FSHD: a clinical follow-up

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INTRODUCTION and OBJECTIVES

Facio-Scapulo-Humeral Dystrophy (FSHD) is one of the most frequent muscular dystrophy of the adult with a prevalence of 1:20.000. It is an autosomal dominant disorder characterized by high clinical variability. It involves facial, shoulder girdle and, in most severe cases, lower limbs muscles (Figure 1 A-D). Over 95% of patients present the deletion of D4Z4 repeated units on chromosome 4q35 that causes hypomethylation of the region. In presence of permissive haplotypes, it determines overexpression of a homeobox gene, *DUX4,* that causes a toxic and pro-apoptotic effect on the muscle cells. FSHD is generally characterized by slow progression of the symptoms but, until now, no study was performed to measure the natural course of the disease. The aim of our study is to evaluate and quantify disease's progression over a 5-years mean follow-up period using the Clinical Severity Score (CSS) previously validated in 2007 by the Italian Network for FSHD.

MATERIALS AND METHODS

55 patients from the Neuromuscular Centre of the University of Padova were studied (Figure 2). Our sample includes 29 males and 26 females (M/F ratio: 1:1.12). All patients were molecularly characterized. D4Z4 fragment ranged between 17-40 Kb. There were 23 (42%) probands and 32 (58%) relatives of whom 19 were asymptomatic. Patients were clustered into 3 groups: probands, symptomatic and asymptomatic relatives. All patients were re-evaluated with CSS after a period of 5.35±1.27 years (range: 3 – 7 years) (Figure 2) by the same neurologist who performed the first visit to reduce the inter-observer variability. The score of every muscular district, the total CSS score and the MRC score were recorded at T0 and T1. Correlations between disease's progression and D4Z4 fragment's size were also evaluated between males and females.

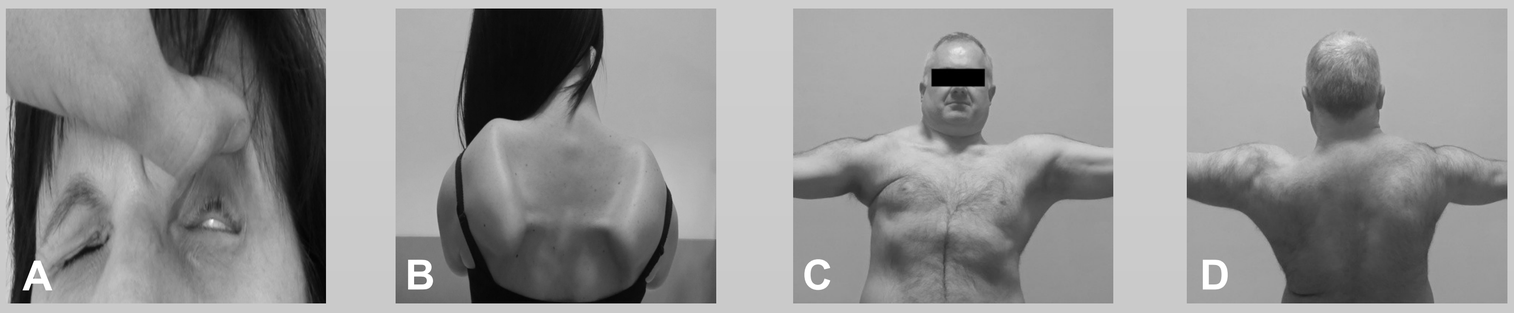

Figure 1: FSHD typical phenotype. In A weakness of orbicularis oculi. In B winging scapulae. In C and D asymmetric scapular involvement with impairment in arms abduction.

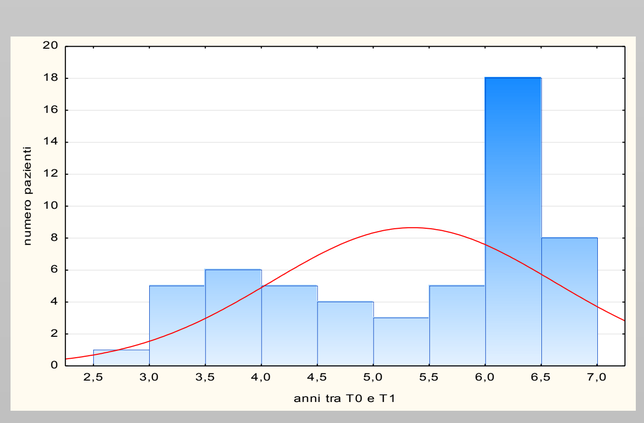

Figure 2: Number of patients clustered according to the follow-up lapse between T0 and T1.

