Facioscapulohumeral Muscular Dystrophy: Clinical, Therapeutic and Regulatory Updates

Facioscapulohumeral muscular dystrophy (MD) is a complex, inheritable muscle disease with an etiology that is rapidly becoming more elucidated. As a single clinical phenotype dominantly affecting the face (facio), scapula (scapulo), and humerus (humeral) muscles, it appears to have varying molecular and genetic determinants with commensurate differences in disease progression. Historically known as Landouzy-Dejerine disease – named after French neurologists Dr Louis Theophile Joseph Landouzy (1845-1917) and Dr Joseph Jules Dejerine (1849-1917) – it is more commonly known today as FSHD or FSH.

Although frequently cited as the third most common type of MD in older reports, many newer sources, such as Orphanet, rank FSHD as the most prevalent type of MD, occurring at a rate of some 7 cases/1000 persons, as compared with Duchenne MD(DMD)/Becker's MD (BMD) (5 cases/1000) and myotonic dystrophy (4.5 cases/1000).[1] The identification of FSHD as the most common type of MD has important ramifications; for example, when allocating future Federal (US) funding for research, and in terms of the potential market size for future FSHD treatments. FSHD has only recently attracted attention from the pharmaceutical industry, largely due to advances in our understanding of the genetic mechanisms of disease, including overexpression of a protein called double homeobox 4 or DUX4.

There is currently no disease-modifying treatment or cure for FSHD. Most treatments proposed to "treat" FSHD have not yet been tested in randomised clinical trials.

This paper will provide an overview of FSHD, discuss major clinical symptoms and ramifications of disease progression, provide a regulatory overview, and discuss two of the more commonly used surgical procedures to treat FSHD.

Key barriers to rapidly finding a treatment for FSHD, as well as a brief discussion of potential pharmaceutical treatments and non-pharmaceutical interventions, will also be provided.

Prevalence

It is impossible to accurately assess the prevalence of FSHD because of disparate databases, differences in regions where clusters of FSHD patients are known to exist (e.g., the Netherlands), the lack of unified patient registries, and the reluctance of some US patients (with mild or moderate forms of FSHD or those whose onset of FHSD symptoms occurs later in life) to obtain either a clinical or molecular diagnosis of FSHD, for fear of insurance coverage discrimination.

Although older sources list FSHD as third or fourth most prevalent of the nine types of MD recognised by the National Institute of Health's (NIH's) National Institute of Neurological Disorders and Stroke (NINDS), Dr Jean Mah and her team recently performed a systemic review and meta-analysis on the epidemiology of the muscular dystrophies and concluded that the studies included in their analysis "differed widely in their approaches to case ascertainment and substantial gaps remain in the global estimates of (muscular dystrophies)."[2]

According to the November 2016 issue of the Orphanet Report Series, the gap may not be as great as some believed in the past, with a prevalence of 4.5/100k for FSHD (using European data) and 4.78/100k for Duchenne muscular dystrophy (DMD, using prevalence data).[3]

According to the University of Massachusetts Medical School's *Wellstone Center of FSHD*, FSHD is the most prevalent hereditary muscular dystrophy affecting men, women and children and is more prevalent than any of the other types of muscular dystrophy. A conservative estimate of incidence for FSHD1, the most common type, is 1 in 14,286 births throughout the world; however, due to increased experience with FSHD, population-based research and improved genetic testing, this estimate may be low; actual incidence may be as high as 1 in 7500.[4]

According to the FSH Society's Website, FSHD is a genetic condition that affects around 1 in 8000 men, women and children and is among the most common forms of muscular dystrophy.[5]

Proposed Mechanism of Action

FSHD is a heterogenous disorder and its genetic bases are complex, involving both genetic and epigenetic factors. Two forms of FSHD are recognised and reported in the literature: FSHD1 and FSHD2. About 95% of patients with FSHD have the FSHD1 form and about 5% have the FSHD2 form.[6]

