What’s in a name? The clinical features of facioscapulohumeral muscular dystrophy

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ABSTRACT
Facioscapulohumeral muscular dystrophy (FSHD) is an inherited and progressive muscle disorder. Although its name suggests otherwise, it comprises weakness of the facial, shoulder and upper arm muscles, and also of the trunk and leg muscles. Its severity and disease course vary greatly and mild or early FSHD can be difficult to recognise. Knowledge of its subtle signs and symptoms can lead directly to the correct diagnosis without diagnostic delay and without needing multiple diagnostic procedures. We give an overview of the signs and symptoms of FSHD in severe as well as in mild cases, to facilitate correct and instant recognition of this relatively common muscle disorder.

BACKGROUND
Facioscapulohumeral muscular dystrophy (FSHD) is—despite being relatively unknown to the general public and perhaps to general neurologists as well—the second most common autosomal dominant muscular dystrophy in adults (after myotonic dystrophy). Most cases are caused by a repeat contraction on chromosome 4. As its name suggests, it affects muscles of the face, shoulder and upper arm. However, many patients also have weakness of the trunk and leg muscles; sometimes these are even the most pronounced symptoms. Moreover, some patients have no or only very mild symptoms. This large variability in presenting symptoms and disease course can hinder its recognition, especially in its early stages.

The well-trained eye of a neurologist familiar with the signs and symptoms can frequently make the correct diagnosis of FSHD at the first encounter. However, the presentation can be subtle or easily attributed to other conditions.

For example, facial weakness—the telltale sign of FSHD—is often not recognised by the patient and consequently may not be explicitly reported. Additionally, facial weakness can be very mild in up to 25% of cases. As a result, we have seen patients with FSHD present with a myriad of symptoms that would not routinely trigger the search for an inherited muscle disorder: unilateral foot drop, shoulder complaints, frequent falling, back pain and fatigue. Screening these patients for the sometimes subtle other clinical signs of FSHD can lead to a swift diagnosis.

FSHD can be diagnosed by clinical observation and by DNA testing, and so its prompt recognition is important to prevent diagnostic delay and unnecessary (often invasive) diagnostic procedures. In this paper, we review the signs and symptoms of FSHD in severe as well as in mild cases, to facilitate the correct recognition of all aspects of this relatively common muscular dystrophy for the ‘non-trained’ eye.

SYMPTOMS AND SIGNS
FSHD is traditionally described as a slowly progressive muscular dystrophy that manifests at age 15–30 years. It starts with weakness of the facial and shoulder girdle muscles, followed by the ankle dorsiflexors and finally the proximal leg muscles. However, many patients do not fit this well-known classical FSHD phenotype. Infantile and late-onset cases are not uncommon and the severity and sequence of involvement of different muscle groups may vary.

The reported symptoms, therefore, differ from patient to patient. Because of the slow progression patients often do
not (spontaneously) report all of their symptoms or may attribute their symptoms to other more common disorders, for example, to frozen shoulder or shoulder tendon rupture. Additionally, although FSHD is an autosomal dominantly inherited disorder, a negative family history certainly does not rule it out. A high percentage of cases, perhaps 10%–30%, are caused by de novo mutations\(^3\)\(^4\) and FSHD families frequently include asymptomatic gene carriers.\(^5\)

Thus, FSHD is easily missed if a physician does not actively ask for and look for its signs and symptoms. Many patients with FSHD have multiple characteristic signs (figure 1), some of which strongly suggest FSHD, whereas other signs might more usually accompany other neuromuscular and orthopaedic disorders. Table 1 gives an overview of FSHD signs and symptoms in each body region.

**Face**

Asymmetrical facial muscle weakness is one of the first and most characteristic signs of FSHD (figure 2). The most commonly affected facial muscles are the circular muscles around the eyes (orbicularis oculi) and the mouth (orbicularis oris) and the zygomaticus major. Facial weakness can be very discreet in up to 25% of cases and sometimes may be visible only as asymmetrical pouting. Patients may be unaware of the facial muscle involvement and physicians may not notice it in up to 60% of cases.\(^6\) Patients rarely report facial weakness symptoms spontaneously, and so physicians should proactively ask about and look for it. For example, patients (and relatives) might be asked if they have noticed a change in facial expression. Some patients describe being perceived as arrogant, grumpy or tired, through their lack of facial expression. Orbicularis oculi weakness gives difficulty in closing the eyelids and so many patients sleep with their eyes partially open, and develop irritated conjunctiva upon awakening. In more advanced cases, a Bell’s phenomenon occurs on attempting to close the eyes (figure 2A). Less pronounced weakness can lead to a ‘signe de cils’—an inability to bury the eyelashes completely when attempting to close the eyes tightly (figure 2C).

