

Facioscapulohumeral muscular dystrophy: hearing loss and other atypical features of patients with large 4q35 deletions

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Background and purpose: Patients affected by facioscapulohumeral muscular dystrophy (FSHD) with unusual large 4q35 deletions tend to present atypical features in early childhood. We explored the clinical presentation of patients with a very short 4q35 fragment (10–13 kb) focusing on hearing loss, a still debated FSHD extra-muscular manifestation. **Patients and methods:** We evaluated six cases with *EcoRI* 4q35 fragment size ranging from 10 to 13 kb. Assessment of hearing function was carried out by otoscopy, audiometry and auditory-evoked brainstem responses (ABR). Patient data were compared with those of 28 similar subjects reported in the literature. **Results:** Sensorineural hearing loss was found in four patients, who presented infantile-onset dystrophic phenotype. Hearing loss was associated with mental retardation in three of them and with epilepsy in two. Auditory ability of the other two cases was mildly impaired. If findings related to 28 similar cases reported to date are also considered, auditory impairment appears evident in 68% of these subjects. **Conclusions:** Hearing loss represents a characteristic feature of FSHD patients with a large 4q35 deletion. Moreover, when considering only cases with 10–11 kb, it appears to be associated with early-onset dystrophic phenotype, with mental retardation (92%) and possibly with epilepsy (58%).

Introduction

The clinical phenotype of facioscapulohumeral muscular dystrophy (FSHD), one of the most frequent autosomal dominant degenerative myopathies, has been associated with a DNA deletion of a 3.3 kb tandem repeat in the chromosome 4q35 region, with a residual fragment size ranging from 10 to 38 kb [1–4]. The disease typically presents in adolescence with facial and upper girdle muscle involvement, followed by a variable clinical course. In these patients, the 4q35 *EcoRI* fragment characteristically ranges from 14 to 38 kb. Very short fragments (10–13 kb) are unusual and mostly underlie a more severe variant of the disease, with early-onset and possible atypical clinical features, including hearing loss [5,6]. This extramuscular manifestation of FSHD represents a controversial clinical issue. In a series of genetically confirmed Dutch patients, auditory impairment was detected in the majority of cases [7].

However, in subsequent reports on other series of typical FSHD patients [8,9] hearing loss was not found to be more common than in the normal population. Because the subjects considered were typical FSHD cases with a 4q35 fragment size > 14 kb, the conclusions of these studies could not be applied to the FSHD patients with unusual shorter fragments.

We report a study on frequency of hearing loss and other clinical manifestations in a series of six personal cases with very short 4q35 fragment. Results are compared with those relating to 28 similar cases from the literature.

Patients and methods

The clinical research protocol was carried out after approval by the Review Board of Padua University and after informed consent of patients or patients' parents.

General clinical and genetic evaluation

The main clinical data on the subjects taking part in this study are represented in Table 1 (two familial and

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Table 1 Clinical data of our six FSHD patients with a very short 4q35 fragment

Patient, no. (gender)	1 F	2 M	3 M	4 M	5 F	6 F
4q35 fragment (kb)	11	10	12	13	13	12
Age (years)	40	21	16	52	61	76
Affected parent	Mother	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>	Mother
Weakness onset	1/1	1/3	2/5	4/8	7/12	10/15
facial/girdle (years)						
Facial weakness	Severe	Moderate	Severe	Severe	Moderate	Moderate
Arm abduction (°)	70	60	30	0	20	30
Walking	Waddling, foot drop	Waddling, foot drop	Wheelchair	Wheelchair	Wheelchair	Waddling, foot drop
Hearing loss	Severe	Severe	Severe	Mild	Mild	Mild (presbycusis)
Mental retardation	Severe	Severe	Moderate	—	—	—
Epilepsy	Moderate	Mild	—	—	—	—
Retinal alterations	Tortuous vessels	—	—	Coat's syndrome	—	—

M, male; F, female; n, normal; +, present; —, absent.

four sporadic FSHD cases from six families). They were three males and three females, with a mean age of 44 years (range 16–76). In all of them, muscle involvement was evaluated according to onset, distribution and clinical course of weakness, neurological examination, serum creatine kinase (CK), electromyography (EMG) and muscle biopsy. Clinical diagnosis was established on the basis of the European Neuromuscular Consortium criteria [10] and subsequently confirmed by detection of the characteristic FSHD 4q35 deletion [3,4]. The molecular analysis was carried out on DNA extracted from peripheral blood. It was digested with the restriction enzyme *EcoRI*, double digested with *EcoRI/BlnI* and hybridized with radioactive labelled probe p13E-11, after separation by pulsed-field gel electrophoresis. These procedures were performed as reported elsewhere [11,12]. In the considered patients, the *EcoRI* fragment size ranged from 13 to 10 kb: 13 kb in cases 4 and 5, 12 kb in cases 3 and 6, 11 kb in case 1 and 10 kb in case 2.