In most cases, FSHD displays an autosomal dominant mode of inheritance with reduced penetrance. However, sporadic cases are frequent, accounting for 10-30% of FSHD1 incidence. Often, *de novo* cases are in the mosaic form and usually have milder phenotype; thus, these patients may go undetected.[7] One study looked at *de novo* FSHD families and found somatic mosaicism in 40% of cases, in either the patient or an asymptomatic parent. Mosaic males were typically affected; mosaic females were more often the unaffected parent of a non-mosaic *de novo* patient.[8]

Both FSHD1 and FSHD2 share a common downstream mechanism – hypomethylation in the D4Z4 region, which leads to epigenetic derepression of the physiologically silenced gene, DUX4.[9] The inappropriate expression of DUX4 is the most probable cause of FSHD.[10]

The DUX4 gene is located within the D4Z4 macrosatellite array on chromosome 4q35. More than 95% of patients have deletion of large repeat segments on 4q35, which are typical for FSHD1. Healthy

individuals display 11 to 100 D4Z4 repeats, while patients with FSHD1 have 1-10 D4Z4 repeats. The fewer the repeats, the earlier the disease onset and the more severe the phenotype.[11]

Less than 5% of FSHD patients do not show contracted D4Z4 array, have at least one permissive chromosome 4qA and demonstrate profound hypomethylation on chromosomes 4 and 10. In these cases, heterogenous mutations in the SMCHD 1 gene on chromosome 18 p11.32 are frequently found.[12] Recently, in several patients, the SMCHD1 mutations were found to be causative in FSHD2, and to be modifiers of disease severity in FSHD1.[10]

Clinical Manifestations of FSHD

FSHD presents with a characteristic pattern of muscle weakness and progression. Although facial muscles are usually affected early on, the presenting sign is frequently finding it difficult or impossible to lift the arm above the shoulder height due to shoulder muscle weakness. The degree of affectation of facial muscles varies from mild involvement manifesting only as a "sad expression" to typical horizontal smile, weak puckering of the lips and difficulty closing the eyes. The scapular stabilizers, such as serratus anterior, rhomboid and middle portion of the trapezius muscles, are weak early on. Weakness of these muscles leads to upward and lateral rotation of the shoulder blades, with subsequent scapular winging and the appearance of trapezius protuberance. Although the deltoid muscle is relatively spared, the sternocostal part of the pectoralis major muscle is frequently weakened.[13] This is in line with MRI studies where the trapezius, teres major and serratus anterior were the most and earliest affected muscles in FSHD, followed by the latissimus dorsi and pectoralis major. This was in contrast to the musculus subscapularis and musculi spinati, which were consistently spared, even in late stages.[14]

The clavicles in FSHD patients are displaced horizontally, with a rounding shape seen in the shoulders. As the disease progresses, the upper arms, trunk and distal lower extremities become affected. Humeral musculature is weakened and forearm muscles become affected in later stages, with more prominent weakness of the wrist extensors than the flexors. Involvement of abdominal as well as paraspinal muscles leads to hyperlordosis. A bent spine phenotype due to prominent axial muscle weakness has been described in FSHD, both as an early and late symptom, and also as an isolated manifestation of FSHD.[15, 16, 17]

In the lower extremities, the tibialis anterior and gastrocnemius muscles are affected initially; proximal leg muscle weakness occurs later in the course of the disease. Due to pelvic muscles being affected in the later course of the disease, patients may have a waddling gait. It is quite common for patients with FSHD to exhibit an asymmetric muscle weakness pattern.

Systemic features have been described in FSHD. Some patients develop respiratory complications. The estimated frequency varies among sources from 1.25% to 13%. In severe cases, respiratory muscle weakness can result in respiratory failure and the need for mechanical ventilation. Imminent respiratory failure may begin with sleep respiratory insufficiency, resulting in excessive daytime sleepiness.[18]

Cardiac involvement does not typically belong to the clinical picture of FSHD. Unlike other muscular dystrophies, dilated cardiomyopathy is not found in FSHD patients; however, subclinical cardiac involvement has been described and approximately 5-12% of patients suffer from asymptomatic supraventricular tachycardia.[19, 20, 21] Increased prevalence of incomplete right bundle branch block (RBBB) with no progression on long-term follow-up has been reported and indicates selective involvement of the His-Purkinje system in FSHD.[22]

