadhyaya M, Maynard J, Rogers MT, et al. Improved molecular diagnosis of facioscapulohumeral muscular dystrophy: validation of the differential double digestion for FSHD. *J Med Genet.* 1997;34:476–479.

7 Orrell RW, Tawil R, Forrester J, et al. Definitive molecular diagnosis of facioscapulohumeral dystrophy. *Neurology.* 1999;52:1822–1826.

8 Upadhyaya M, MacDonald M, Ravine D. Molecular prenatal diagnosis in 12 facioscapulohumeral muscular dystrophy (FSHD) families. *Prenat Diagn.* 1999;19:959–965.

9 Upadhyaya M, Cooper DN. Molecular diagnosis of facioscapulohumeral muscular dystrophy. *Expert Rev Mol Diagn.* 2002;2:160–171.

10 Thomas NS, Wiseman K, Spurlock G, et al. A large patient study confirming that facioscapulohumeral muscular dystrophy (FSHD) disease expression is almost exclusively associated with an FSHD locus located on a 4qA-defined 4qter subtelomere. *J Med Genet.* 2007;44:215–218.

11 Rose MR, Tawil R. Drug treatment for facioscapulohumeral muscular dystrophy. *Cochrane Database Syst Rev.* 2004;(2): CD002276.

12 Tawil R, Van Der Maarel SM. Facioscapulohumeral muscular dystrophy. *Muscle Nerve.* 2006;34:1–15.

13 Kissel JT. Facioscapulohumeral dystrophy. *Semin Neurol.* 1999;19:35–43.

14 Fitzsimons RB. Facioscapulohumeral muscular dystrophy. *Curr Opin Neurol.* 1999;12:501–511.

15 Rogers MT. Facioscapulohumeral muscular dystrophy: historical background and literature review. In: Upadhyaya M, Cooper DN, eds. *Facioscapulohumeral Muscular Dystrophy.* New York, NY: Bios Scientific Publishers; 2004:17–40.

16 Tyler FH, Stephens FE. Studies in disorders of muscle, II: clinical manifestations and inheritance of facioscapulohumeral dystrophy in a large family. *Ann Intern Med.* 1950;32:640–660.

17 Padberg GW. *Facioscapulohumeral Disease* [thesis]. Leiden, the Netherlands: Leiden University; 1982.

18 Padberg GW, Lunt PW, Kochm M, et al. Diagnostic criteria for facioscapulohumeral muscular dystrophy. *Neuromuscul Disord.* 1991;1:231–234.

19 Trevisan CP, Pastorello E, Armani M, et al. Facioscapulohumeral muscular dystrophy and occurrence of heart arrhythmia. *Eur Neurol.* 2006;56:1–5.

20 Galetta F, Franzoni F, Sposito R. Subclinical cardiac involvement in patients with facioscapulohumeral muscular dystrophy. *Neuromuscul Disord.* 2005;15:403–408.

21 Genetics home reference. U.S. National Library of Medicine. Available at: http://ghr.nlm.nih.gov/ghr/glossary/Glossary/show/a. Accessed September 28, 2007.

22 Lemmers RJL, de Kievit P, van Geel M, et al. Complete allele information in the diagnosis of facioscapulohumeral dystrophy by triple DNA analysis. *Ann Neurol.* 2001;50:816–819.

23 Zatz M, Marie SK, Passos-Bueno MR, et al. High proportion of new mutations and possible anticipation in Brazilian facioscapulohumeral muscular dystrophy families. *Am J Hum Genet.* 1995;56:99–105.

24 van der Maarel SM, Deidda G, Lemmers RJ, et al. De novo facioscapulohumeral muscular dystrophy: frequent somatic mosaicism, sex-dependent phenotype, and the role of mitotic transchromosomal repeat interaction between chromosomes 4 and 10. *Am J Hum Genet.* 2000;66:26–35.

25 Lunt PW, Jardine PE, Koch MC, et al. Correlation between fragment size at D4F104S1 and age at onset or at wheelchair use, with a possible generational effect, accounts for much phenotypic variation in 4q35-facioscapulohumeral muscular dystrophy (FSHD). *Hum Mol Genet.* 1995;4:951–958.

26 van der Maarel SM, Frants RR, Padberg GW. Facioscapulohumeral muscular dystrophy. *Biochim Biophys Acta.* 2007;1772: 186–194.

27 Padberg GW, Frants RR, Brouwer OF, et al. Facioscapulohumeral muscular dystrophy in the Dutch population. *Muscle Nerve.* 1995;2:S81–S84.