Weakness of the orbicularis oris may lead to an asymmetrical mouth in the resting position (figure 2B). This becomes more visible when the patient attempts to prune the lips or blow the cheeks (figure 2D). Activities like whistling, blowing a balloon or drinking through a straw can become more difficult. Some patients lose mobility of the upper lip. Zygomaticus muscle weakness causes an inability to raise the corners of the mouth. On attempting to smile, the mouth moves horizontally, producing a so-called ‘transverse smile’, which may look like a grin. In severe cases, other facial muscles can be involved as well, giving an unwrinkled and expressionless ‘myopathic face’. The extraocular muscles are never affected.\(^7\)

**Upper limbs**

In the upper limbs, there is often involvement of the scapular fixator muscles, in particular the trapezius and serratus anterior. This results in scapular winging, which is often bilateral and frequently asymmetrical, and which typifies FSHD (figure 3). Mild scapular winging is not always visible at rest. The most sensitive way to detect scapular winging is to observe the scapula while the patient slowly lowers the arms forwards and/or sidewards.\(^8\) Another important sign is the ‘overriding scapula’, an upward movement of the scapula due to loss of its inferior fixation. Scapular instability together with muscle weakness causes difficulty in abduction and forward flexion of the arms above shoulder height. Patients complain first about difficulty in working above shoulder height, then as their symptoms progress, all activities requiring lifting of the arms become more difficult, for example, combing hair or removing a sweater.

Selective muscle wasting causes some characteristic physical signs that may point to FSHD. So-called ‘Popeye’ arms result from the contrast between the atrophied perihumeral muscles, especially the biceps, and the sparing (and subsequent normal bulk) of the muscles of the forearms and relatively sparing of the distal deltoid (figure 4). More severe cases may show the ‘poly-hill’ sign (figure 5),\(^9\) resulting from selective wasting of muscles. The first hill arises from atrophy of the trapezius muscle combined with upward movement of the superior angle of the scapula. More laterally, the second hill arises through displacement of the acromioclavicular joint. Next, the proximal deltoid muscle is wasted while its distal part forms a bulk (the third hill) and the biceps brachii again is wasted. The supraspinatus and infraspinatus muscles often appear fairly intact.

**Trunk**

Abdominal muscle weakness is an early and prominent feature of FSHD, though often under-recognised. Patients may have difficulty in rising from a supine to a sitting position, for example, when getting out of bed. As the weakness progresses, turning from one side to the other when supine becomes more difficult. On examination, the (asymmetrically) protruding abdomen can be mistaken for abdominal fat instead of muscle weakness. More specifically for FSHD, there may be a positive Beevor’s sign: an upward movement of the umbilicus on flexing the neck in the supine position. Because the distal part of the rectus abdominis muscle is weaker than the proximal part, the umbilicus gets pulled upwards (see figure 6 and online supplementary video). Abdominal muscle weakness also contributes to the lumbar hyperlordosis that most patients have.

The other trunk muscles often affected are erector spinae and pectoralis major. Erector spinae muscle weakness can rarely cause ‘bent spine syndrome’...
The combined weakness of abdominal and back muscles is an important contributor to patients’ loss of balance and subsequent falling. \[11\]

Atrophy of pectoralis major results in an, often asymmetrical, extra anterior axillary fold (figure 7).