As in other muscular dystrophies, a number of characteristic extramuscular manifestations are present in FSHD and usually these are found in patients with smaller numbers of D4Z4. Vision is typically normal; however, more than half of patients with FSHD1 show peripheral retinal abnormalities, with funduscopic examination frequently revealing retinal vessel telangiectasia.[23] This finding – which corresponds to a developmental abnormality of the peripheral retinal blood vessels – is not progressive and remains clinically asymptomatic and often underdiagnosed. Nevertheless, a few patients with FSHD can develop an exudative retinopathy resembling Coats' disease, with the risk of recurrent retinal detachment, a major complication that causes vision loss in the most severe cases.[24] Bilateral Coats' disease has been described in FSHD patients.[25]

Findings related to the frequency of hearing loss in FSHD are controversial, with one study reporting high-frequency hearing loss in nearly 50% of patients,[26] while others conclude that the hearing loss in FSHD is typically no more prevalent than in the normal population.[27] Specifics related to infantile onset of FSHD are discussed later.

Pain is a common problem, occurring in up to 82% of FSHD patients;[28] this is usually located in back, legs and shoulders. The pain in the shoulder region exacerbates the already-impaired shoulder and upper limb function.[29]

Considerable differences in both FSHD presentation and progression exist. Notably, a number of genetically confirmed variants have been identified, such as scapulohumeral dystrophy with facial sparing, limb girdle muscular dystrophy phenotype, distal myopathy, etc.[30] Even within one family, a significant variability of clinical pictures may occur. The disease onset is usually before the second decade, and in milder cases the diagnosis is often delayed to early adulthood or even late adulthood. The loss of ambulation and need for wheelchair use occurs in about 20% of subjects older than 50 years old and life expectancy is not usually shortened.[31]

In general, the earlier the onset of symptoms in childhood, the more debilitating the course of the disease that ensues, including both the severity and rapidity of progression. The so-called "infantile" variant of FSHD accounts for approximately 4% of FSHD patients, and represents the most severe form. This involves initial presentation of facial weakness in the first few years of life, rapidly followed by shoulder girdle and hip girdle weakness, hyperlordosis and wheelchair confinement by the age of 12 or even earlier.[32] Facial weakness is often severe, the children are unable to close eyes during sleeping and often cannot smile or show a facial expression. In an early childhood onset patient, delayed development of gross motor milestones was also noted.[33] Respiratory insufficiency and swallowing difficulties have been described.[34] Contrary to the more classical form, children with the infantile variant often demonstrate more systemic and extramuscular signs such as hearing impairment, retinal telangiectasia, cardiac arrhythmias and CNS involvement manifesting as mental retardation and seizures.[35]

Both FSHD1 and FSHD2 have similar clinical presentation, although it is possible that the striking similarity among FSHD1 and FSHD2 is due to ascertainment bias. Screening for FSHD2 among unidentified muscular dystrophies may reveal a wider FSHD2 clinical spectrum.[36]

Barriers to a Cure

In addition to differences in molecular structure associated with FSHD1, FSHD2 and possibly infantile onset FSHD, there appears to be marked variation in the severity and progression of disease in individuals diagnosed with FSHD. Although this list is not exhaustive, other key hurdles to the approval of products for treatment of FSHD include:

