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Workshop report

171st ENMC International Workshop: Standards of care and management of facioscapulohumeral muscular dystrophy

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1. Introduction

An ENMC workshop on standards of care and management of facioscapulohumeral muscular dystrophy (FSHD) patients was held on January 15–17, 2010 in Naarden, The Netherlands. Twenty-four participants from eight countries participated. The primary objective was to develop standards of care in the diagnosis and management of patients with FSHD. Recommendations were formulated based on evidence, when available, or on the consensus of expert opinion. The workshop also identified areas where further studies are needed. Additionally, given the recent progress in understanding the underlying pathophysiology of FSHD, the workshop also examined issues of trial readiness in FSHD including the availability of appropriate outcome measures and access to patients through registries.

2. Diagnosis

2.1. Clinical diagnosis

FSHD is an autosomal dominant condition with high (*de novo*) mutation frequency. The diagnosis of FSHD is suspected in patients who present with selective involvement of face and shoulder girdle muscles in the absence, as a rule, of masticatory, lingual and extraocular muscle involvement. Supporting clinical evidence for FSHD is the presence of prominent asymmetric weakness of the face and shoulder muscles as well as weakness of the abdominal muscles. In patients presenting in infancy or early childhood, the presence of hearing loss or retinal vasculopathy, virtually confirms the diagnosis of FSHD [1]. Once FSHD is suspected, the diagnosis can be genetically confirmed with a highly sensitive and specific DNA test. In absence of genetic confirmation, however, additional investigations by EMG and muscle biopsy should show no evidence of an alternative diagnosis. Despite the characteristic clinical presentation of FSHD, the combination of prominent scapular winging and facial weakness can be seen in other myopathies (Table 1).

2.2. Genetic diagnosis

The large majority (>95%) of patients with FSHD have a partially deleted D4Z4 repeat array on one of their chromosomes 4 (FSHD1). This repeat array is polymorphic in copy number, with alleles varying between 11 and 100 units in the general population. Patients with FSHD1 carry one allele with 1–10 D4Z4 units [1]. In order to be pathogenic, this shortened D4Z4 repeat array needs to reside on the 4qA background of chromosome 4. Contraction of a similar repeat array on chromosome 10 or on chromosome 4qB has not been shown to cause FSHD [2].

Genetic confirmation of FSHD1 is routinely done on peripheral blood lymphocyte DNA by Southern blotting and hybridization of a set of probes to allow for the establishment of the size of the repeat array on 4q35 and often also determine the genetic background of chromosome 4q (A/B). In unaffected individuals this method will show two 4q35 alleles of >40 Kb on the basis of an EcoRI DNA digestion. In individuals with FSHD one of the two 4q35 allele will be between 10 and 38 Kb. The interval between 40 and 50 Kb is often considered inconclusive. When testing is done on patients who fit the clinical criteria for FSHD, the genetic test used in most diagnostic laboratories is highly sensitive and specific. Rare cases of false positive tests can result from the detection of contractions on a 4qB background. If a false positive test is suspected, most diagnostic laboratories will, upon request, do additional testing to determine the 4qA/B background.

Since the above methodology is a labor- and time-intensive, novel techniques have been developed to facilitate the genetic diagnosis of FSHD, such as long range PCR [3]. One of the newest techniques is molecular combing which allows visualization and sizing of the D4Z4 repeat array in its genetic context on stretched single DNA fibers by fluorescence microscopy.

There are potential pitfalls in the genetic diagnosis of FSHD that can result in false positive or false negative results. This only concerns a minority (<5%) of patients. Nevertheless, considering the complexity of the genetic lesion and the progress made in the past decade, there is a strong need for best practice guidelines for FSHD DNA diagnosis. One important subgroup of FSHD patients for example (FSHD2; ~3%) have no contraction of the D4Z4 repeat array but show changes in the chromatin structure of D4Z4 similar to what is observed in FSHD1 [4]. Diagnosis can only be done on re-

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Table 1
Neuromuscular disorder that mimic the clinical presentation of FSHD.

Scapuloperoneal muscular dystrophy
Scapuloperoneal spinal muscular atrophy
Neuralgic amyotrophy
Davidenkow syndrome
Limb girdle muscular dystrophy
Proximal myotonic myopathy
Polymyositis
Inclusion body myositis/myopathy
Acid maltase deficiency
Mitochondrial myopathy
Congenital myopathy

search basis and there is currently no validated genetic test available for this FSHD subgroup.

