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Recommendations

Recommendations for the management of facioscapulohumeral muscular dystrophy in 2011

Recommandations pour la prise en charge de la dystrophie musculaire facioscapulohumérale en 2011

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ABSTRACT

Facioscapulohumeral muscular dystrophy (FSHD) is a neuromuscular disease, characterized by an autosomal dominant mode of inheritance, facial involvement, and selectivity and asymmetry of muscle involvement. In general, FSHD typically presents before age 20 years. Usually, FSHD muscle involvement starts in the face and then progresses to the shoulder girdle, the humeral muscles and the abdominal muscles, and then the anterolateral compartment of the leg. Disease severity is highly variable and progression is very slow. About 20% of FSHD patients become wheelchair-bound. Lifespan is not shortened. The diagnosis of FSHD is based on a genetic test by which a deletion of 3.3 kb DNA repeats (named D4Z4 and mapping to the subtelomeric region of chromosome 4q35) is identified. The progressive pattern of FSHD requires that the severity of symptoms as well as their physical, social and psychological impact be evaluated on a regular basis. A yearly assessment is recommended. Multidisciplinary management of FSHD — consisting of a combination of genetic counselling, functional assessment, an assessment by a physical therapist, prescription of symptomatic therapies and prevention of known complications of this disease — is required. Prescription of physical therapy sessions and orthopedic appliances are to be adapted to the patient's deficiencies and contractures.

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RÉSUMÉ

La dystrophie musculaire facioscapulohumérale (DMFSH) est une affection musculaire d'hérédité autosomique dominante caractérisée par l'atteinte faciale, la sélectivité et l'asymétrie de l'atteinte musculaire. L'âge de début est généralement inférieur à 20 ans. L'atteinte musculaire débute habituellement par la face, puis progresse à la ceinture scapulaire, aux muscles huméraux, puis évolue vers les muscles abdominaux et la loge antéroexterne de la jambe. La gravité de la maladie est très variable. L'évolution est lentement progressive. Environ 20 % des patients requièrent l'utilisation d'un fauteuil roulant. L'espérance de vie n'est pas écourtée. La DMFSH est diagnostiquée par un test génétique qui identifie la délétion de copies d'un motif répété de l'ADN de 3,3 kb, D4Z4, située dans la région subtélomérique du chromosome 4q35. Le caractère évolutif de la DMFSH nécessite une évaluation régulière de l'intensité des troubles observés et de leurs répercussions physiques, sociales et psychologiques. Un bilan annuel de suivi est recommandé. La prise en charge de la DMFSH doit être multidisciplinaire, associant le conseil génétique, le bilan fonctionnel, la prescription de traitements symptomatiques et la prévention des complications connues de cette maladie. La prescription des séances de kinésithérapie et d'appareillage sont à adapter en fonction des déficiences et des rétractions. Un bilan ergothérapique peut être proposé.

1. Introduction

The national plan on rare diseases for 2005–2008 developed by the French ministry of Health led the Comité National Consultatif de Labellisation (NCCL; National Consultative Committee for Certification), with the support of the French Muscular Dystrophy Association (AFM), was formed to designate 12 reference centers for neuromuscular diseases. The aim of these centers is, in particular, to set up good professional practices concerning each of these diseases, in cooperation with national and international teams working in the same field (ministry note DHOS/DGS04/SDSD # 2006-479 of 9 November 2006 pertaining to a call for projects with university teaching hospitals [CHU] for the certification of "Centers of reference for a rare disease or a group of rare diseases").

As part of a series of clinical research one-day meetings on neuromuscular diseases organized by the AFM, two physicians belonging to these "Centers of reference for neuromuscular diseases" were designated to coordinate the development of recommendations following a thematic workshop.

For each of the main neuromuscular diseases, a workshop was arranged at which the coordinating physicians proposed to paramedical and medical specialists a first version of their recommendations, based on a systematic literature review of the subject. Comments and discussions resulted in a new wording, incorporating the experience of the specialists in neuromuscular diseases. Following these one-day clinical research meetings, this version was then revised by the coordinators according to the feedback provided by the various participants at the workshop to whom this version had been submitted during the first round; and a final version of the recommendations was thus issued.

2. Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy in terms of incidence after dystrophinopathies and myotonic muscular dystrophies. The estimated incidence of FSHD is one case in 20,000 people (Lunt and Harper, 1991; Padberg, 1982). In a more recent study, its estimated incidence was higher, at one case per 15,000 people (Flanigan et al., 2001). Its prevalence is between 2.2 and 66 cases per 100,000 people with wide variations depending on the populations studied. According to the majority of authors, a mean prevalence of one case per 20,000 people is acceptable (Padberg et al., 1995b); based on this mean prevalence, the total number of people affected in France would be estimated at 3,000 cases. Traditionally, Landouzy and Dejerine are considered as the first to identify this disease. FSHD is considered as one of the three major varieties of primary muscular disease (Landouzy and Déjerine, 1884). Muscular changes in FSHD are characterized by their selectivity and asymmetry. The first symptoms occur at a variable age of onset, generally during the second decade of life, with the extremes, occasional instances of very early childhood forms and of middle-age onset forms, i.e., in subjects over 50 years of age.

3. Clinical presentation

In the majority of cases, changes to the facial muscles are characteristic and readily recognizable. The patient shows a lack of facial expression, features of indifference, with little deep wrinkles and lines as the result of involvement of the facial muscles (zygomaticus, orbicularis oculi, and orbicularis oris muscles). The masseter temporalis, and extraocular muscles are typically spared. Involvement of the orbicularis oculi muscle occurs early and results in incomplete closure of

the eyes during sleep ("the patient sleeps with his/her eyes open"). Lower facial weakness is usually more pronounced than weakness of eye closure, with an inability to bury the lashes or to purse the lips. The smile may take on a transverse or asymmetrical nature, which may be accompanied by a characteristic dimpling at the corners of the month. It is important to note that facial involvement is sometimes very subtle and can be totally absent. This facial muscular weakness is poorly progressive and is rarely the reason for the patient's complaints. Conversely, it can be a cause of discomfort (repeated conjunctivitis, social embarrassment as a result of the lack of facial expression, inability to drink with a straw or to play a woodwind musical instrument). Concomitant swallowing disorders almost never exist (frequency of less than 2%).

On inspection, the shoulders are rounded, forward sloping and the clavicles are straight. The upper limbs are often affected with impairment in lifting the arms overhead, as a result of weakness of the fixator muscles of the scapula, while, in contrast, the abductor muscles (deltoid) of the shoulder are spared for a very long time. Scapula winging (*scapulum alatum*) ("winged scapula") is frequently found, reflecting weakness of the serratus anterior muscle.

Because of preferential weakness of the lower trapezius, the scapulae often jut upwards ("trapezius hump" sign).

The pectoral muscles may be atrophic and an axillary crease is often evident. Arm muscles are often affected (biceps and triceps brachialis muscles) in contrast to a normal trophicity of the forearm muscles giving the arm a "Popeye" appearance. A notable exception is brachioradialis atrophy. Occasionally during progression of the most severe forms, the distal wrist extensors may become involved and a "wrist drop" may be observed.

Abdominal muscles are often affected at some point in the progression of the disease, with this tending to occur at a later stage. If it is present at the first examination, this deficiency can be an important clue for the diagnosis. Variable from one subject to another, it often results in protrusion of the abdomen. Involvement of the subumbilical muscles, even when mild, can be revealed by Beevor's sign (during antiflexion of the head with the subject supine, upward movement of the navel occurs). This sign is found in 90% of patients with FSHD (Awerbuch et al., 1990; Shahrizaila and Wills, 2005). Paravertebral muscles are sometimes deficient and this can contribute to worsening scoliosis which, generally, is moderate or gives rise to a lumbar hyperlordosis. Recently an atypical FSHD phenotype with isolated camptocormia has been reported (Jordan et al., 2010).A large number of patients develop a weakness in their lower limbs. This deficiency is often of early onset, affects muscles of the anterior compartment of the lower leg (tibialis anterior muscle, peroneus lateralus muscles). The patient walks with a foot drop gait during walking and climbing stairs, thus easily falling. At a more advanced stage, proximal involvement also plays an important part in generating falls, when associated with distal deficiency (Horlings et al., 2009). Upon examination, when the gluteal muscles are affected, this produces a forward tilt of the pelvis, thus resulting in lumbar hyperlordosis and a waddling gait.

Sensory disturbances have been reported in FSHD (Padberg et al., 1995b). Hearing loss, very often bilateral, can be evidenced on an audiogram. It is dominant for high pitch frequencies. Its severity is variable and progresses with age (Brouwer et al., 1995). The origin of this hearing loss seems to be a cochlear anomaly in view of the normal aspect of auditory evoked potential (Voit et al., 1986). Retinal disorders are observed in 75% of patients. This involves microaneurysms, occlusion of small arteries or telangiectasia (Fitzsimons et al., 1987; Padberg et al., 1995a). However, except when severe forms of FSHD occur in children, generally, such disorders do not produce any clinical symptoms. To date, the causal mechanism is unknown.

