Facioscapulohumeral Muscular Dystrophy

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Summary: Facioscapulohumeral muscular dystrophy (FSHD), a dominantly inherited disorder, is the third most common dystrophy after Duchenne and myotonic muscular dystrophy. No known effective treatments exist for FSHD. The lack of an understanding of the underlying pathophysiology remains an obstacle in the development of targeted therapeutic interventions. The genetic defect is a loss of a critical number of a repetitive element (D4Z4) in the 4q subtelomeric region. The loss of the repeats results in specific changes in chromatin structure, although neither the molecular nor the cellular consequences of this change are known. Nevertheless, these epigenetic changes in chromatin structure offer a potential therapeutic target. This review discusses current management strategies in FSHD as well as potential therapeutic interventions to slow down or reverse the progressive muscle atrophy and weakness. **Key Words:** FSHD, facioscapulohumeral muscular dystrophy, muscular dystrophy, myostatin, chromosome 4.

INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is a dominantly inherited dystrophy, with a prevalence of 1:20,000,[1] and is the third most common dystrophy after the dystrophinopathies and myotonic dystrophy.

CLINICAL MANIFESTATIONS

FSHD is characterized by onset of weakness in an initially restricted and characteristic distribution, starting with facial weakness, which is often mild and asymptomatic, and followed sequentially by scapular fixator, humeral, truncal, and lower-extremity weakness. The most common initial symptom is difficulty reaching above shoulder level, related to weakness of the scapular fixators. The clinical severity is wide ranging, from asymptomatic individuals to individuals who are wheelchair-dependent. Extraocular and bulbar muscles are typically spared in FSHD, and symptomatic respiratory weakness occurs in only approximately 1% of affected individuals.[2]

Extramuscular manifestations also occur in FSHD, the most common being mild high-frequency hearing loss and asymptomatic retinal telangiectasias, which occur in 75% and 60% of affected individuals, respectively.[3,4] Rarely, in severely affected individuals, the retinal vascular abnormalities can cause potentially catastrophic retinal exudation leading to retinal detachment (Coats disease).[5] Cardiac involvement, manifesting as a predilection to atrial arrhythmias, is seen in approximately 5% of patients, few of whom require treatment.[6]

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GENETICS

Genetic defect in FSHD

FSHD results from a deletion of a repetitive element on 4q35 known as D4Z4. In healthy individuals, the D4Z4 repeat consists of 11 to 100 D4Z4 repeats, each 3.3 kb in size. Patients with autosomal-dominant FSHD, however, carry one array of 1 to 10 units (FIG. 1).[7] There is an inverse relationship between the residual repeat number and the age at onset and severity of disease.[8,9] Nonetheless, affected individuals within the same family, and carrying the same size deletion, can show a wide spectrum of severity, indicating that deletion size is not the only determinant of severity. Monosomy of 4q does not cause FSHD, suggesting that the FSHD-associated deletion leads to a deleterious gain of function.[10]

Molecular mechanism in FSHD

Despite identification of the genetic defect associated with FSHD, the pathologic effects of this deletion remain largely unknown. The simplest and most parsimonious explanation is that loss of a critical number of D4Z4