The respiratory muscles are not primarily involved in FSHD. However, weakness of the trunk muscles, including accessory respiratory muscles, and chest wall deformities can give difficulty in breathing, but patients rarely require ventilatory assistance. \[12\] \[13\]

**Lower limbs**
Although the disease is called FSHD, the vast majority of patients also have weakness in the lower limbs. In one observational study (122 patients), 20% presented with lower limb weakness. \[14\]

The sequence of

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**Table 1** Signs and symptoms characteristic for FSHD

<table>
<thead>
<tr>
<th>Body region</th>
<th>Specific symptoms in history</th>
<th>Specific signs in neurological examination</th>
<th>Most commonly affected muscles</th>
<th>Red flags suggesting another diagnosis</th>
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<td>Face</td>
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<tr>
<td></td>
<td>Change in facial expression</td>
<td>Bell’s phenomenon</td>
<td>Orbicularis oculi</td>
<td>Weakness of extraocular muscles or masseter</td>
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<td></td>
<td>Difficulty in whistling</td>
<td>Signe de cils</td>
<td>Orbicularis oris</td>
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<td></td>
<td>Sleeping with eyes open</td>
<td>Asymmetrical pursing lips or blowing cheeks</td>
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<td>Transverse smile</td>
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<td>Asymmetrical winging of scapula and over-riding scapula</td>
<td>Trapezius</td>
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<td>Difficulty in working above shoulder height</td>
<td>Poly-hill sign</td>
<td>Serratus anterior</td>
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<td>Shoulder pain</td>
<td>‘Popeye’ arms</td>
<td>Distal part of deltoid</td>
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<td></td>
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<td>Horizontal axillary fold, often asymmetrical</td>
<td>Triceps and biceps brachii</td>
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<td>Beevor’s sign</td>
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<td>Horizontal clavicles</td>
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<td>Prominent abdomen with hyperlordosis</td>
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<td>Difficulty in moving from supine to sitting position</td>
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<td>Adductor magnus</td>
<td>Weakness of sternocleidomastoid</td>
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<td>Loss of balance</td>
<td>Trendelenburg’s sign</td>
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<td>Quadriceps femoris</td>
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<td>Tibialis anterior</td>
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<td>Tripping, falling</td>
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<td>Difficulty in walking up stairs or rising from a chair</td>
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FSHD, facioscapulohumeral muscular dystrophy.
involvement of the leg muscles differs between patients. A classical feature of FSHD is weakness of the tibialis anterior muscle, eventually causing foot drop. Foot drop is prevented for a long time by hypertrophy of the extensor digitorum brevis, often cited as a feature distinguishing the myopathy from a neuropathy.

Hamstrings weakness is very common but usually does cause functional limitations to daily life. The calf and quadriceps muscles may also be affected (figure 8). Trendelenburg’s sign is not specific for FSHD, but is frequently develops the advanced cases when walking becomes difficult.

Pain and fatigue
Approximately 75% of patients with FSHD experience moderately severe chronic pain, mostly in the lower back, legs, shoulder region and neck. Around 60% experience severe fatigue, related to multiple perpetuating factors including pain, sleep disturbance, physical activity and impairment.

Systemic involvement
Cardiac involvement includes an increased prevalence of (incomplete) right bundle branch block, though without cardiac symptoms or progression to clinically relevant cardiac arrhythmias. FSHD does not cause cardiomyopathy; finding this should prompt suspicion of other disorders.

Retinal vasculopathy is associated with FSHD. It is mostly subclinical but can, mostly in severely affected early onset cases with very short repeat sizes, progress to Coat’s syndrome. Coat’s syndrome is a treatable condition, characterised by retinal vascular abnormalities and leakage that can cause exudative retinal detachment and blindness. High-frequency hearing loss may occur in patients with FSHD but appears mostly to be subclinical. Patients with early onset severe disease may develop hearing loss requiring hearing aids. Pectus excavatum occurs in 5%–16% of patients with FSHD and occasionally may be severe. There are a few case reports describing mental retardation and/or epilepsy in patients with severe FSHD.

DIAGNOSTIC INVESTIGATIONS
The history and physical examination are the keystones to the diagnosis; direct DNA testing can confirm it if there is a high clinical suspicion. Muscle biopsy and laboratory tests are not sufficiently specific to make the diagnosis of FSHD. The serum creatine

Figure 2 Weakness of the orbicularis oculi results in difficulty or inability in closing both eyes (A) and a ‘signe de cils’ (C). (B) The mouth is asymmetrical in its resting position. (D) Orbicularis oris weakness causes difficulty in pursing the lips (D).
kinase concentration is either normal or slightly elevated (but never more than five times of normal).