Cardiac disorders have been reported in patients with FSHD (Laforet et al., 1998; Stevenson et al., 1990). It is almost certain that an asymptomatic right bundle branch block occurs with an increased frequency, compared to the general population, in about one-third of cases,. Other abnormalities have been described, including rhythm or conduction defects, or even ventricular dysfunction; however, and due to their rarity, these isolated cases are difficult to interpret and raise the question of their causal relationship with muscular dystrophy.

Less than 20% of patients may present with chronic respiratory insufficiency related to a combination of factors: respiratory muscular weakness, and chest deformities due to scoliosis and/or hyperlordosis. Initiation of assisted ventilation may be necessary in about 3% of patients (Wohlgemuth et al., 2004). Sleep disorders, associated with severity of the disease, in particular sleep apnea syndrome, have been reported (Della Marca et al., 2007, 2009).

4. Diagnosis

In the vast majority of cases, the reason for the initial visit is difficulty in lifting the upper limb(s), protrusion of the scapula, or difficulty in walking. Symptoms progress slowly, over several years. Facial involvement, generally present for a very long time, is rarely a source of concern. Sometimes, the mode of onset is acute or sub-acute, suggesting a paralysis of a limb or segment of a limb, sometimes with a concomitant painful component. Pain itself can also be the reason for the first visit (Bushby et al., 1998). When an abnormal aspect of the scapula is observed, the presentation can then be extremely misleading with long thoracic neuropathy or accessory neuropathy. The diagnosis will be suggested based on minor deficiency signs and on paraclinical evidence, but sometimes, only disease progression makes it possible to provide a conclusive diagnosis.

The childhood form accounts for 5% of cases of FSHD. It is more common in sporadic forms (Padberg et al., 1995a, 1995b). It is characterized by the onset of a facial muscle deficit before the age of 5 years, a shoulder girdle deficiency before the age of 10 years and a more rapid and more disabling, although variable, progression. Facial involvement can occur during the first year of life, sometimes leading to a facial diplegia. Diagnostic certainty is often challenged by a constellation of puzzling clinical symptoms: hypotonia, delayed learning acquisition, sensory disorders (in particular hearing), epilepsy, hyperlordosis, and gait disorders (Funakoshi et al., 1998).

5. Diagnostic approach

5.1. *Genetic anomaly*

The genetic anomaly associated with FSHD is a contraction of the 3.3 kb macrosatellite repeat called D4Z4 in the subtelomeric region of the long arm of chromosome 4 (4q35). The number of repeats is greater than ten in the general population while it ranges from one to ten on one of the two 4q35 alleles in patients with FSHD (Fig. 1) (Wijmenga et al., 1992, 1993). Since the discovery of this genetic anomaly, a major effort has been made to clone the putative gene involved in FSHD. Its mapping is made difficult by frequent recombinations and translocations between the sub-telomeric locus of chromosome 4q35 containing D4Z4 and the chromosome 10q26 sub-telomeric region which presents a strong sequence homology. This results in an appreciable discrepancy between physical and genetic distance estimated using different molecular and cytogenetic techniques (Bakker et al., 1995; Deidda et al., 1995; Lemmers et al., 1998; van der Maarel et al., 1999).

Currently, it is accepted that this contraction is pathogenic only against certain 'permissive' chromosomal backgrounds. Human 4qter and 10qter share a high degree of similarity, including the D4Z4 repeat array; however, contractions affecting the 10qter repeat are nonpathogenic. Van Geel et al. (van Geel et al., 2002) detected a polymorphic segment of 10 kb directly distal to D4Z4, which they called alleles 4qA and 4qB. Although the 2 alleles are equally common in the general population, FSHD is associated solely with the 4qA allele (Lemmers et al., 2002). Contractions of D4Z4 on 4qB subtelomeres do not cause FSHD (Lemmers et al., 2004). The 2 allelic variants of 4q, 4qA and 4qB, exist in the region distal to D4Z4. Thus, in addition to a contraction of D4Z4, additional cis-acting elements on 4qA may be required for the development of FSHD. Genetic follow-up studies unveiled consistent polymorphisms in the FSHD locus resulting in the recognition of at least 17 genetic variants of distal 4q (Lemmers et al., 2010b). Contractions in the common variant 4A161 cause FSHD, while contractions in many other variants such as the common 4B163 do not cause FSHD. Thus it appears that chromosome 4A161-specific sequence variants are causally related to FSHD. Therefore, the 4A161 chromosome is permissive for disease (Lemmers et al., 2007).