Hearing assessment

All six FSHD patients underwent otological evaluation according to a protocol including a clinical questionnaire, otoscopic examination, audiometry and auditory-evoked brainstem responses (ABR). The clinical questionnaire focused on personal history of clinical risk factors for deafness as recurrent or chronic ear infections, previous relevant ear trauma, chronic exposure to noise or ototoxic substances. The relative data were obtained by direct questioning in cases 4–6 and by information from parents in cases 1–3, because of their mental retardation. Pure tone audiometry was obtained using an electronic clinical audiometer in a soundproof booth [Amplaid 455 (Amplifon, Milan, Italy) or Interacoustic AD229 (Interacoustics A/S, Assens, Denmark)]. Audiograms were obtained for both ears by measuring hearing ability at 250–500–

1000–2000–4000–8000 Hz. Subsequently, the audiometric thresholds of each patient were compared with standardized tables derived from normal population data and corrected for age [13]. When a patient failed to cooperate (cases 1–3), objective definition of auditory thresholds was obtained by determining impedance by cochlear–stapedial reflex threshold and/or ABR. This neurophysiological assessment, which was also performed in collaborating patients (cases 4–6), was carried out using an Evopac-Medea instrument (Venice, Italy). At least 2000 clicks (0.1 ms, 120 dB SPL, 11 Hz) were twice delivered, first to one ear and then to the other. Recording electrodes were placed at both ear lobes, and at the scalp vertex site Cz (impedance < 5000 ω). The amplitude and latency of the first five waves were evaluated according to standardized methods [14], including a search for the decreasing wave V threshold.

Additional clinical investigations

All patients were also evaluated for possible brain involvement (mental retardation and epilepsy) by clinical history, neurological and psychiatric examination, mental testing, electroencephalography (EEG), brain computed tomography (CT) or magnetic resonance imaging (MRI). Furthermore, all cases had an ophthalmological examination, including direct ophthalmoscopy for possible retinal abnormalities, as tortuous vessels, telangiectasia or exudative vascular retinopathy. Retinal fluorescence angiography was performed in case 4 only.

Results

Clinical muscle involvement

The main dystrophic manifestations of our six patients are summarized in Table 1. The first four cases fulfilled

the clinical criteria for infantile-onset FSHD [5], i.e. presentation of facial weakness before 5 years and shoulder girdle deficit before 10 years of age. In cases 5 and 6, the disease showed the typical onset in adolescence. In cases 2 and 3, pelvic girdle weakness was apparent before the onset of upper girdle weakness, as different from all the other cases. Weakness showed a progressive clinical course in all cases.

Muscle involvement appeared to be of the severe type in cases 2–4. At 21 years of age, case 2 presented a clear-cut waddling gait and his arm abduction reached about 50° bilaterally. Case 3, a 16-year-old boy, was able to walk only a few steps in a waddling fashion with ability to abduct arms by just 30°. Patient 4, a 52-year-old man, had been wheelchair bound since his late 30s and was unable to move his arms from his body. A moderate type of muscle involvement was apparent in the other three patients (cases 1, 5 and 6). At 40 years of age, case 1 was able to abduct her arms to 70° and to walk independently with a waddling gait and mild bilateral foot drop. Case 5, a 61-year-old woman, walked independently until the end of her fifth decade and was currently able to abduct her arms by 20°. Case 6, at 76 years of age, was still able to abduct her arms by 30° and to walk without assistance with a waddling gait and clear-cut foot drop.

CK serum level was in the normal range in cases 4–6, while it was slightly increased in the other three patients. EMG and muscle biopsy detected mild-to-severe characteristic features of myopathy in all patients.