2.2.1. Prenatal diagnosis

Prenatal diagnosis is available for FSHD1 based on the genetic tests described in the previous paragraph. Conditions for inclusion for prenatal diagnosis include confirmed FSHD1 in the family, and availability of DNA from parents and index case. Because genetic diagnosis for FSHD can take several weeks to complete, diagnosis on DNA isolated from chorionic villi is preferred over amniocentesis.

Caution should be taken with preimplantation genetic diagnosis (PGD) as the Southern blot genetic test is not applicable to single cell PGD. Consequently, the disease-associated D4Z4 repeat can only be detected indirectly with the use of polymorphic markers, but the relatively high recombination frequency and the availability of few polymorphic markers specific for the region proximal to D4Z4 hampers PGD significantly.

2.2.2. Genetic counseling

Patients with FSHD seek genetic counseling for information regarding diagnosis, prognosis, risk to offspring and pregnancy. Patients should be counseled that FSHD is dominantly inherited with a penetrance of >95% by age 20. Although mosaicism is frequent in *de novo* FSHD and can be detected by Southern blot analysis, in the absence of firm data about gonadal mosaicism, these patients should be counseled as patients with a clearly dominant family history. Providing reliable prognostic information is more difficult given the often wide spectrum of intrafamilial variability and the lack of good correlation between genotype and phenotype except a small residual repeat number, corresponding to allele sizes of 10–19 Kb, predict severe or infantile-onset FSHD. Prenatal counseling should take into account the limitations of prenatal diagnostic testing outlined in Section 2.2.1.

3. Clinical management

Patients with FSHD share many of the same challenges as other patients with inherited myopathies in addition to some FSHD-specific complications. While minimally symptomatic adults may require infrequent follow-up and minimal intervention, patients with infantile-onset FSHD require close monitoring in a multidisciplinary care clinic.

3.1. Role of physical therapy and rehabilitation

It is recommended that all patients with FSHD who have functional limitations get an initial rehabilitation consult. Such a consultation may address functional limitations including assessment of balance and gait, posture, and the need for orthoses. Complaints of fatigue and pain have to be specifically addressed as well. Recommendations regarding an appropriate exercise regimen including stretching, resistive and aerobic training can be provided based on the physical therapy evaluation and the current evidence for exercise in FSHD (see Section 3.2). Follow-up physical therapy evaluations will depend on the ongoing needs of individual patients. Patients with mild functional disabilities may require yearly follow-up whereas patients with severe infantile-onset disease, may require ongoing input from a physical therapist, orthotist, an occupational therapist and a speech pathologist. A detailed physical therapy brochure for FSHD, commissioned by the FSH Society, can be downloaded at the following link: http://www.fshsociety.org/assets/pdf/PhysicalTherapyAndFSHD.pdf.

3.2. Role of exercise in FSHD

Several studies have shown that exercise with moderate weights or resistance is not detrimental to patients with FSHD [5,6]. More recently, a study showed that consistent aerobic training in patients with FSHD not only improves cardiovascular fitness but also improves strength [7]. When training is indicated, aerobic training is to be recommended to patients with FSHD. This training should be performed at least three times a week for 30 min, at an intensity that achieves the age-adjusted target heart rate for aerobic fitness [7]. In patients unable to engage in aerobic exercise, a moderate resistance training program is recommended as a substitute.

3.3. Pain and fatigue

Pain is a common and underestimated complaint in FSHD. Using the McGill pain questionnaire and a self observation list on daily observed pain prospectively, pain was present in 77% of a group of 79 FSHD patients [8]. An unpublished survey by the AFM (Association Française Contre les Myopathies) showed that 55% of FSHD patients complained of pain at least several days a week. More recent studies have also documented the effect of pain on patients with FSHD [9,10]. The etiologies of the pain are multiple and should be dealt with using standard approaches to the management of chronic pain such as, where appropriate, physical therapy and pain medications [11]. Fatigue is also a frequent complaint, is multifactorial in origin and is experienced by patients with a number of dystrophies [12]. Energy conservation strategies can help some patients as can aerobic training [7]. It is worth noting that mood disorders although not present at a higher frequency than in the normal population, can amplify both symptoms of pain and fatigue and should be appropriately addressed when present.[12].