One of the currently proposed hypotheses is that DUX4 is the gene involved in FSHD (Gabriels et al., 1999; Padberg and van Engelen, 2009). FSHD patients carry specific single nucleotide polymorphisms in the chromosomal region distal to the last D4Z4 repeat. This FSHD-predisposing configuration creates a canonical polyadenylation signal for transcripts derived from DUX4, a double homeobox gene of unknown function that straddles the last repeat unit and the adjacent sequence. Transfection studies revealed that DUX4 transcripts are efficiently polyadenylated and are more stable (Snider et al., 2010) when expressed from permissive chromosomes. These findings suggest that FSHD arises through a toxic gain of function attributable to the stabilized distal DUX4 transcript (Lemmers et al., 2010a).

An alternative hypothesis is the effect of the telomere position. This involves a regulatory effect of sequences upstream of a gene on the transcription rate of the gene in question, sometimes distant by several dozens of kilobases (kb). In some cases, a "gradient" effect can be observed: the nearer the mutation is located to the gene, the more severe is its phenotypical effect. In FSHD, contraction of D4Z4 can lead to a variation in the expression of one or more genes at a distance. These genes can be non-muscle genes activated or overexpressed by deletion in the muscle promoter region of the gene, as, for example, FRG1 overexpression (Gabellini et al., 2006). The presence of forms, which are not related to

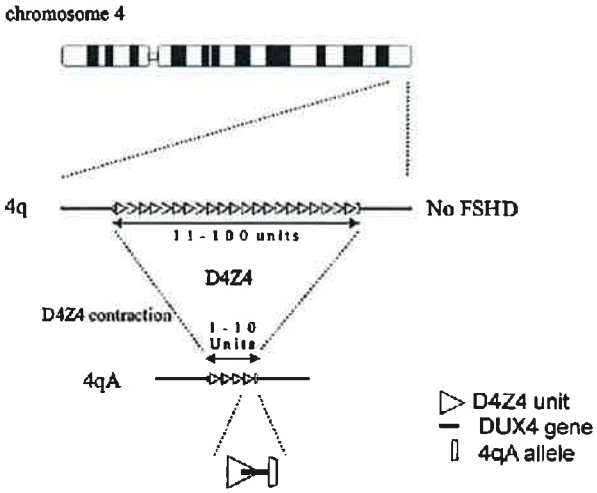

Fig. 1 – The genetic anomaly associated with facioscapulohumeral muscular dystrophy (FSHD) is a contraction of the 3.3 kb macrosatellite repeat allele D4Z4 in the subtelomeric region of 4q35. The number of repeats is greater than 10 in the general population while it ranges from 1 to 10 on one of the two 4q35 alleles in patients with FSHD. This contraction is pathogenic only if it is associated with the 4qA allele. This FSHD-predisposing configuration creates a canonical polyadenylation signal for transcripts derived from DUX4 that straddles the last repeat unit and the adjacent sequence. Then DUX4 transcripts are efficiently polyadenylated and are more stable. These findings suggest that FSHD arises through a toxic gain of function attributable to the stabilized distal DUX4 transcript.

L'anomalie génétique associée à la dystrophie musculaire facioscapulohumérale (DMFSH) est une délétion de copies d'un motif répété de l'ADN de 3,3 kb, D4Z4, situé dans la région subtélomérique du chromosome 4q35. Dans la population générale, le motif est répété plus de dix fois tandis chez les patients présentant une DMFSH, un des deux allèles 4q35 ne présente qu'une à dix répétitions. Cette contraction est pathogénique uniquement en association avec un allèle 4qA. Cette configuration prédisposant à la DMFSH crée un signal de polyadénylation canonicale pour les transcrits dérivés de DUX4 à cheval sur le dernier motif répété et la séquence adjacente. Ensuite, les transcrits DUX4 subissent une polyadénylation efficace et deviennent plus stables. Ces constatations suggèrent que la DMFSH est le résultat d'un gain fonctionnel toxique attribuable à une stabilisation distale du transcrit DUX4.

chromosome 4 suggests that more than one mechanism may be responsible for FSHD (de Greef et al., 2008).