Hearing loss

All our patients showed hearing loss on clinical and/or instrumental testing (Table 1). Case 1, a 40-year-old female, had presented severe hearing loss since infancy, associated with moderate mental retardation. She did not tolerate hearing aids, prescribed in early life. Because of poor collaboration, reliable data were not obtained on her pure tone audiometry. However, impedance measures revealed a type A tympanogram, with the absence of cochlear–stapedial reflexes bilaterally. ABR examination showed absence of responses in her right ear, even at maximum stimulation intensity (120 dB SPL). In her left ear, the wave V threshold was detected at 80 dBHL. This patient had a normal clinical and instrumental middle ear examination, ruling out that her hearing loss could be due to a conductive type pathology. Similar results were obtained in both cases 2 and 3, two males who had suffered from severe hearing loss since infancy associated with mental retardation and autistic-type behavioural disorders. Case 4, a 52-year-old male, with early-onset weakness and no signs of brain abnormalities, had

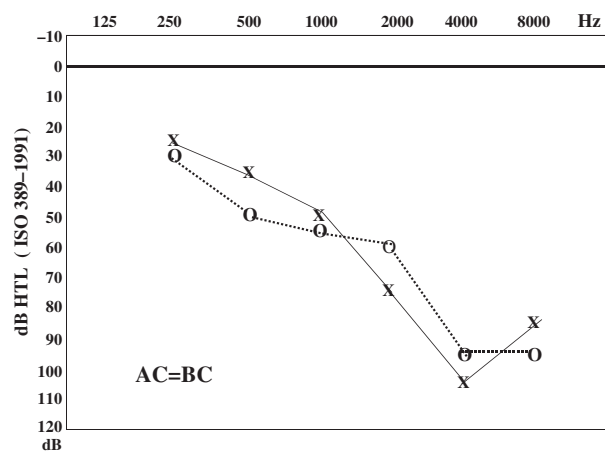


Figure 1 Pure tone audiometry of case 4, a 52-year-old male, with early-onset weakness and no signs of brain abnormalities. The findings clearly indicate high-frequency sensorineural hearing impairment.

been aware of mild hearing loss as adolescence. His pure tone audiometry detected high-frequency sensorineural hearing impairment as shown in Fig. 1. In the same patient, ABR examination showed a delay of wave I latency, indicating integrity of the brainstem auditory pathways. Case 5, who had moderate, typical adolescence-onset FSHD muscle involvement, was unaware of hearing loss. However, audiometry detected bilateral high frequency sensorineural hearing loss, with the maximum abnormality evident at 8000 Hz (60 dB). ABR in the same patient suggested a cochlear pathology and normal auditory brainstem pathways. In case 6, a 76-year-old female with typical FSHD, pure-tone audiometric evaluations in the last years revealed mild high frequency hearing impairment (50 dB at 8000 Hz). These findings appeared normal when compared to data derived from the normal population of the same age [13]. Her auditory impairment was thus considered to result from presbycusis. As in the other patients, ABR indicated normal auditory brainstem pathways.

Table 2 shows the findings on hearing function for our six FSHD patients compared with those of 28 similar cases of FSHD with large 4q35 deletions reported to date.

Additional clinical manifestations

Evidence of brain involvement was clear for cases 1–3. Delayed of psychomotor development and signs of mental retardation had been noticed by the parents of all of them, as early life. Case 1, a 40-year-old woman, had learned to speak a few words at 4–5 years of age. She had never been able to attend school and,

Table 2 Summary on hearing loss and atypical clinical features of 34 FSHD patients with a very short 4q35 fragment

