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Atypical onset in a series of 122 cases with FacioScapuloHumeral Muscular Dystrophy

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ABSTRACT

Introduction: FacioScapuloHumeral Muscular Dystrophy (FSHD), a disease linked to a heterozygous D4Z4 deletion on chromosome 4q35, typically starts with shoulder-girdle and facial muscle involvement. Atypical presentations have occasionally been reported, but their frequency has still not been defined.
Patients and methods: We studied the occurrence rate of FSHD with atypical onset in 122 symptomatic subjects from 76 unrelated families with genetically confirmed FSHD. These 75 males and 47 females, with a mean age of 49 years (range: 11–85), had a mean EcoRI fragment of 25 kb (range: 11–38).
Results: Typical shoulder-girdle or facial weakness at onset was reported by 88 patients (72%). Unusual presentations included: foot drop in 16 (13%) and proximal lower limb weakness in eight patients (7%). Two cases at onset manifested quite atypical, apparently non-FSHD-related syndromes: a 42-year-old woman presented with infantile epilepsy and a 41-year-old man with myoglobinuria. In the latter patient, DNA analysis detected a 4q35 deletion associated to an heterozygous CAPN3 mutation.
Conclusion: FSHD presentation with foot drop or lower limb proximal weakness appeared to be more frequent than expected. This type of weakness at onset has to be considered premature, but still representative of disease-related muscle involvement. Quite atypical onset appears very rare and calls for further investigation on non-FSHD-related etiology.

1. Introduction

In Western countries, FacioScapuloHumeral Muscular Dystrophy (FSHD) has a prevalence rate of about $4–5 \times 10^{-5}$, making it one of the most frequent hereditary muscle disorders [1–3]. For this autosomal dominant disease, whose locus is on chromosome 4q35, genetic studies have defined a characteristic deletion of the D4Z4 3.3 kb tandem repeat on EcoRI digested DNA, with a residual fragment of 10–38 kb [3–5]. On clinical grounds, current and historical reviews [3,6,22–24] indicate that FSHD generally starts during adolescence and the presenting symptoms are typically variable degrees of muscle weakness, involving the facial and shoulder-girdle muscles. In genetically confirmed FSHD patients, clinical presentation with foot drop has occasionally been described [7,8], but its frequency has still not been determined. In 2000, van der Kooi et al. [7] reported atypical disease onsets characterized by weakness in the posterior leg compartment or proximal lower limb muscles. These types of presentation were subsequently confirmed by others [8–10]. Congenital extraocular muscle weakness, a more unexpected disease onset, was observed in three FSHD cases from the same family only by Krasnianski et al. [11].

The aim of our investigation was to identify the rate of occurrence and the clinical features of non-typical versus typical disease onsets in a series of 122 FSHD cases, belonging to 76 unrelated families with genetically confirmed diagnosis.

2. Patients and methods

2.1. General clinical data

Our investigation was carried out as a collaborative study involving the Neuromuscular Centre of the Department of Neurosciences of the University of Padua and the Clinical Centre for Neuromuscular Diseases of UILDM, the Muscular Dystrophy Association of Padua. Our cohort of cases with a molecular diagnosis of FSHD included 156 consecutive subjects, belonging to 76 unrelated families. Of these individuals, 122 were symptomatic, whereas 34 manifested no signs or symptoms of the disease. Our study included only the symptomatic cases. These 122 patients consisted of 76 index cases and 46 additional symptomatic subjects, who were identified by a thorough clinical and molecular investigation of family members. In the index cases, FSHD was defined according

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to the European Neuromuscular Consortium criteria including evidence of myopathy at muscle biopsy, in the absence of features indicative of alternative diagnosis [12]. Determination of the 4q35 D4Z4 deletion on EcoRI digested DNA, extracted from peripheral blood, was carried out as previously reported [13–15].

As shown in Table 1, the 122 symptomatic cases comprised 75 males and 47 females with a mean age of 49 years (range: 11–85). In these patients, the mean EcoRI fragment detected by molecular analysis was 25 kb in length (range: 11–38 kb).