5.2. *Molecular diagnosis*

Currently, molecular diagnosis of FSHD is based on the Southern blotting technique, which, at least in the simplest cases, makes it possible to evaluate the number of D4Z4 repeat units on each of the two allelic variants of chromosome 4q and to differentiate chromosomes 4 and 10 (Fig. 2). This technique is based on double digestion of genomic DNA by EcoRI and BlnI restriction enzymes, (Lemmers et al., 2001; van der Maarel et al., 1999), linear or pulsed-field gel electrophoresis, and hybridization with a p13E-11 probe located in the adjacent region centromeric to D4Z4. In atypical or "formes frustes" FSHD, it is recommended to determine the distal variant (4qA or 4qB), a procedure not performed in routine practice (Lemmers et al., 2002). This method makes it possible to establish a diagnosis with close to 98% reliability; however, it has major limitations. Primarily, the Southern blotting technique has major limitations for diagnosing noncanonical variants such as somatic mosaics, locus rearrangements and extensive deletions involving the p13E-11 probe region. Yet, these genomic variants are relatively common in patients. Furthermore, the Southern blotting technique has lengthy handling time, requires use of radioactive materials and laboratory expertise. For the diagnosis of FSHD, it is only available in France in two molecular biology laboratories. Since the above methodology is labor- and time-intensive, novel techniques have been developed to facilitate the genetic diagnosis of FSHD, such as long range PCR. 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 (Nguyen et al., 2011).

Mosaicism for the D4Z4 contraction is a frequent observation in FSHD. Pulsed field gel electrophoresis (PFGE) was highly instrumental in our understanding of the frequency and mechanism of mosaicism in FSHD. Mitotic D4Z4 contractions can be encountered in 40% of *de novo* families. A relationship was established between severity and a combination of residual repeat size and proportion of affected cells. There is a prominent gender effect in mosaic cases: whereas mosaic males are mostly affected, mosaic females with an equal complement of affected cells are more often asymptomatic carriers of the disease allele.

5.3. *Progression*

Traditionally, involvement of facial muscles shows little or no progression. Involvement of limb muscles varies to a major extent from one subject to another, even within a given family, with the deficiency progressing in a descending fashion. Several studies suggest that men may be more symptomatic than women, with all other parameters being equivalent (in particular the size of the residual D4Z4 repeats). To date, this difference has not been explained.

Early involvement of the muscles of the anterior compartment of the lower leg is an exception to this rule. Most often, symptom progression is slow and insidious. However, many patients report long periods of stability following spurts of rapid deterioration, often preceded by pain in the affected limb. Studies of the natural history of FSHD have not confirmed this process, which has often been reported (though anecdotally) (The FSH-DY Group, 1997); Stubgen, 2010 #205}. There may also be an inverse relationship between age of

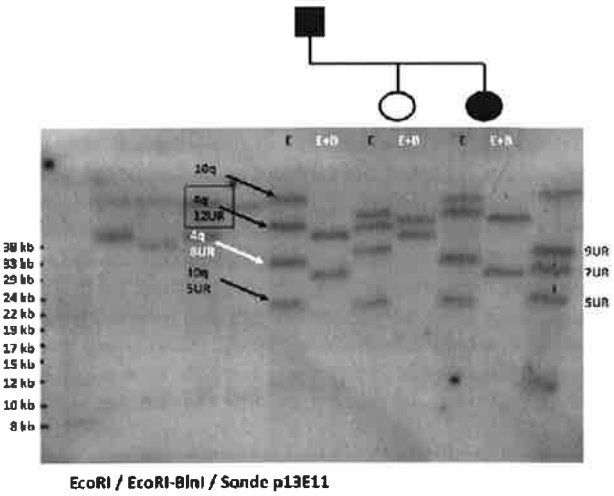

Fig. 2 – Currently, molecular diagnosis of facioscapulohumeral muscular dystrophy (FSHD) is based on the Southern blotting technique which is based on double digestion of genomic DNA by EcoRI (E) and BlnI (B) restriction enzymes, linear or pulsed-field gel electrophoresis, and hybridization with a p13E-11 probe located in the adjacent region centromeric to D4Z4. One of the daughters of a FSHD patient illustrated here inherited the abnormal 8 UR allele from his father (indicated by white arrow). For each individual, the first lane contains the EcoRI digest, and the second lane contains the EcoRI/BlnI double digest. Fragment sizes of the marker lanes are indicated at the left of the gel in kilobases (kb). A pathologic control with alleles of known size is indicated at right. By sample digestion (E), four fragments were observed corresponding to two fragments from 4q and two fragments from 10q. In double digestion (E + B) only 4q fragments were visible.