Report	Case no. Sex (age in years)	Fragment (kb)	Onset (years)	Hearing loss	Mental retardation (IQ)	Epilepsy	Retinal abnormalities
Jardine <i>et al.</i> [21]	3-F (9)	13	0	–	nr	nr	–
	4-F (24)	13	1	–	nr	nr	–
	8-M (20)	13	2	+ (HF)	nr	nr	–
	13-F (20)	13	5	+ (HF)	nr	nr	–
	21-M (19)	13	11	–	nr	nr	–
Brower <i>et al.</i> [6]	5-F (18)	13	0	+ (HF)	–	nr	Mild
	8-M (17)	13	3	+ (HF)	+	–	–
Funakoshi <i>et al.</i> [17]	1-F (6)	10	4	–	+ (38)	+	ns
	2-F (14)	10	1	+	+ (45)	+	ns
	3-M (4)	10	0	–	+	–	ns
	4-M (11)	10	1	+	+	+	ns
	5-M (17)	10	5	+	+ (35)	–	ns
	6-F (9)	11	0	+	–	–	ns
	7-M (10)	11	1	+	+ (26)	+	ns
	8-F (25)	11	3	+	+ (29)	–	ns
	9-F (20)	10	2	+	+ (40)	–	ns
	10-M (7)	13	0	+	–	–	ns
	11-F (13)	13	4	+	–	–	ns
	12-M (10)	13	3	–	–	–	ns
	13-F (3)	13	0	–	–	–	ns
Klinge <i>et al.</i> [20]	1-F (13)	9	1	+ (HF)	nr	nr	–
	2-F (24)	10	4	+ (HF)	nr	nr	–
	3-F (13)	10	0	–	nr	nr	–
	5-M (29)	11	4	–	nr	nr	–
	6-M (14)	11	0	–	nr	nr	–
	7-M (10)	9	0	+ (HF)	nr	nr	Mild
Hobson-Webb and Caress [18]	1-M (26)	12	2	+	+	+	nr
Saito <i>et al.</i> [19]	1-F (20)	10	0	+	+	+	–
Present study	1-F (40)	11	1	+ (HF)	+ (34)	+	Mild
	2-M (21)	10	3	+	+	+	–
	3-M (16)	12	5	+	+	–	–
	4-M (52)	13	4	+ (HF)	–	–	Coat's syndrome
	5-F (61)	13	12	+ (HF)	–	–	–
	6-F (76)	12	15	–	–	–	–

M, male; F, female; +, present; –, absent; HF: high frequency; ns, not specified; nr, not reported.

according to her relatives, had always behaved like a small child. Her IQ score (Stanford-Binet LM) was 0.36 at 16 and 0.34 at 38 years of age.

Besides a delay in their psychomotor milestones, cases 2 and 3 had always presented autistic-type behavioural disorders. On psychological observation, the mental retardation appeared to be severe in case 2 and moderate in case 3. IQ quantification was not obtained in these patients because of the poor cooperation. Episodes of grand mal attacks were experienced by patients 1 and 3, with EEG characterized by epileptic abnormalities. At the age of 40, case 1 still needed treatment with carbamazepine and phenobarbital.

Visual disturbances were not reported for any of our six FSHD patients. By direct ophthalmoscopy, normal data were found in cases 2–6, while tortuous retinal vessels were detected in cases 1 and 4. Fluorescein angiography, in patient 4, defined the retinal abnormality

as a form of exudative vascular retinopathy (Coat's syndrome).

Table 2 shows the data on mental retardation, epilepsy and retinal pathology of our six FSHD patients with a large 4q35 deletion, compared to those of 28 similar FSHD cases reported to date.

Discussion

With prevalence rates approaching 1:15,000 [15,16] FSHD represents one of the most frequent muscular dystrophies. Genetically, this autosomal dominant disease has been mapped to the chromosome 4q35 region, where a deletion of a tandem repeat of 3.3 kb (D4Z4) has been detected [1,2]. This non-transcriptional DNA sequence seems to have a peculiar position effect on proximal upstream transcriptional genes [6,7]. In the typical phenotype, the disease presents onset in late

adolescence with slowly progressive weakness involving the face, upper girdle and arms [3,4].

In patients with a very short 4q35 fragment (10–13 kb), the disease frequently shows an unusual atypical phenotype, as in four of our six cases, with onset in the first years of life [4–6]. This early-onset variant is often referred to as infantile FSHD. Considering our group of patients and the 28 FSHD cases reported to date as a whole (Table 2), it is evident that this early-onset variant of FSHD is often, but not always, determined by a fragment size of 10–12 kb [17–20]. Occasionally, a fragment size of 13 kb [6,21] may underlie the same phenotype, as in one of our cases. An early-onset phenotype has also been described in association with fragment size as great as 19 kb [21], 20 kb [17], 21 kb [20] and 22 kb [6], which are mutations that usually determine typical adolescence onset FSHD [3,4,8,9]. These data indicate absence of a close correlation between 4q35 fragment size and severity of muscle involvement in FSHD patients; on the other hand, it is also suggested by two of our cases who, despite a very short *EcoRI* fragment (12 and 13 kb), presented the typical FSHD phenotype with adolescence onset. Altogether, these data corroborate the hypothesis that the FSHD phenotype, determined by the 4q35 deletion, may be modified by other genetic or environmental factors [4,12,22,23].