2.2. Disease onset

All 122 symptomatic patients were evaluated by a clinical questionnaire focusing on first clinical disturbance manifested by the patient and age of onset. To avoid potential patient bias, the patient or relatives answered the questionnaire with the assistance of one of the clinicians involved in this investigation. Either the patient's own recollection of initial symptoms or the first clinical abnormality observed by relatives, as in the case of children or patients' siblings, were considered significant. The record of each subject' first neuromuscular examination was reviewed in order to have an objective description of early overall muscle weakness. Muscle groups were defined by their topographical distribution: face, upper or lower girdle, upper or lower limbs, with an additional distinction between proximal or distal compartments.

Early extra-muscular symptoms or signs of hearing, visual, cerebral, or cardiac involvement were also sought. This part of our investigation was planned due to the occasional symptoms reported by FSHD patients, related to auditory impairment, visual abnormalities, mental retardation, epilepsy or heart arrhythmias [15–20].

3. Results

Mean age at onset in our unselected series of 122 FSHD patients was 23 years, with a wide range from childhood to adulthood (Table 1). When the 76 index cases were considered separately from their 46 affected relatives, mean age at onset was 21 years (range: 4–60). Instead, in affected relatives it was 26 years (range: 9–56).

As shown in Table 2, scapulo-humeral muscle weakness was reported at onset in 80 out of 122 cases. In all, associated signs of facial weakness were clearly demonstrable at initial neuromuscular examination. Weakness was asymmetrical in 32 of these 80 cases (40%). Their mean EcoRI fragment was 24 kb, ranging from 14 to 38. In only eight cases (7%), facial weakness was the predominant clinical manifestation at onset. However, when first examined, all these patients also showed variable degrees of weakness in the scapulo-humeral region. Their EcoRI fragment had a mean value of 18 kb (range: 14–30). Altogether, disturbances related to facial or scapulo-humeral weakness, which are the typical onset disorders according to the FSHD diagnostic criteria of the European Neuromuscular Centre [12], were reported to be the presenting symptoms by 88 of our 122 symptomatic FSHD patients (72%).

In seven cases (Table 3), the disease showed a late-onset presentation at a mean age of 39, with shoulder-girdle weakness in

Table 1
General clinical data of the 122 FSHD subjects considered in the study.[c]

Number of patients	122
Index cases	76
Symptomatic relatives	46
Male/female	75/47
Present age (mean)	49 years (range: 11–85)
Eco RI fragment (mean)	25 kb (range: 11–38)
Age at onset (mean)	23 years (range: 4–60)
Type of clinical onset	
Typical[a]	72%
Scapulo-humeral	80/122
Facial	8/122
Non-typical[a]	28%
Facial-sparing[b]	7/122 (6%)
Foot drop	16/122(13%)
Proximal lower limbs	8/122 (7%)
Other	3/122 (2%)

[a] Typical or non-typical onset according to the FSHD diagnostic criteria of the European Neuromuscular Centre (Ref. [12]).
[b] Cases which maintained the "facial-sparing" phenotype during the disease course.
[c] The table summarizes all the different FSHD onset types observed in our 122 cases.

Table 2
FSHD clinical onset: the predominant types.[a]

Facio-scapulo-humeral onset	
Scapulo-humeral symptoms	80/122
M/F	56/24
Age at onset	24 years (range: 5–60)
Unilateral	32/80
Bilateral	48/80
Signs of facial weakness	78/80
Eco RI fragment (mean)	24 kb (range: 14–38)
Facial symptoms	8/122
M/F	3/5
Age at onset	8 (range: 4–23)
Signs of scapulo-humeral weakness	8/8
Eco RI fragment (mean)	18 kb (range: 14–30)
Foot drop onset	16/122
M/F	9/7
Age at onset	27 (range: 10–53)
Unilateral	12/16
Bilateral	4/16
Signs of scapulo-humeral weakness	14/16
Signs of facial weakness	15/16
Eco RI fragment (mean)	27 kb (range: 19–38)

[a] The onset type represented in the table concerns 104 out of 122 patients

Table 3
Some data of 18 FSHD patients with non-typical onset.