Actuellement, le diagnostic de la dystrophie musculaire facioscapulohumérale (DMFSH) se fait par une technique de Southern blot grâce à une digestion double de l'ADN génomique par les enzymes de restriction EcoRI et BlnI (B), une électrophorèse linéaire ou sur gel à champ pulsé et une hybridation par une sonde p13E-11 située dans la région centromérique près de D4ZA. Une des filles d'un patient atteint de DMFSH présenté ici a hérité d'un allèle anormal 8UR (flèche blanche). Pour chaque individu, les première et deuxième pistes correspondent respectivement aux produits de digestion simples (EcoRI) et doubles (EcoRI/BlnI). Les tailles des fragments des pistes témoin sont indiquées à gauche en kilobases (kb). Le témoin pathologique ayant des allèles d'une taille connue est indiqué à droite. Par digestion d'un échantillon (E) on obtient quatre fragments correspondant aux deux fragments de 4q et deux fragments de 10q. Seuls les fragments 4q sont visibles sur la double digestion (EcoRI/BlnI).

onset and clinical severity of the disorder (Tawil et al., 1996; Zatz et al., 1995). Functional impact is generally compatible with subnormal activity up to the age of about 30–40 years. Since cardiac and respiratory complications are extremely rare in FSHD, lifespan in cases of this muscular disorder is comparable to that of the general population except for early onset forms in children or a few very progressive forms in adults. As a result of these characteristics, FSHD has earned a false reputation for being a benign condition insofar as the functional prognosis is very uncertain. Thus, in 15–20% of cases, depending on the report, patients eventually require use of a wheelchair (Padberg et al., 1991). Even though, currently, no accurate estimate is available for asymptomatic forms, their high incidence should be emphasized.

6. Management recommendations

Management of FSHD should involve multidisciplinary care, including functional assessment, symptomatic therapies and prevention of known complications of this disease such as pain, fatigue, foot drop and cardiac dysfunction. The progressive pattern of FSHD requires that the severity of the disorders observed, as well as their physical, social, and psychological impact, be assessed on a regular basis. It is recommended to perform a yearly monitoring assessment in a centre of reference or in a centre experienced in neurological muscular diseases. However, some "formes frustes" or poorly progressive forms may only require follow-up every two years. The assessment should include a neurological, functional, respiratory and cardiac evaluation. Pain should be systematically evaluated. Multidisciplinary management should be conducted by the referring neurologist. A major role should be given to the clinical interview to informally understand the patient's psychological condition and possibly also that of his/her family. Whenever possible, it should provide information on the status of advances and of the different clinical trials which are ongoing or under development. It should be send, ideally within two weeks, a synthetic report on the patient's assessment to healthcare professionals who are managing him/her, produced in a simple and understandable manner, enabling a group multidisciplinary exchange of information.

6.1. *Genetic counseling*

Genetic counselling is essential for the management of patients with FSHD. Indeed, this disease shows autosomal-dominant inheritance. Therefore, traditionally, an affected patient has a 50% risk of transmitting it to his/her offspring. However, many components related either to the disease itself or to diagnostic difficulties can complicate genetic counselling, firstly, due to both incomplete penetrance and variable expressivity. Penetrance, of about 80%, is higher in men (95%) than in women (70%). Asymptomatic or poorly symptomatic forms of the disease seem to be concentrated in some particular families, while more severe forms affect other families (Tonini et al., 2004). Variable expressivity is observed between families but also within a given family; variable expressivity is also observed between genders, with clinical severity being more serious in men than in women. Currently, in genetic counselling, it is not possible to predict whether an at-risk subject will develop the disease and to what degree of severity. Second, FSHD occurs sporadically in 10 to 30% of cases. Isolated cases in families with no previous history are due either to a penetrance default, or to a *de novo* mutation in the index case, or in about 40% of cases to the existence of somatic mosaicism in the index case or in one of his/her asymptomatic parents (van der Maarel et al., 2000). In genetic counselling, the frequency of this somatic mosaicism should be taken into account when evaluating the risk of transmission. Third, although a rough correlation exists between the size of the contracted D4Z4 array on chromosome 4 and clinical severity, it is not possible to determine a genotype-phenotype correlation on an individual scale. Indeed, for a given size of allele, high clinical variability is observed, in particular, within the border area between normal alleles (> 10 repeats) and pathological ones (< 10 repeats), i.e., between eight and 12 repeats. Indeed, some carriers of alleles with 10–12 repeats present with the typical and familial form of FSHD, whereas carriers of alleles with fewer than 10 repeats remain totally asymptomatic. Therefore, genetic counseling is especially difficult in subjects carrying alleles in the "grey zone" (eight to ten repeats).