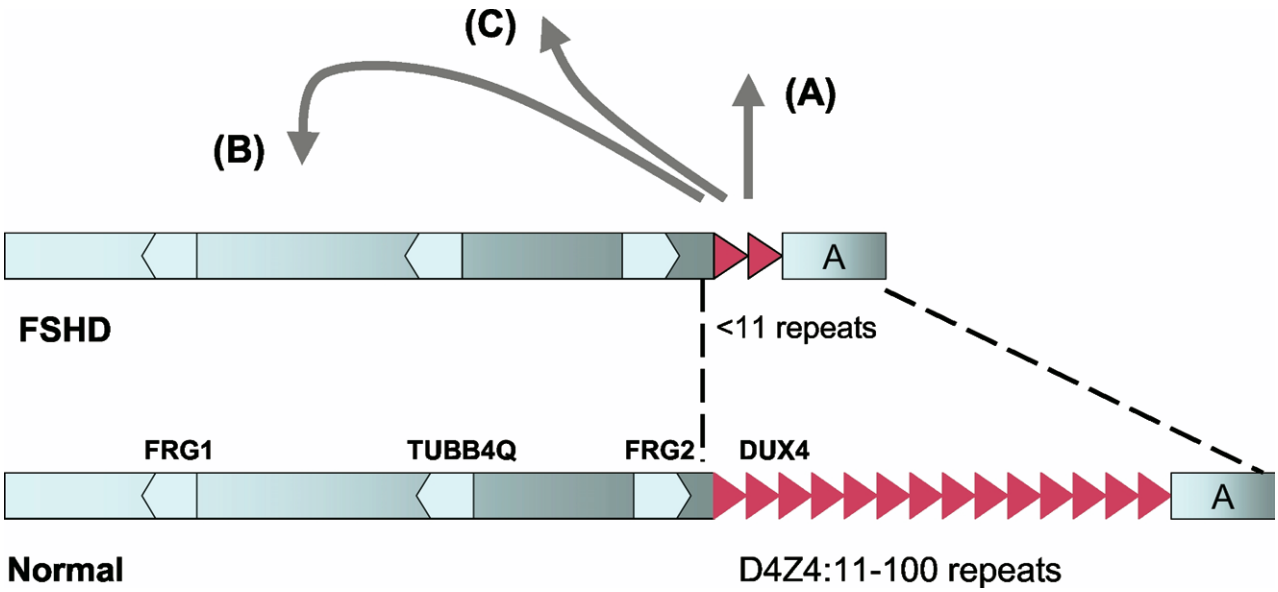

FIG. 1. The subtelomeric region of chromosome 4q35 in normal individuals and in those with facioscapulohumeral muscular dystrophy (FSHD). Normal individuals have between 11 and 100 D4Z4 repeats on both 4q35 alleles, whereas individuals with FSHD have less than 11 repeats in one 4q35 allele. Possible consequences of the deletion include (A) activation of expressed sequences within D4Z4 (*DUX4*), (B) altered regulation of genes, in *cis*, on 4q35 proximal to the deletion, *FRG1* being the leading candidate gene, or (C) altered regulation of genes, in *trans*, on other chromosomes.

repeats compromises the structure of an FSHD gene located within the repeats. Each D4Z4 repeat contains a single open reading frame encoding a putative double homeobox gene, designated *DUX4*.[11-13] However, *in vivo* expression of *DUX4* has never been clearly established, despite recent evidence that the *DUX4* is evolutionarily conserved.[14] An alternative hypothesis is that the FSHD-associated contraction influences the transcription, in *cis*, of genes proximal to the repeats on 4q35; however, definitive proof that proximal 4q35 genes are dysregulated remains elusive.

One such candidate gene is *FRG1*,[15] located 120 kb from the repeats. This gene encodes an evolutionarily highly conserved nuclear protein that may play a role in RNA biogenesis.[16,17] Its expression in FSHD muscle is highly controversial.[15,18-21] Investigations by Gabellini et al.[18] found significant upregulation of *FRG1* in FSHD muscle that was attributed to the loss of transcriptional repressor complexes that are present on the D4Z4 repeats; the group went on to demonstrate that transgenic mice overexpressing *FRG1* at very high levels develop a myopathy. Other investigators have failed to confirm *FRG1* upregulation in either FSHD muscle or FSHD myoblast cell line.[19-21] These contradictory findings make it uncertain as to whether the *FRG1*-overexpressing mouse is a valid animal model of FSHD. Nevertheless, there are a number of features of the D4Z4 repeats and their flanking regions that are altered by contraction of the D4Z4 repeats, indicating that they play a role in epigenetic control of gene expression. Moreover, such control may be exerted not only in *cis* on chromosome 4q, but potentially in *trans* on other chromosomes (FIG. 1). These features include the preferential localization of 4q35 to the nuclear membrane, the presence of nuclear matrix attachment sites proximal to the repeats, and specific hypomethylation patterns in the contracted repeats.[22-24]