Facial-sparing[a]: 7 cases			
M/F			5/2
Present age			63 (range: 44–79)
Age at onset			39 (range: 22–59)
Signs of scapulo-humeral weakness			7/7
Eco RI fragment			36 kb (range: 32–38)
Lower limbs proximal weakness: 8 cases			
M/F			0/8
Present age			59 (range: 34–78)
Age at onset			36 (range: 15–64)
Unilateral			0/8
Bilateral			8/8
Signs of scapulo-humeral weakness			8/8
Signs of facial weakness			8/8
Eco RI fragment (mean)			22 kb (range: 15–27)
Other types of onset (3 cases):	Case 1	Case 2	Case 3[b]
Apparent onset type:	Sural triceps weakness	Epilepsy and mental retardation	Myoglobinuria
Age at onset	21 years	Infancy	18 years
Scapulo-humeral weakness	−−−	++−	−−−
Facial weakness	−−−	+++	−−−
EcoRI	38 kb	11 kb	24 kb
Present age	43 years	42 years	41 years
[c]FSHD weakness scale			
Present grade	I	IV	IV

[a] Persistent "facial-sparing" phenotype during disease course.
[b] In this patient heterozygous CAPN3 mutation was associated with the 4q35 deletion.
[c] As previously described [18], the FSHD Weakness Scale ranges from 0 (no weakness) to VII (maximal weakness).

the absence of facial involvement. This "facial-sparing" phenotype appeared persistent over a mean disease course of 24 years. In these patients the EcoRI fragment size (mean value 36 kb, range: 32–38 kb) indicated a very small 4q35 deletion.

Foot drop was recollected as the first clinical symptom by 16 of our 122 cases (13%), mostly unilaterally (12/16 cases: see Table 2). This type of onset was only experienced by index cases (9 males and 7 females), with a mean age at onset of 27 years (range: 10–53). Moreover, at first neurological evaluation scapulo-humeral or facial weakness was detected in all but one index case. The EcoRI fragment in these patients had a mean value of 27 kb (range: 19–38).

Onset with atypical proximal weakness in the lower limb muscles was reported by eight patients (7%), as shown in Table 3. They were all females with a mean age at onset of 36 years (range: 15–64). All were index cases, mostly with bilateral weakness of the quadriceps muscle and less involvement of the iliopsoas. At first neurological examination, associated weakness in the scapulo-humeral muscle region was identified in all of them. Likewise, all showed variable facial muscle deficit. In these eight cases, the 4q35 fragment ranged from 15 to 27 kb (mean 22 kb).

Clinical presentation with unilateral sural triceps involvement was evident in only one of our FSHD subjects. The clinical features of this 43-year-old man are listed in Table 3 (case 1). Since age 21, he had difficult walking on tip-toes and standing on his left leg. Since the disturbance was associated with altered serum CK (three-fold the normal value) he was referred to our outpatient clinic for neurological evaluation. His neuromuscular examination showed moderate left leg triceps weakness and hypotrophy without other abnormalities. His fraternal twin brother, who had already been diagnosed elsewhere with FSHD, showed moderate weakness of the scapulo-humeral muscles; he had complained of these disturbances since adolescence. Evaluation of the EcoRI fragment (38 kb) revealed a small 4q35 deletion in both brothers.

Quite atypical onsets were reported by two FSHD subjects. The first (cases 2, Table 3) was a 42-year-old woman, whose mother suffered from a mild form of FSHD myopathy and rare sporadic grand mal seizures. The patient had long been considered affected by an idiopathic encephalopathy. She had been treated with antiepileptic drugs since her first year of life due to tonic or tonic–clonic seizures. Moreover, her psychomotor development was delayed, with ability to walk at three and to speak a few words at five years of age. There were no evident causes of brain pathology either in the clinical history (pregnancy and perinatal period uneventful) or from analysis of her karyotype (no chromosomal abnormalities). Her IQ score was 0.36 at 16 and 0.34 at 38 years of age. Interictal EEG findings were normal, aside from a few occasions (at 7, 15 and 35 years) when brief diffuse discharges of spikes and polyspikes were detected. At 38, her brain MRI was normal. Hearing loss had also appeared in early childhood. Some facial weakness was evident before age five, while difficulty in arm abduction and other signs of shoulder-girdle muscle weakness had appeared at age 14. At present, she walks independently with a mixed stepping and waddling gait and can abduct her arms by 70°. Facial weakness and mild bilateral foot drop are also evident. Analysis of her DNA identified a 4q35 fragment of 11 kb. Some clinical details of this case have been described in a previous report on the infantile variant of FSHD [25].