FSHD1 can be diagnosed genetically by assessing the size of the repeat contraction on chromosome 4; finding ≤10 repeat units on a 4qA allele is consistent with the diagnosis. FSHD1 is the most common type (95%) of FSHD. Repeat size is reported as EcoRI band, in which fragments ≤38 kb are consistent with FSHD1. The reported EcoRI/BlnI band is used only to confirm that the repeat contraction is located on chromosome 4 and not on a similar repeat array on chromosome 10. In case of a repeat contraction on chromosome 4, the EcoRI/BlnI band is 3 kb shorter than the EcoRI band. Because FSHD1 is caused by a repeat contraction, current high yield genetic sequencing such as exome sequencing techniques fail to detect FSHD1.

In case of a negative test (fragment size >38 kb) and a high clinical suspicion for FSHD, it is worth testing for FSHD2. This accounts for 5% of patients who have heterozygous mutations in the SMCHD1 gene, and has a clinical phenotype indistinguishable
from FSHD1.22 There are reports of patients with very severe FSHD who carry mutations for FSHD1 as well as for FSHD2.23 A small number of patients with an FSHD phenotype have negative tests for both FSHD1 and FSHD2 and cannot be explained genetically at this moment. In case of negative genetic testing for FSHD1 and/or FSHD2, other diagnoses should be considered.24 A more detailed description of genetic testing lies beyond the scope of this paper and can be found elsewhere.25 26

COUNSELLING AND MANAGEMENT

FSHD is an autosomal dominantly inherited disorder. The muscle weakness is typically slowly progressive, although the disease severity varies greatly between and within families. When compared with other muscular dystrophies, FSHD may have a more stepwise disease progression, sometimes with years of stabilisation of progression, followed by a period with relatively fast progression of muscle weakness. Therefore, it is not possible at present to predict an individual disease course. One in five patients with FSHD becomes wheelchair dependent by the age of 50 years.27 Factors associated with a more severe phenotype are the early onset of symptoms and very short repeat sizes (10–20 kb).28 Life expectancy is generally not reduced.29 Patients should be referred for genetic counselling for information regarding recurrence risk. Preimplantation genetic diagnosis is technically very difficult for FSHD, because of the large amount of DNA that is required to perform the Southern blot analysis. In large families, it is possible to use proximal flanking markers, but this technique has a 5% chance of false result because the FSHD repeat lies distally on chromosome 4q and because this area has a high recombination frequency.

There is currently no cure or medicinal treatment available for FSHD. Treatment is focused on improving functional limitations and maintaining an optimal physical condition. Therefore, all patients with functional limitations should have a rehabilitation consultation.24 Several studies have focused on treating the symptoms of physical limitations and fatigue. Aerobic exercise can help chronic fatigue, physical activity and fitness.30 31 Cognitive behavioural therapy can also help chronic fatigue through tackling fatigue-perpetuating factors.30

There is a recently developed evidence-based guideline for managing and screening for complications of FSHD.28 This advises obtaining baseline pulmonary function tests on all patients with FSHD, especially those severely affected (wheelchair users and/or with chest wall deformities). It is not necessary to undertake routine cardiac screening. Also, routine assessment for retinal vasculopathy and hearing loss is not necessary, except in severe infantile cases (using dilated indirect ophthalmoscopy and screening audiometry). All patients with FSHD undergoing elective surgery need preoperative screening, to include an assessment of respiratory function.

CONCLUSION

FSHD is an inherited progressive muscle disorders that—despite its name—comprises more than just weakness of the facial, scapular and humeral muscles. An awareness of the signs and symptoms of FSHD, which may be subtle, allows prompt diagnosis, and hence reduced diagnostic delay and avoidance of (often invasive) diagnostic procedures. The diagnosis can be confirmed genetically. Treatment is currently aimed at improving functional limitations.

Key points

▸ The muscle weakness in facioscapulohumeral muscular dystrophy (FSHD) includes the facial and shoulder girdle muscles, and also the trunk and the legs.
▸ Patients often do not recognise the typical signs, which emphasises the importance of the neurological examination in these patients.
▸ Familiarity with its variability and subtleness of signs and symptoms allows the physician to diagnose FSHD at the first clinical encounter and to confirm it by genetic testing.

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