DIAGNOSIS

Clinical diagnosis of FSHD can be made with relative certainty in most patients given the distinctive pattern of muscular involvement within the setting of an autosomal-dominant family history. The diagnosis is confirmed with molecular diagnosis, bypassing the need for muscle biopsy in most instances. Standard molecular testing for FSHD demonstrates the presence of a contraction of the D4Z4 repeats in one copy of 4q35. The normal allele size of the DNA fragment detected by probe p13E-11 after *Eco*RI digestion is greater than 50 kb. Individuals with FSHD have one allele that is between 10 and 38 kb. The standard testing procedure performed by most laboratories is highly sensitive (95%) and specific (95%).[25,26]

TREATMENT

Given that the underlying pathophysiology of FSHD remains uncertain, no disease-specific therapeutic strategies are possible at the present time. A number of nonpharmacologic interventions can provide symptomatic and functional improvement, as well as preventing known complications of the disease.

Medical management

Use of assistive devices. Custom molded ankle–foot orthoses (AFO) are helpful in the management of foot drop in patients with FSHD. Simple AFOs, however, are a hindrance in patients who have foot drop combined with knee extensor weakness due to quadriceps atrophy. In such instances, fixed AFOs can actually worsen the gait, by preventing hyperextension and mechanical locking of the knee. An alternative strategy in such instances is use of floor-reaction ankle–foot orthoses (FRAFO). The anterior tibial lock of the FRAFO provides extension force to the knee upon floor contact, preventing buckling of the knee while also preventing foot drop by keeping the ankle in a neutral angle. Another alternative for patients with a combination of foot drop and knee extensor weakness is knee–ankle–foot orthosis (KAFO). Classic KAFOs tended to be bulky, relatively heavy, and impractical. Newer KAFOs utilizing lighter material and having more sophisticated, dynamic hinging at the knee offer more practical alternatives. Nevertheless, in our experience, KAFOs are a workable alternative for only a small percentage of patients. Bracing to reduce scapular winging and to improve shoulder range of motion is typically futile. Figure-eight braces can reduce visible scapular winging, but cannot apply enough force to fix the scapulae enough to improve shoulder range of motion. Moreover, figure-eight braces are uncomfortable if worn for prolonged periods and if applied too tightly risk compressing the brachial plexus. Use of such braces for short periods may have a role in reducing discomfort in patients with intractable shoulder pain due to laxity of the shoulder joint.

Pain. Pain is a frequent complaint among many patients with FSHD.[27] A survey done by the AFM (Association Française Contre les Myopathies) revealed that 55% of FSHD patients complained of pain at least several days a week (unpublished data). The pain is musculoskeletal in character and commonly involves joints where the surrounding muscles are weak. This would include the shoulders and upper back, the knees, and the lumbosacral region because of the hyperlordosis typical of these patients. The use of nonsteroidal anti-inflammatory drugs and, if the pain is chronic, antidepressants is warranted in these patients.

High-frequency hearing loss. Symptomatic hearing loss is often seen in infantile-onset FSHD. If it is not detected and treated early, it can interfere with language development and may be mistaken for cognitive impairment. Audiograms should be performed on all patients diagnosed with infantile FSHD.

Retinal telangiectasias. Retinal telangiectasias are rarely symptomatic, but, if undetected and untreated, asymptomatic exudates can eventually lead to blindness. There is no consensus about the need or frequency for surveillance retinal studies in FSHD; however, given that this condition is eminently treatable with laser, surveillance is justified with periodic examination of patients by indirect ophthalmoscopy by an experienced retinal specialist.[28] Because most reported cases of Coats disease occur in the most severe infantile-onset FSHD, dilated indirect ophthalmoscopy should be performed as screening in all such cases, followed by fluorescein angiography, if indicated.

Respiratory insufficiency. Symptomatic respiratory involvement in FSHD can be seen in approximately 1% of patients,[2] typically those with advanced FSHD and in patients who develop significant kyphoscoliosis. As with other slowly progressive neuromuscular disorders, the onset of respiratory insufficiency can be insidious. Patients should be routinely asked about subtle signs of chronic hypercarbia, such as nonsatisfying sleep, morning headaches, and daytime hypersomnolence. Routine measurement of forced vital capacity, both supine and sitting, should be instituted in patients with severe weakness or those who have become wheelchair-bound. Symptomatic respiratory insufficiency can be initially managed with nighttime noninvasive pressure support (BiPAP) but may in severe cases require the use of a volume ventilator.