A myoglobinuric attack during adolescence characterized disease onset in a 41-year-old man (cases 3, Table 3). At 18 years of age, he suffered from acute rhabdomyolysis triggered by prolonged muscle activity. Urinalysis indicated massive myoglobinuria. The patient improved but clinical investigations failed to identify any recognized cause of myoglobinuria, including infections, exposure to drugs or toxic factors, trauma or inherited errors of metabolism. After recovery, his neurological examination revealed only a mild hypotrophy of the left leg muscles. Muscle biopsy showed no glycogen or lipid storage and no evidence of mitochondrial myopathy. Normal biochemistry of muscle phosphorylase, phosphofructokinase and carnitine-palmitoyl-transferase ruled out the relative metabolic causes of myoglobinuria. Routine muscle histology showed non-specific myopathic changes. In the following years, immunoblot analyses of dystrophin, dysferlin, sarcoglycans, caveolin yielded normal results. At 30 years of age, he developed impaired arm abduction, suggesting the diagnosis of FSHD. His DNA examination confirmed the clinical diagnosis revealing a 4q35 fragment of 24 kb, inherited from his asymptomatic father. Since FSHD did not provide an adequate explanation for rhabdomyolysis at onset, a complete molecular study of the calpain3 gene (CAPN3) was also carried out in muscle DNA. The molecular analysis, performed as elsewhere reported [21], revealed an heterozygous mutation in CAPN3 exon 4 (c.505C>T R169C), in addition to the previously identified FSHD 4q35 deletion.

In all our patients with atypical onset, clinical heart examination and 24-h ECG Holter monitoring gave normal results. Previous cardiologic assessment in the majority of the patients included in the present investigation has been described earlier [18].

Table 4 compares the main findings of our clinical research with those of two similar studies reported to date on series of FSHD cases with 4q35 analysis [10,11]. In the first, Butz et al. [10] re-evaluated 39 patients, confirming the FSHD diagnosis in 34 with an EcoRI fragment ranging from 32 to 41 kb; they searched among them for possible non-typical FSHD phenotypes according to the FSHD diagnostic criteria of the European Neuromuscular Centre [12]. The

Table 4
Type of disease onset: comparison of our study with the two reports on FSHD series of cases with 4q35 analysis.

Series of cases	Butz et al.[c] [10]	Krasnianski et al. [11]	Present study
General data			
Number of cases	34 (from 39[c])	41	122
M/F	26/13	Not reported	75/47
Mean age (range)	46 years (18–75)	Not reported	49 years (11–85)
Onset type[a]			
Typical [b] (facial or scapulo-humeral)	24 cases (71%) (22 cases: 32–41 kb) (2 cases: >41 kb)	35 cases (85%) (<35 kb)	88 (72%) (14–38 kb)
Facial-sparing[d] (scapulo-humeral)	6 cases (18%) (32–41 kb)	3 cases (7%)(30–34 kb)	7 cases (6%) (32–38 kb)
Tibialis anterior (foot-drop)	Not evaluated	Not evaluated	16 cases (13%) (19–38 kb)
Proximal lower limbs	2 cases (6%) (35 kb)	–	8 cases (7%) (15–27 kb)
Non-progressive pectoralis' atrophia	2 cases (6%) (35–41 kb)	–	–
Sural triceps	–	–	1 case (38 kb)
Progressive Ext. ophthalmoplegia	–	3 cases (7%) (20 kb)	–
Myoglobinuria	–	–	1 case (24 kb)
Brain involvement	–	–	1 case (11 kb)

[a] Muscles or tissues involved are indicated (in brackets the EcoRI fragment kb).
[b] Typical onset according to the FSHD diagnostic criteria of the European Neuromuscular Centre (Ref. [12]).
[c] 39 cases were re-examined in this series: 34 were confirmed as FSHD, 5 were classified as non-FSHD.
[d] Persistent "facial-sparing" phenotype during disease course.

aim of Krasnianski et al.'s [11] clinical investigation was to analyze the occurrence of atypical clinical presentations among 41 unselected FSHD patients with an EcoRI fragment size lower than 35 kb. Table 4 mainly underlines the divergent results yielded by the three investigations on the types of atypical presentation.

4. Discussion

In the vast majority of our FSHD patients, the characteristic symptoms at onset were related to muscle weakness in the shoulder-girdle and facial regions, in agreement with the classical description of the disease [22–24] and the two most recent studies on series of FSHD cases with 4q35 analysis [10,11]. Accordingly, the initial prominent clinical problem in these subjects was characterized by a variable and often asymmetrical difficulty in arm abduction. Early neurological examination revealed variable wasting of the related muscles, including the serratus anterior, lower trapezius, pectoralis major and scapular fixators. An associated characteristic sign in most of the same cases was facial weakness, although patients were not always aware of this. In only a minority of our patients (7%) facial weakness was reported as the first clinical manifestation: these were mostly children, in whom the facial abnormality was noted by parents. As expected, in subjects presenting with facial weakness, the first neuromuscular evaluation documented a variable degree of associated weakness in the scapulo-humeral region.