Lastly, molecular investigation remains difficult even when using current methods; furthermore, it is often incomplete and does not always make it possible to characterize a genetic defect in a patient. When the molecular diagnosis is uncertain, genetic counselling is difficult; it is impossible, in particular, to offer predictive genetic testing for at risk, asymptomatic related subjects. Indeed, due to incomplete penetrance and variable expressivity with possible late age of onset, prediction is very limited in an asymptomatic carrier subject and uncertainties still remain with genetic testing (Tawil et al., 2010).

Therefore, testing should be associated with accurate information as part of multidisciplinary management. When an at-risk child, under the age of 18, is involved, genetic counselling should be discussed on a case-by-case basis after the age of 10 years and where there is an unquestionable benefit to knowing the diagnosis: for example, if the child's occupational orientation is involved.

Prenatal diagnosis of FSHD is also possible when the molecular defect has been well identified beforehand in the carrier parent. However, uncertainties of clinical expression of the disease are more important in the context of prenatal diagnosis when a decision on a therapeutic abortion is involved. It is difficult for couples to manage these uncertainties; therefore, accurate information and listening to couples are essential to best assist them in their decision-making. Very often, it is necessary to have the most robust family genetic study possible before any prenatal diagnosis is established, to characterize with certainty the molecular defect responsible for the disease in a particular family.

6.2. *Functional workup*

A functional workup should be carried out by a physical rehabilitation specialist physician, if possible with the aid of a physiotherapist. The interview should focus on functional abilities: self-sufficiency indicators, orthopaedic appliances, walking distance and number of stairs, which the patient can climb.

Examination should consist of the following: measurement of joint amplitude, manual measurement of muscle strength and functional score (Walton score, Brooke score and/or MFM score). Prescription of physical therapy sessions is to be adapted according to deficiencies and contractures. Two weekly sessions are usually sufficient; they usually combine fight against contractures, passive mobilization or active-assist mobilization and analgesic massages; balneotherapy can be beneficial. A letter for the referring physiotherapist will help to better adapt the type of management. Prescription of orthoses (for example foot drop brace, lumbar support belt) is guided by the functional evaluation. An ergotherapy assessment can be proposed to evaluate accessibility of the patient's home and suggest moving, home adaptation and/or prescribing technical aids in agreement with the physical rehabilitation physician and according to the availability of the centre.

6.3. *Psychological condition*

Assessment of psychological condition is desirable during the multidisciplinary assessment; more regular psychological assistance can be beneficial and should be considered in principal.

6.4. *Respiratory evaluation*

Respiratory evaluation systematically screens for symptoms and signs related to potential respiratory insufficiency: signs of dyssomnia, dyspnoea, or orthopnea. Respiratory functional tests with simple spirometry should be performed (measurement of VC, the VC/theoretical VC ratio), measurement of maximum inspiratory and expiratory pressures (PiMax, PeMax) would give further useful information, however not systematically performed. Measurement of blood gases is optional and rarely necessary. When dyssomnia is observed, nocturnal respiratory disorders should ideally be studied by polysomnography. However, its complexity and lack of availability are such that nocturnal oximetry is often preferred because it is easier to perform.

6.5. *Cardiac evaluation*

Cardiac evaluation is to screen for functional signs during the interview. It should include measurement of cardiac parameters (heart rate and BP), and a systematic ECG. Initially, echocardiography and 24-hour ECG monitoring are usually proposed. No consensus exists on follow-up procedures. An ECG can be proposed at the multidisciplinary assessment, with a more thorough assessment when clinical symptoms and/or electrocardiographic abnormalities are observed.

6.6. *Sensory assessment*

A sensory assessment is performed when visual or auditory presenting symptoms are observed: an audiogram and/or fundoscopy at the slightest doubt (this test should be systematically performed in infantile forms of FSHD). Fluorescence angiography can be proposed if fundoscopy demonstrates retinal damage.