The role of exercise. Vigorous exercise is typically proscribed for patients having muscular dystrophies with sarcolemmal abnormalities leading to friable muscle membranes. There are no indications, however, that FSHD muscle fibers are more susceptible to mechanical injury than is seen in dystrophies with sarcolemmal abnormalities. In fact, several studies have shown at least a short-term beneficial effect of both strength training and aerobic exercise in FSHD.[29-32] These observations were confirmed recently in a prospective 1-year trial.[33] These studies notwithstanding, a note of caution is in order. Depending on individual disease severity, certain types of exercises will put patients at risk of falls, in the presence of ankle or knee weakness, or overuse and stretch injuries, in the presence of shoulder and periscapular weakness.

Surgical interventions

Scapular fixation. One of the major early functional limitations in FSHD is the inability to raise the arms to or above shoulder level. Surgical scapular fixation was shown, in retrospective case series, to significantly enhance arm mobility.[34-37] This technique has not, however, been subjected to a prospective controlled study.[38] Consequently, neither the indications for this procedure nor the optimal technique are clearly defined. Potential complications include a break in the wire, with consequent loss of the functional gain and, rarely, brachial plexus injuries.[39,40] Bedside, manual fixation of the scapula can give the examining physician an idea of the potential functional improvement that surgical fixation

will provide. Surgery should be considered only in patients with stable or slowly progressive disease and in those with reasonably preserved upper-arm strength.

Other surgical interventions. A number of other surgical interventions can be considered in individual patients with FSHD. Severe weakness of the orbicularis oculi muscle results in an inability to fully close the eye, which can lead to exposure keratitis. One potential solution is the use of gold weights implanted into the upper eyelids to correct lagophthalmos.[41] Another patient followed in our clinic, on consultation with an orthopedic surgeon, underwent a tendon transfer to fix a foot drop. The patient's gait improved, and the benefit was sustained for many years. Other FSHD patients with the typical combination of weakness of the anterior leg compartment and foot drop, but with preserved calf muscles and a slowly progressive disease, could benefit from such an intervention. Finally, severe orbicularis oris muscle weakness can result in a markedly everted lower lip, which can, apart from its cosmetic aspects, impair speech and cause drooling of saliva. One such patient, followed in our clinic, underwent corrective plastic surgery, which resulted in improved appearance and improved speech, as well as control of drooling.

Pharmacologic interventions

A number of pharmacological strategies have been tested in FSHD, aimed at slowing or halting progression:

Corticosteroids. Inflammation is a common finding in FSHD muscle, at times mimicking inflammatory myopathies. Consequently, corticosteroids have been tried in a number of cases, but with inconsistent results.[42-44] Based on these case reports, a prospective open-label trial of high-dose corticosteroid was given for 3 months but failed to show improvement in strength or muscle mass.[45]

Albuterol. The $\beta 2$ agonists have a number of effects on muscle metabolism and function, including proliferation of satellite cells, increased muscle protein synthesis, and inhibition of muscle proteolysis.[46,47] These compounds were shown to be protective of muscle mass and function in animal models of denervation, sepsis, and corticosteroid atrophy, as well as in animal models of muscular dystrophy.[48-51] Similar results were obtained in studies of normal human volunteers, demonstrating the anabolic effects of the $\beta 2$ agonists.[52] Based on this evidence, we undertook a pilot, 3-month, open-label trial of a sustained-release albuterol in FSHD, which then led to a 1-year, randomized, placebo-controlled trial.[53] In this latter study, 90 FSHD patients were randomized to receive two different doses of sustained-release albuterol (8 mg and 16 mg, twice daily). Strength was not improved at the end of 1 year of treatment, but muscle mass, estimated using dual-energy X-ray absorptiometry, was significantly increased at 1 year in the active drug groups in a dose-dependent fashion.[53] In a subsequent controlled trial of sustained-release albuterol (8 mg twice daily), with or without training,[33] a similar positive effect on muscle mass, measured by computerized tomography scan, was noted after 26 weeks, along with a modest and statistically significant improvement in strength in several muscles. Both studies showed a consistent anabolic effect of albuterol in FSHD, but the magnitude of the increased muscle mass did not translate into significant functional improvement in strength. Based on the available information, albuterol cannot be recommended for patients with FSHD.