3.4. Respiratory dysfunction

Clinically significant respiratory insufficiency occurs in less that 1% of patients with FSHD [13]. Nevertheless, clinicians need to remain vigilant as compensated respiratory insufficiency may be unmasked by medical stressors. It is recommended that patients with moderate to severe FSHD, defined as those with proximal lower extremity weakness, be routinely screened for symptoms of hypoventilation. Measurement of supine and sitting forced vital capacity (FVC) is recommended for any patient with FSHD prior to any surgical procedure requiring general anesthesia or conscious sedation. Yearly FVC is recommended for all patients who are (1) wheelchair bound, (2) have pelvic girdle weakness and superimposed pulmonary disease, and (3) have moderate to severe kyphoscoliosis or lumbar hyperlordosis or chest wall deformities such as pectus excavatum. FVC measurements in patients with FSHD should always be performed with a full facial mask rather than a mouthpiece to avoid measurement of falsely low values from air leakage due to weakness of lip closure. Signs and symptoms of nighttime hypoventilation or a drop of FVC to less than 50% of pre-

dicted value warrants the consideration of non-invasive ventilatory support devices such as BiPAP.

3.5. Surgical scapular fixation

A recent Cochrane review concluded that surgical scapular fixation is effective in improving shoulder function in FSHD [14]. This is confirmed in reviews of more recent case series [15–18]. Scapulodesis, the fixation of the scapula with screws, wires or plates with bone grafting (arthrodesis), is the preferred surgical procedure and should be performed by an experienced surgeon. Patients considering surgery should have reasonable residual upper arm strength and should weigh the potential benefits against the possible complications of the procedure. Reduction of FVC appears to be minimal and of uncertain clinical consequence. Potential surgical or post surgical complications include breaks in the wire with consequent loss of the functional gain and, rarely, brachial plexus injuries [19]. The potential gain in range of motion from surgical fixation can be tested at the bedside by manual fixation of the scapula. The proper indications for the procedure in FSHD have not been prospectively determined.

3.6. Cardiac dysfunction

Cardiac involvement in FSHD, manifested as a predilection to atrial arrhythmias, is seen in about 5% of patients without other cardiac risk factors, few of whom require treatment [20]. The most common ECG finding is an increased frequency of RBBB which is mostly of no clinical importance. There is insufficient data to warrant routine ECG screening on all patients with FSHD. The presence of clinically significant cardiac dysfunction should lead to the consideration of other diagnoses.

3.7. Pregnancy in FSHD

Pregnancy outcomes in FSHD are generally good although two case series have conflicting reports about an increased incidence of operative deliveries and preterm births [21,22]. Some of the differences may be due to differences in obstetrical practice in the countries where the studies were conducted. Resolving this discrepancy necessitates further prospective studies. In addition, about 25% of pregnant women with FSHD report subjective, persistent worsening of motor function related to pregnancy which is commensurate with what is observed in other neuromuscular disorders. Based on available information, it is recommended that pregnant women with FSHD be followed by high risk obstetricians and that delivery occurs in a center that can provide comprehensive perinatal care. Additionally, it is recommended that pregnant women with FSHD and reduced lung function have serial monitoring of their FVC during the course of their pregnancy.

3.8. Hearing loss

Subclinical hearing loss in FSHD occurs in up to 75% of affected individuals but the frequency is not different from a control population [23]. Infantile-onset patients with FSHD are at risk to have the most profound hearing loss that if not detected can lead to delayed language development and even the false perception that the child is cognitively delayed. Consequently, hearing should be tested routinely in infants and preschool children diagnosed with FSHD. Older-aged children diagnosed with FSHD do not require an audiogram if hearing is routinely tested in school and if they demonstrate normal language development. Adults diagnosed with FSHD do not require audiograms unless they are symptomatic.