28 Flanigan KM, Coffeena CM, Sexton L, et al. Genetic characterization of a large, historically significant Utah kindred with FSHD. *Neuromuscul Disord.* 2001;11:525–529.

29 Padberg GW. Facioscapulohumeral muscular dystrophy: a clinician's experience. In: Upadhyaya M, Cooper DN, eds. *Facioscapulohumeral Muscular Dystrophy.* New York, NY: Bios Scientific Publishers; 2004:41–54.

30 Bushby KMD, Pollitt C, Johnson MA, et al. Muscle pain as a prominent feature of facioscapulohumeral muscular dystrophy: four illustrative case reports. *Neuromuscul Disord.* 1998;8:574–579.

31 van der Kooi AJ, Visser MC, Rosenberg N, et al. Extension of the clinical range of facioscapulohumeral dystrophy: report of six cases. *J Neurol Neurosurg Psychiatry.* 2000;69:114–116.

32 Felice KJ, Moore SA. Unusual clinical presentations in patients harboring the facioscapulohumeral dystrophy 4q35 deletion. *Muscle Nerve.* 2001;24:352–356.

33 Wohlgemuth M, de Swart BJM, Kalf JG, et al. Dysphagia in facioscapulohumeral muscular dystrophy. *Neurology.* 2006;66: 1926–1928.

34 Awerbuch GI, Nigro MA, Wishnow R. Beevor's sign and facioscapulohumeral dystrophy. *Arch Neurol.* 1990;47:1208–1209.

35 Shahrizaila N, Wills AJ. Significance of Beevor's sign in facioscapulohumeral dystrophy and other neuromuscular diseases. *J Neurol Neurosurg Psychiatry.* 2005; 76:869–870.

36 The FSH-DY Group. A prospective quantitative study of the natural history of facioscapulohumeral muscular dystrophy: implications for therapeutic trials. *Neurology.* 1997;48:38–46.

37 Olsen DB, Gideon P, Jeppesen TD, Vissing J. Leg muscle involvement in facioscapulohumeral muscular dystrophy assessed by MRI. *J Neurol.* 2006;253:1437–1441.

38 Johnson EW, Braddon R. Over-work weakness in facioscapulohumeral muscular dystrophy. *Arch Phys Med Rehabil.* 1971; 52:333–335.

39 Brouwer OF, Padberg GW, Van Der Ploeg RJO, et al. The influence of handedness on the distribution of muscular weakness of the arm in facioscapulohumeral muscular dystrophy. *Brain.* 1992;115:1587–1598.

40 Tawil R, McDermott MP, Mendell JR, et al. FSHD: design of natural history study and results of baseline testing. *Neurology.* 1994;44:442–446.

41 Wohlgemuth M, van der Kooi EL, van Kasteren RG, et al. Ventilatory support in facioscapulohumeral muscular dystrophy. *Neurology.* 2004;63:176–178.

42 Fitzsimons RB, Gurwin EB, Bird AC. Retinal vascular abnormalities in facioscapulohumeral muscular dystrophy: a general association with genetic and therapeutic implications. *Brain.* 1987;110:631–648.

43 Padberg GW, Brouwer OF, de Keizer RJ, et al. On the significance of retinal vascular disease and hearing loss in facioscapulohumeral muscular dystrophy. *Muscle Nerve.* 1995;2:S73–S80.

44 Urtizberea JA. Results of a French survey of individuals with FSHD. *FSH Watch (Publication of FSH Society USA).* 1997; summer:37–40.

45 Koetsier CP. Pain related to FSH dystrophy: an underestimated problem? Results of an inquiry in the Netherlands, Baarn VSN. *FSH Watch (Publication of FSH Society USA).* 1997;summer:23–24.

46 Kalkman JS, Schillings ML, van der Werf SP, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. *J Neurol Neurosurg Psychiatry.* 2005;76:1406–1409.

47 Brooke MH. *A Clinician's View of Neuromuscular Diseases.* Baltimore, Md: Williams & Wilkins; 1977.

48 Carroll JE, Brooke MH. Infantile facioscapulohumeral dystrophy. In: Serratrice G, Roux H, eds. *Peroneal Atrophies and Related Disorders.* New York, NY: Masson Publishing USA; 1979:305–319.

49 Brouwer OF, Padberg GW, Wijmenga C, et al. Facioscapulohumeral muscular dystrophy in early childhood. *Arch Neurol.* 1994;51:387–394.