RESULTS

After 6 years follow-up, the mean CSS difference between T0 (6.0) and T1 (7.8), and MRC score at biceps, triceps and tibialis anterior reached significance in the group o probands only. In all relatives, symptomatic or asymptomatic, differences were not significant (Table 1, Figure 3-4). Analyzing separately the CSS of every muscle district, the lower limbs presented the most significant progression of motor impairment (Figure 5). When the period of observation (T0-T1) was shortened to 3-5 years no significant differences were detected in CSS and MRC scores in any subset of patients (p = 0.78) (Figure 6). No differences in CSS and MRC score were found between sexes. Males and females progress similarly. Disease progression seems to be independent from D4Z4 fragment's size (Figure 7).

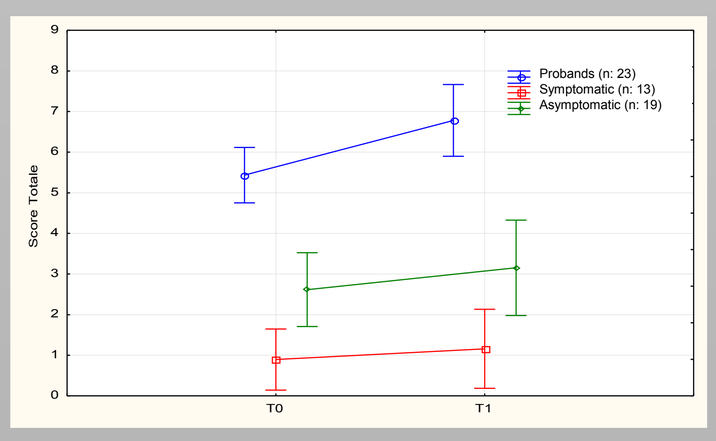

Figure 3: Mean CSS difference after a periodo of 3-7 years follow-up in the groups of probands (blue line), symptomatic (green line) and asymptomatic (red line) relatives. Differences reached significance in the group of probands only.

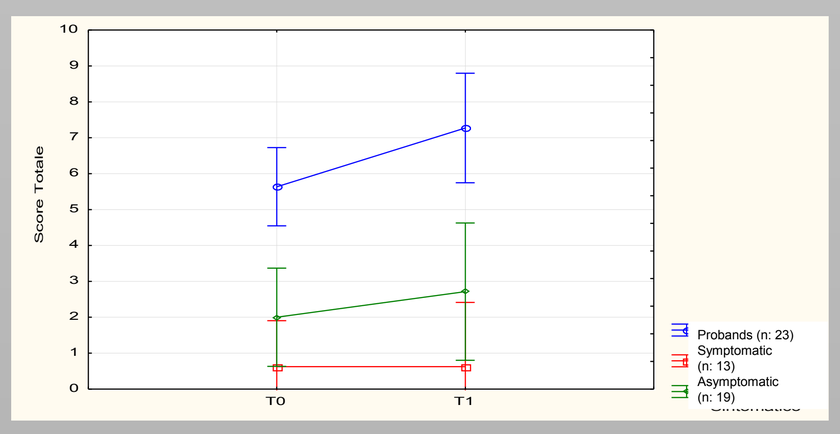

Figure 4: Mean CSS difference in a period of 6 years follow-up in the groups of probands (blue line), symptomatic (green line) and asymptomatic (red line) relatives. Differences reached significance in the group of probands only.

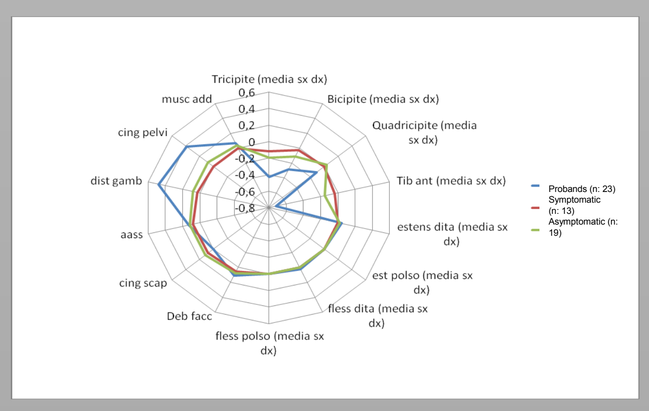

Figure 5: Radar chart showing CSS and MRC values of eachmuscular district in t he groups of probands (blue line), symptomatic (green line) and asymptomatic (red line) relatives. MRC score at biceps, triceps and tibialis anterior and the Pelvic girdle score reached significance in the group of probands.