Creatine monohydrate. Aside from the fact that phosphocreatine is the immediate source of energy during vigorous muscle contraction, there is evidence that phosphocreatine stores are depleted in some dystrophic muscle and that creatine may have cellular protective characteristics.[54-55] A randomized double-blind, crossover trial, in a mixed population of dystrophies (12 of which were FSHD) demonstrated slight improvement in overall strength following short-term (8-week) supplementation with creatine monohydrate (10.6 g/day for 10 days followed by 5.3 g/day thereafter).[56] Although no conclusion could be reached regarding the effect of creatine on FSHD from the published data, additional data provided to the Cochrane review from the same study showed that the trial was negative for FSHD.[57]

Myostatin inhibition. There is currently intense interest in therapeutic interventions that block the effects of myostatin, a negative regulator of muscle growth.[58] Indeed, a phase II, dose-ranging trial has been recently completed using MYO-029 (Wyeth Laboratories), a monoclonal antibody raised against human myostatin.[59] The trial compared patients randomized to placebo to those randomized to receive MYO-029 in each of three subject groups: FSHD, Becker's dystrophy and limb-girdle muscular dystrophy. No significant toxicity but also no benefit on function or strength was noted after 54 weeks of weekly infusions of MYO-29.

Novel therapeutic interventions

Folic acid and methionine supplementation. Contraction of the D4Z4 repeats on 4q35 is associated with marked hypomethylation of the shortened D4Z4 allele. Moreover, rare patients with phenotypic FSHD and no contraction of either D4Z4 allele show profound hypomethylation of both alleles.[60] These findings suggest that hypomethylation plays a critical role in the pathogenesis of FSHD. Folic acid and vitamin B_{12} are essential for the synthesis of methionine, required in the maintenance of DNA methylation.[61] Van der Kooi et al.[61] undertook a pilot study to test the hypothesis that folic acid and methionine supplementation in FSHD can alter the methylation level at D4Z4. Despite achieving serum concentrations of folate previously demonstrated to enhance

DNA methylation, no such effect was noted in either FSHD or controls after 12 weeks of supplementation. The authors suggest that higher doses of folic acid in combination with vitamin B_{12} may be needed.

Novel myostatin inhibitors. Soluble activin type IIB receptors are inhibitors of myostatin and can cause a dramatic increase in muscle mass when given to wild-type mice, an effect that can also be reproduced in myostatin double-knockout mice.[62] A newly developed soluble activin type IIB receptor was recently shown to improve muscle mass and function in the *mdx* mouse.[63] Such a molecule could potentially be used to treat any muscle wasting condition, including FSHD.

Muscle stem cell therapy. Transplantation of cultured myoblasts by intramuscular injection has been considered for a number of dystrophies. To explore such a therapeutic option in FSHD, Vilquin et al.[64] examined myoblast cultures derived from histologically unaffected FSHD muscle and found them normal in all aspects of division and differentiation. The authors suggest that such myoblasts could be used for autologous cell therapy in FSHD. Another myogenic mesodermal stem cell, mesangioblasts, is present in perivascular tissue of skeletal muscle. Mesangioblasts, were shown to improve muscle morphology and function when injected intra-arterially in animal models of dystrophy. A recent study showed that mesangioblasts derived from pathologically affected FSHD muscle were morphologically abnormal and had a block in differentiation. Mesangioblasts derived from morphologically normal FSHD muscle showed no such abnormalities.[65] These findings raise the possibility of using autologous cell therapy with mesangioblasts. Unlike myoblasts, which require local delivery to individual muscles (a limitation to practical use), mesangioblasts can be systemically delivered through the circulation.

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