- FSHD is an autosomal-dominant disorder localised to 4q35. Neither the gene nor gene product has been identified. The molecular basis for FSHD is not yet completely worked out.
- Variability between males and females.
- A lack of understanding around the clinical asymmetry associated with FSHD.
- Animal models of MD do not accurately reflect human disease and thus, the majority of drugs tried in animal models have failed in human clinical trials.[37, 38] There is a need for increased rigour and higher standards in the preclinical MD space. Current data suggest that there is a tendency to move to MD clinical trials too soon, based on insufficient data.[39, 40]
- It is difficult to define and measure the rate of change in slowly progressing conditions.
- Variety and differences in the genetic mode of transmission (e.g., autosomal dominant inheritance, germline mosaic [resulting from a mutation during development which is propagated to only a subset of the adult cells, like sperm or eggs], *de novo* mutations, etc.).
- Heterogeneity of the phenotypes within each form of FSHD with varying treatment goals at each stage.
- Variability related to degree of ambulation.
- Low numbers of patients available or eligible for study in clinical trials (thus FDA's willingness to classify them as "orphan," and garnering significant advantages for the sponsor, such as regulatory exclusivity and reduced fees during the application process).
- Paediatric neuromuscular disease presents a challenge because patients lose muscle function as they grow into adolescence. The therapies, if not definitively curative, must provide a risk/benefit ratio acceptable to patients as well as caregivers; these two parties may not calculate the risk/benefit ratio in the same way.[41]
- Currently, many registries are only offered in one geographic area (e.g., big cities). The lack of a fully operational central/national registry database is problematic, but large patient advocacy groups are attempting to remedy this situation.[42, 43,44, 45]
- Lack of protein identification and complete mechanism of action in FSHD.
- Lack of regulatory agreement on a pathway for the treatment of FSHD (see Regulatory Guidance below). Regulatory guidance is needed to de-risk the programmes of sponsors seeking to study and provide treatments for FSHD.
- Lack of regulatory agreement on primary and secondary endpoints in the US for FSHD trials.

Preclinical Models[46, 47]

Ongoing studies of preclinical animal models for FSHD are examining:

- Zebra fish, with work underway to establish a DUX4 transgenic zebrafish to determine how the expression of DUX4 causes the FSHD phenotype.
- Canine models, such as golden retrievers with the Duchenne mutation, which may also be relevant to FSHD.
- Mouse models, with research being conducted at the University of Maryland in Baltimore, assessing the pathologic role of DUX4 in a humanised mouse model.

Regulatory Landscape

Because FSHD can be life-threatening, new disease-modifying (serving to slow or halt progression) and curative treatments are desperately needed. No regulatory guidance exists in the highly regulated markets (e.g., US, EU), but the stage may be set for change.

The European Medicines Agency issued a concept paper in 2011 and draft guidance for treatments related to Duchenne MD in early 2013.[48, 49] Responding to an absence of FDA guidance and at the agency's invitation, the Project Muscular Dystrophy (PPMD) organisation and more than 80 representatives of the Duchenne community submitted the first-ever patient advocacy-initiated draft guidance to the agency in June 2014.[50] The FDA reviewed their submission and issued its own draft guidance on DMD/BMD in June 2015.[51]

Since FDA draft guidance for MD now exists, this DMD/BMD template could potentially be used as a template by patient advocacy groups representing other types of MD, including FSHD.

Overview of Pharmaceutical Treatments and Non-pharmaceutical Interventions

There are no approved pharmaceutical treatments to cure or slow progression of FSHD. Symptomatic treatment can include physical therapy, speech therapy, and in some cases orthotic devices and surgical procedures. The encouraging news is that the number of interventional trials has increased in the past few years lending optimism that new treatments and interventions may soon be available. To assess treatments, we reviewed clinicaltrials.gov, PubMed and Orphanet for trial listings and publications related to research and treatment for patients with FSHD.

From 2014–2017, there have been 19 studies registered with clinicaltrials.gov. Of these, 14 are interventional in nature. Several have been registered to assess investigational products, including ATYR1940 and ACE-083. In addition, studies are ongoing to assess albuterol, creatine monohydrate, and antioxidant supplementation. These will be explored in greater detail in a subsequent paper.

There are several publications referencing treatment options for comorbidities and symptoms associated with FSHD. One case example highlights the potential risk for exudative maculopathy in patients with FSHD. In this case, a solution of intravitreal anti-vascular endothelial growth factor injections combined with focal laser photocoagulation was found to be beneficial.[52]

There are several studies that look at the potential for non-pharmaceutical interventions, such as diet and exercise to improve muscle strength and performance. These studies have had mixed results. Strength training and aerobic exercise have been shown in one study to benefit patients,[53] while an older meta-analysis did not show any benefit to patients.[54] Overall, these studies did not show an increased risk to patients.