Extramuscular manifestations have often been reported in patients with FSHD [3,4,7–9,24]. Auditory impairment appears to be the most frequently detected manifestation, although its clinical significance in FSHD is still the subject of debate [4,8,9]. As the first report by Small *et al.* [25], hearing loss has been anecdotally described in many cases with FSHD, often of infantile type [26–30]. Padberg *et al.* [7] reported the first investigation primarily designed to evaluate auditory impairment in unselected series of genetically confirmed FSHD cases. They detected hearing loss in 64% of 39 patients. Conversely, in other two series of FSHD patients [8,9], hearing loss was not found to be more common than in the normal population. The patients considered in these reports presented typical adolescence onset FSHD with a 4q35 fragment size greater than 14 kb [8,9], and thus the conclusions of these studies could not be applied to the less frequent FSHD cases with a very short 4q35 fragment (10–13 kb). Comparative analysis of hearing function in 34 such patients (the six reported herein and 28 from the literature) indicated that the vast majority of them (68%) suffered from hearing loss, with prominent high frequency involvement. Limiting the evaluation to the cases with the shortest remaining fragment (11 kb or less), auditory impairment was so severe that hearing aids were needed in about half of them [17,20]. Differ-

ently, in two out of five FSHD patients with 13 kb, Jardine *et al.* [21] found a milder hearing loss. Comparison of all the analogous cases reported to date (Table 2), seems to confirmed that most patients with 13 kb (eight out of 13) present high frequency hearing loss of the mild type.

In agreement with findings on previously reported patients [26–28,30], the ABR study of our FSHD cases indicated that auditory impairment was due to a cochlear pathology, with integrity of the pathways to the temporal cortex.

The phenotype of FSHD with a large 4q35 deletion appears to be atypical also considering the frequent presence of mental retardation or epilepsy, as clinical manifestations of brain involvement, typically not reported in FSHD cases with fragment sizes greater than 13 kb [3,4]. Analysing the intelligence levels in our patients as well as in those reported to date (Table 2), it is evident that many of these 34 cases presented mental retardation. In particular, considering only the 23 in which specific intelligence evaluation was performed, clear-cut mental deficiency was found in 61% (14/23). Focusing on only the cases with 10–11 kb, the percentage increases to 92%. Moreover, in the same series of 34 FSHD patients with large deletion, epilepsy appeared often associated with mental retardation (58%). On the other hand, neither mental retardation nor epilepsy were observed in the patients with a fragment size of 13 kb, aside from one early-onset case reported by Brower *et al.* [6]. Finally, as in our cases, it is noteworthy that CT scan or MRI never detected abnormalities [4], when evaluated in patients with a very short 4q35 fragment and brain involvement.

Mild retinal abnormalities are considered part of the clinical phenotype of FSHD, although visual symptoms are generally not reported for either early-onset or typical cases [3,4]. Using retinal angiography, in a study designed to explore eye involvement in a series of FSHD cases, Padberg *et al.* [7] detected signs of mild-to-moderate retinal vasculopathy in about half of a series of 37 patients. By contrast, using routine fundoscopy, Klinge *et al.* [20] and Funakoshi *et al.* [17] produced evidence of minor retinal vessel abnormalities in 30% of their cases with a very short 4q35 fragment. Accordingly, in two of our six cases, vessel abnormalities were found by direct ophthalmoscopy, in the absence of visual complaints. In any event, the real frequency of retinal vessel alterations in such FSHD patients remains undefined as evaluation was not generally performed by fluorescein angiography, which is the only exam able to rule out retinal vascular pathology [3,7].

Taken together, the complete clinical data set on our FSHD patients with a large 4q35 deletion and 28

similar reported cases, clearly indicate that sensorineural hearing loss affects the vast majority of these subjects, as different from typical FSHD cases, in which auditory impairment did not appear to be more common than in the normal population. In addition, patients with a large 4q35 deletion, who usually present the early-onset variant of the disease, are often affected by mental retardation and epilepsy. This atypical FSHD phenotype associated with a very short 4q35 fragment size might be explained by the current pathogenetic hypothesis on FSHD [4,12], which suggests that proximal transcriptional genes may be altered by 4q35 deletion. Accordingly, larger deletions would alter a greater number of such upstream genes and possibly reach ones involved in cochlear and brain functions.

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