3.9. Retinal vascular disease

Retinal vasculopathy is relatively frequent in FSHD but rarely leads to a symptomatic exudative retinopathy (Coat's syndrome) which can, in turn, result in significant visual loss [24,25]. Yet, the retinopathy is eminently treatable with laser treatment of pathologically dilated retinal vessels. It is therefore recommended that all patients with FSHD be referred to an Ophthalmologist for a dilated indirect ophthalmoscopy. If no significant retinal vascular disease is detected in adult patients, no further follow-up is warranted unless the patients develop visual symptoms. In early onset disease, where the incidence of Coat's syndrome is more common, yearly follow-up indirect ophthalmoscopy is recommended until the child is deemed mature enough to report visual symptoms.

4. Clinical trials readiness

Recent developments in our understanding of the pathophysiology of FSHD may soon translate to identification of rational therapeutic targets. It is critical therefore that the components needed to efficiently conduct clinical trials in FSHD be in place. Two of the critical components of trial readiness include validated outcome measures and access to patients.

4.1. Outcome measures

Traditional outcome measures in muscular dystrophy trials have typically consisted primarily of direct measurements of strength either by manual or quantitative muscle testing methods and timed functional tests. The validity, reliability and sensitivity of strength measurements and functional tests have been established in previous natural history study as well as FSHD clinical trials [6,26–29]. Whereas such measures may still be useful in early phase trials or as secondary outcome measures, drug regulatory agencies such as the FDA in the United States and EMA in the European Union now favor the use of more clinically meaningful and preferably patient-reported instruments as primary outcome measures. There are several disease severity rating scales based on functional abilities with established reliability; however, their sensitivity to change and true relevance to FSHD patients has not been established. Other instruments, such as the Individualized Neuromuscular Quality of Life questionnaire (INQoL) may have utility in FSHD; however, the initial development and testing of this instrument utilized both FSHD and non-FSHD neuromuscular populations. Ideally, future FSHD patient-reported outcome measures should represent all of the unique issues and symptoms important to FSHD patients while excluding issues that are not relevant to this population. Disease-specific FSHD quality of life instruments are well suited to accomplish this task [30,31]. Composite instruments comprised of objective and subjective measures may also have utility. There is therefore, a need to develop and validate clinically meaningful outcome measures in FSHD that are either patient-reported or administered by clinicians.

A common surrogate measure of change in muscle function in myopathies has been measurement of in muscle mass. This has been done using dual energy X-ray absorptiometry (DEXA) and MRI, both of which were used as surrogate outcome measures in previous FSHD clinical trials [28,29]. Although both DEXA and MRI are reliable, whether a change in muscle mass is a good reflection of a change in the underlying disease state remains unknown. Imaging modalities such as MRI can also be used to look at changes in skeletal muscle signal or function through MR spectroscopy. Another emerging muscle imaging modality is muscle ultrasound [32].Other disease-specific biomarkers will have to await further

elucidation of pathophysiologic cascade responsible for muscle weakness and atrophy in FSHD.

4.2. Registries

Difficulty with patient recruitment has been the greatest obstacle in the conduct of successful clinical trials in the last decade. Patient registries which facilitate access to patients interested in participating in clinical trials, therefore, represent an important aspect of clinical trial readiness. The National Registry for Myotonic Dystrophy and FSHD Patients in the United States represents the most well-established of such registries. Additionally, there is a large Italian National Registry (www.fshd.it) as well as other smaller informal FSHD registries that exist in other countries or are in the development phase. FSHD Europe (http://www.fshd-europe.org/) is planning to establish a European registry. Developing a global registry, following the model of TREAT NMD that combines an agreed upon minimal dataset from all existing registries, would help further facilitate the conduct of future trials in FSHD.

4.3. Future plans

Workshop participants identified a number of issues that required further study and working groups were formed to address selected issues. Prominent issues to be addressed by the working groups include: Accessibility to DNA testing and development of best practice parameters to harmonize gene testing across diagnostic labs; a more comprehensive assessment of pain, pregnancy and delivery, and orthopedic interventions in FSHD. From a trial readiness perspective, working groups were formed to address the development of core registry data sets and the development of clinical and surrogate outcome measures relevant to FSHD. Workshop participants agreed to tentatively reconvene in approximately 1 year to reexamine outstanding issues.

4.4. Feedback regarding FSHD standards of care

The meeting organizers would like to solicit feedback regarding the proposed FSHD standards of care. Comments should be addressed to lead author Rabi Tawil at the following Field Center link (http://www.urmc.rochester.edu/fields-center/contact.cfm).

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