There are also theories regarding oxidative stress. To reduce or eliminate oxidative stress, several studies have evaluated vitamins and minerals to support muscle endurance and a reduction in oxidative stress. There is some evidence that vitamins can support patients with FSHD[55, 56] and ongoing studies continue to look at the use of muscle oxygenation as a diagnostic tool (NCT02789059) to understand the impact of modification.

Additionally, orthotic devices are often used to compensate for muscle loss; these include back and leg braces, girdles and other support clothing, or wheelchairs.

Overview of Potential Surgical Treatments

Weakness of the thoracoscapular muscles is a typical feature of FSHD, with patients having difficulties reaching upwards, washing, dressing, combing their hair and brushing their teeth. When shoulder elevation is attempted, the relatively spared deltoid muscle takes over, the scapula rotates and lifts off the chest wall, losing strength at the glenohumeral joint. This subsequently leads to an inability to sustain shoulder abduction and flexion.[57] Surgical fixation of the scapula to the back of the thorax may enhance shoulder function, especially in regard to abduction, which should subsequently lead to improvement in activities of daily living. Besides a functional problem, winging scapula presents cosmetic deformity and contributes to pain in the shoulder region.

There are two main types of surgical interventions in FSHD; thoracoscapular arthrodesis (scapulodesis) or thoracoscapular soft tissue fixation without arthrodesis (scapuloplexy). Scapulodesis fixes the scapula to the chest wall with screws, wires or plates, with or without a bone graft, to produce solid fusion. In scapuloplexy, fascial or synthetic slings are used to improve scapular fixation. The latter procedure might be better suited for individuals with impaired respiratory function and for whom prolonged immobility would be particularly high risk.[58] Both procedures aim to achieve long-term stability of the scapula with maximal glenohumeral movement and reduced pain.[59, 60, 61] The procedure may be performed both unilaterally and bilaterally. Historically, data have been published on bilateral procedures done at the same time; however, most frequently they are done separately.[62, 63]

The indication for surgery has been recently published in the 2015 American Academy of Neurology/American Association of Neuromuscular and Electrodiagnostic Medicine (AAN/AANEM) guideline. This states that "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 post-surgical bracing." A comprehensive overview of the indication criteria has been also published.[64]

Although quite rare, both early and late post-operative complications have been reported and may include pneumothorax, hemothorax, non-union, pain, infection and decline in respiratory function.[65, 66]

Summary

Facioscapulohumeral MD, likely the most prevalent form of MD, currently has no cure. The main regions affected by FSHD are in the face and arms; however, weakness in the legs and abdominal muscles are also common. Pain is a very common problem in patients with FSHD. In general, the earlier the onset of symptoms in childhood, the more debilitating the course of the disease. Cardiac complications are uncommon. Respiratory, peripheral, and hearing problems have all been reported and mental health in patients with FSHD is a significant factor that needs to be considered as well.

The phenotypic differences in severity among patients with FSHD continue to pose problems in our understanding of FSHD. Varying rates of progression in different anatomical regions further add to the complexity of the clinical assessment.

Although the over-expression of the DUX4 protein has been identified as a factor in FSHD, the gene and gene product have not been identified. There is currently no regulatory guidance available in ICH countries available for sponsors of FHSD treatments and there are currently no good animal models of the disease.

There are only two main surgical interventions for FSHD. Scapulodesis screws the scapula to the chest wall, while scapuloplexy uses fascial or synthetic slings to improve scapular fixation.

Regarding nutritional supplements and treatments, there is currently no definitive evidence of any significant effect on FSHD. Certainly, maintaining a healthy diet, getting enough sleep, and keeping as active as possible without straining the muscles are all important for the patient.

As FSHD becomes better understood, there is increasing investment by pharmaceutical companies in this rare disease area. It is hoped that ongoing and future clinical trials, with participants identified using "best in class" registries that gather natural history data, the disease mechanisms will become better elucidated and disease-modifying or curative treatments will reach the patients who need them.

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