6.7. *Laboratory test assessment*

A laboratory test assessment is not essential at monitoring visits, CPK values do not necessarily reflect progressiveness of the disease. Generally, a visit with a geneticist can be proposed to the patient to organize a test, if applicable, and to propose to see any relatives requiring an opinion.

6.8. *Pain*

Neuromuscular pain is very common in FSHD. An unpublished investigation conducted by the AFM reported that 55% of patients complain about continued pain, with these results being recently confirmed by a team in Italy (Padua et al., 2009). Evaluation of pain should be performed systematically and, where necessary, be followed by prescription of an analgesic or a non-steroidal anti-inflammatory agent in the absence of contraindications. A depressive syndrome should systematically be sought, because it can enhance the patient's perception of pain thus justifying initiation of treatment with an antidepressant agent.

6.9. *Ophthalmological care*

A gel eye-drop can be prescribed upon request. 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 (Fitzsimons et al., 1987; Padberg et al., 1995a). The retinopathy is 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.

6.10. *Orthopaedic care*

Orthopaedic care: the usefulness of scapulopexia (or scapulothoracic arthrodesis) is highly debatable and currently is only rarely proposed. Indeed, no controlled prospective study has been conducted on this technique and the risks of perioperative (pre-and post-operative) complications are high (Mummery et al., 2003; Orrell et al., 2010). When proposed, it should be thoroughly discussed with the patient and the orthopedist and should be performed only after allowing a sufficient period of time for reflection. Since the result sought is usually a functional gain in lifting the arms, patients who present at the outset with a significant deficiency of the deltoid or triceps muscle (< 4/5 on the MCR score) should be excluded. Other types of orthopaedic surgery can be considered, always in exceptional cases and as a last resort after mature reflection by both the patient and the orthopaedic surgeon. Orthopaedic surgery can involve a tendon transposition procedure to correct a disabling steppage gate, for management of hyperlordosis or scoliosis (Tawil et al., 2008). Follow-up by a physician specializing in rehabilitation medicine is necessary for prescription of orthopaedic shoes, small orthopaedic appliances for the lower limbs and physiotherapy sessions.

6.11. *Anesthesia*

In light of current knowledge, if anesthesia is necessary, no specific anesthetic precaution need be taken in patients with FSHD; in particular, there is no increased risk of malignant hyperthermia. These precautions are identical to those taken for all patients with neuromuscular diseases. Generally vaccinations are not contraindicated.

6.12. *Pregnancy*

Most pregnancies in women with FSHD are generally uneventful. Two retrospective studies have reported opposite results concerning the delivery risks and those of premature birth (Ciafaloni et al., 2006; Rudnik et al., 1997). In addition, a worsening of muscular weakness after delivery was reported by 25% of patients. While waiting for prospective study results, pregnancy in patients with FSHD should be considered at risk. In addition, if respiratory insufficiency is present, serial measurements of the VC are indicated. (Tawil et al., 2010).

6.13. *Social management*

Adjustment of the patient's workstation or decision to declare the patient disabled should be studied on a case-by-case basis depending on the impairment. It is recommended to give the patient the name, address and phone number of patient associations (AFM and its local branches) but also contacts for patient groups, and web addresses for patient forums.

6.14. *Management of pediatric forms*

Children with early onset and serious forms require specialized multidisciplinary monitoring coordinated by a neuropaediatrician. The recommended frequency of monitoring visits is at least twice a year. Special attention should be paid to respiratory problems. An initial neurocognitive assessment should be performed followed by initiation of orthophonic, psychomotor, school and appropriate educational management. If epilepsy occurs, conventional anti-epileptic treatment should be initiated. Systematic auditory follow-up is necessary before early installation of hearing aids. An initial ophthalmological examination should be performed to look for possible retinal complications. Yearly follow-up indirect ophthalmoscopy is recommended until the child is deemed mature enough to report visual symptoms.

7. Conclusion

The management of FSHD requires that the severity of symptoms as well as their physical, social and psychological impact, be evaluated on a regular basis. A yearly assessment is recommended. Multidisciplinary management of FSHD consisting of a combination of genetic counselling, functional assessment, an assessment by a physical therapist, prescription of symptomatic therapies and prevention of complications of this disease is required. Prescription of physical therapy sessions and orthopedic appliances are to be adapted depending on the patient's deficiencies and contractures. One of the prominent issues to be addressed is the accessibility to DNA testing and development of best practice parameters to harmonize gene testing across diagnostic labs.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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