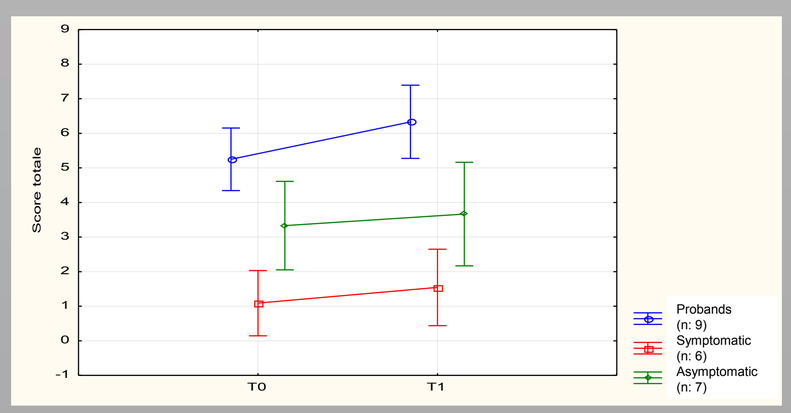

Figure 6: Mean CSS differencein a period of 3-5 years follow-up in the groups of probands (blue line), symptomatic (green line) and asymptomatic (red line) relatives. No group reached significance.

Muscley	Probands		Asymptomatic		Symptomatic		Kruskal Wallis	Mann Whitney		
	Mean	SD	Mean	SD	Mean	SD		P vs A	P vs S	A vs S
Triceps sn	-0.45	0.58	-0.13	0.32	-0.11	0.36	0.0340	0.0450	0.0800	1.0000
Triceps dx	-0.39	0.47	-0.10	0.31	-0.26	0.43	0.0450	0.0140	0.4000	0.3600
Biceps sn	-0.30	0.36	-0.02	0.11	-0.11	0.21	0.0070	0.0030	0.1800	0.4000
Biceps dx	-0.26	0.54	-0.02	0.11	-0.11	0.30	0.0400	0.0170	0.2700	0.6200
Quadriceps sm	-0.19	0.55	0.00	0.00	0.07	0.27	0.0300	0.0600	0.2500	0.7300
Quadriceps dx	-0.02	0.10	0.00	0.00	0.00	0.00	0.5000			
Tibialis anterior sn	-0.69	0.71	0.00	0.28	-0.07	0.34	0.0001	0.0006	0.0060	0.9000
Tibialis anterior dx	-0.73	0.63	-0.07	0.25	-0.23	0.63	0.0003	0.0002	0.0200	0.7600
Finger extensor sn	0.02	0.23	0.00	0.00	0.00	0.00	1.0000			
Finger extensor dx	0.06	0.31	0.00	0.00	0.03	0.13	0.5200			
Wrist extensor sn	0.00	0.00	0.00	0.00	0.00	0.00	1.0000			
Wrist extensor dx	0.00	0.00	0.00	0.00	0.00	0.00	1.0000			
Finger flexor sn	0.04	0.20	0.00	0.00	0.00	0.00	0.4500			
Finger flexor dx	0.00	0.00	0.00	0.00	0.00	0.00	1.0000			
Wrist flexor sn	0.00	0.00	0.00	0.00	0.00	0.00	1.0000			
Wrist flexor dx	0.00	0.00	0.00	0.00	0.00	0.00	1.0000			
Muscular district										
Face	0.17	0.38	0.05	0.22	0.07	0.27	0.4200			
Upper girdle	0.04	0.20	0.05	0.22	0.07	0.27	0.9100			
Upper limbs	-0.04	0.20	0.10	0.31	0.15	0.37	0.1100			
Distel lower limbs	0.30	0.55	0.05	0.22	0.07	0.27	0.0900			
Pelvic girdle	0.65	0.88	0.00	0.00	0.07	0.27	0.0004	0.0008	0.0400	0.7300
Abdominal muscles	0.13	0.34	0.00	0.00	0.07	0.27	0.2600			

Table 1: CSS and MRC scores between T0 and T1 in the three groups of probands, asymptomatic and symptomatic relatives.

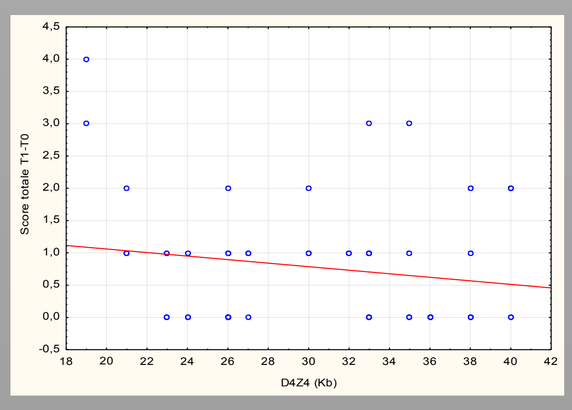

Figure 7: No correlation was found between D4Z4 size and disease progression.

CONCLUSIONS

Our study confirms the slow course of the disease and quantified the progression of motor impairment in patients affected by FSHD. Muscle wasting mainly involves proximal muscles in the upper limbs and distal muscle in the lower limbs. Deambulation seems to be the most impaired motor function in long-standing disease. CSS is a valuable tool for patients assessment but it is not enough sensible for detection of clinical variability in the short period (i.e. less than 1 year). Our study suggests that more reliable outcome measure (clinical, biochemist or imaging) are needed for trial readyness in FSHD.