50 Klinge L, Eagle M, Haggerty ID, et al. Severe phenotype in facioscapulohumeral muscular dystrophy. *Neuromuscul Disord.* 2006;16:553–558.

51 Funakoshi M, Goto K, Arahata K. Epilepsy and mental retardation in a subset of early onset 4q35-associated facioscapulohumeral muscular dystrophy. *Neurology.* 1998;50:1791–1794.

52 Barnett ND, Mander M, Peacock JC, et al. Winging of the scapula: the underlying biomechanics and an orthotic solution. *Proc Inst Mech Eng (H).* 1995;209: 215–223.

53 Mummery CJ, Copeland SA, Rose MR. Scapular fixation in muscular dystrophy. *Cochrane Database Syst Rev.* 2003;(3): CD003278.

54 *Facts About Facioscapulohumeral Muscular Dystrophy.* Tucson, Ariz: Muscular Dystrophy Association; 2005.

55 van der Kooi EL, Lindeman E, Riphagen I. Strength training and aerobic exercise training for muscle disease. *Cochrane Database Syst Rev.* 2005;(1):CD003907.

56 Lindeman E, Leffers P, Spaans F, et al. Strength training in patients with myotonic dystrophy and hereditary sensory motor neuropathy: a randomized controlled trial. *Arch Phys Med Rehabil.* 1995:76;612–620.

57 van der Kooi EL, Vogels OJM, van Asseldonk RJGP, et al. Strength training and albuterol in facioscapulohumeral muscular dystrophy. *Neurology.* 2004;63:702–708.

58 Olsen DB, Orngreen MC, Vissing J. Aerobic training improves exercise performance in facioscapulohumeral dystrophy. *Neurology.* 2005;64:1064–1066.

59 Phillips BA, Mastaglia FL. Exercise therapy in patients with myopathy. *Curr Opin Neurol.* 2000;13:547–552.

60 Fowler WM. Consensus conference summary: role of physical activity and exercise training in neuromuscular diseases. *Am J Phys Med Rehabil.* 2002;81(suppl):S187–S195.

61 Krivickas LS. Exercise in neuromuscular disease. *J Clin Neuromusc Dis.* 2003;5:29–39.

62 Noonan V, Dean E. Submaximal exercise testing: clinical application and interpretation. *Phys Ther.* 2000;80:782–807.

63 Kraemer WJ, Adams K, Cafarelli E, et al. American College of Sports Medicine position stand: progression models in resistance training for healthy adults. *Med Sci Sports Exerc.* 2002;34:364–380.

64 American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc.* 1998;30:975–991.

65 Haskell WL, Lee IM, Pate RR, et al; American College of Sports Medicine; American Heart Association. Physical activity and public health: updated recommendations for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081–1093. Epub 2007 Aug 1.

Appendix.

Glossary of Genetic Terms[21]

Allele: any of the alternative forms of a gene that may occur at a given locus; variant forms of the same gene; different alleles produce variations in inherited characteristics such as eye color or blood type.

Gene expression: process by which the coded information of a gene is translated into the structures present and operating in the cell (either proteins or RNAs); detectable effect of a gene; gene expression can be controlled by regulatory proteins that bind to specific sites on DNA.

Möbius syndrome: congenital bilateral paralysis of the facial muscles in association with other neurological disorders.

Mosaicism: postfertilization occurrence of 2 or more cell lines with different genetic or chromosomal constitutions within a single individual or tissue.

Phenotype: observable physical characteristics, biochemical characteristics, or both of the expression of a gene; clinical presentation of an individual with a particular genotype.

Polymorphic: of, relating to, or having polymorphism.

Polymorphism: natural variations in a gene, DNA sequence, or chromosome that have no adverse effects on the individual and that occur with fairly high frequency in the general population.

Sequence: continuous or connected series, specifically, the exact order of bases in a nucleic acid or of amino acids in a protein. **Repeat sequences:** genetic duplication in which the duplicated parts are adjacent to each other along the chromosome; multiple copies of the same base sequence on a chromosome, used as a marker in physical mapping.

Telomere: segment at the end of each chromosome arm that consists of a series of repeated DNA sequences that regulate chromosomal replication at each cell division; some of the telomere is lost each time a cell divides, and eventually, when the telomere is gone, the cell dies.

Transcription: process of copying information from DNA into new strands of messenger RNA (mRNA); mRNA then carries this information to the cytoplasm, where it serves as the blueprint for the manufacture of a specific protein.