In our research, some cases presented with a late-onset "facial-sparing" phenotype, which was maintained during the clinical course. This infrequent clinical manifestation of the disease, as originally reported by Felice and Moore [8], appeared to be related to very small 4q35 deletions, with EcoRI fragments ranging from 30 to 38 kb. Similar correlations were also observed in the investigations of large series of genetically evaluated cases reported by Butz et al. [10] and Krasnianski et al. [11]. These studies on non-typical FSHD presentation are compared with ours in Table 4.

It is generally accepted that FSHD typically starts in the second decade of life [3,6,22–24]. However, our clinical study showed that the mean age of disease presentation among index cases was 21–22 years, with a wide variability in age at onset (4–60 years).

Foot drop is generally considered rare among the initial symptoms reported by FSHD patients. Conversely, we observed stepping gait, often unilateral, in 13% of our series of cases, showing that – when carefully investigated – foot drop is not an uncommon feature of disease onset. This finding, however, should not be surprising since the tibialis anterior muscle is often affected during the advanced course of the disease [3,6,22–24]. Only one of our patients had foot drop at presentation without facio-scapulo-humeral muscle involvement, as described by van der Kooi et al. [7] and Felice and Moore [8].

The atypical FSHD presentation characterized by lower girdle muscle weakness was found in 7% of our patients. All of them also showed variable degrees of facial and shoulder-girdle muscle involvement. This FSHD onset type, which has been extensively described by other authors [7,10,11], is not so unexpected because pelvic girdle muscle involvement is a common occurrence in the later stages of the disease. In our patients with this onset type, the 4q35 deletion was similar to the one found in typical FSHD cases. Differently, the deletion was very small in the two patients studied by Butz et al. [10], with a residual fragment size of 35 kb. The unusual FSHD clinical presentation with difficult toe walking due to unilateral triceps weakness was very rare in our series, involving only one FSHD subject. This type of onset has previously been reported by other authors [7,9]. Overall, the main non-typical FSHD onset includes weakness in distal or proximal lower limb muscles, which are generally involved at a later stage of the disease [3,6,22–24].

Seizures in early infancy, with associated delay in psychomotor development, was another atypical presentation among our subjects. It was observed in a patient who had been considered encephalopathic until her dystrophic symptoms became apparent in adolescence. Epilepsy seems to be a phenotypic feature particularly of the early onset FSHD variant, in which epilepsy and mental retardation have been associated with 4q35 deletion fragment sizes of 10–12 kb [6,25].

In a young patient of ours, a puzzling disease onset was represented by an acute episode of rhabdomyolysis with myoglobinuria. This syndrome, that has occasionally been described in patients with other type of muscular dystrophies (namely the ones determined by mutations in sarcolemma-related proteins [24]), has never been reported in FSHD cases. After the peculiar onset, our patient developed a typical FSHD, confirmed by detection of the characteristic 4q35 deletion (residual fragment 23 kb). Subsequently, however, a heterozygous mutation in the calpain 3 gene (CAPN3) was also identified in the same subject. Considering that mild myopathy in this patient could be related to the heterozygous CAPN3 mutation [21], acute myoglobinuria could also be attributed to the second muscle disease.

Progressive external ophthalmoplegia, the uncharacteristic disease onset described in an FSHD family by Krasnianski et al. [11], was not observed in any of our patients. This unexpected disease onset was reported in three siblings who subsequently developed an FSHD phenotype with evidence of the 4q35 deletion and no mitochondrial myopathy.

5. Conclusion

On the whole, our study showed that non-typical FSHD presentation with distal or proximal weakness in the lower limbs was more frequent than expected. On the other hand, since lower limb muscle weakness characterizes the advanced stages of the disease, observation at onset seems to constitute a premature rather than an unrepresentative FSHD clinical feature. It also confirms the substantial homogeneity of overall muscle involvement in FSHD. Quite atypical disease presentations are very rare and need further research on concomitant non-FSHD-related etiological factors.

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