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ARTICLE

A multinational study on motor function in early-onset FSHD

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Abstract

Objectives

To investigate motor function associations with age, sex, and *D4Z4* repeats among participants with early-onset facioscapulohumeral muscular dystrophy (FSHD) type 1 as defined by weakness onset before 10 years of age.

Methods

We collected standardized motor assessments, including manual muscle testing (MMT), quantitative muscle testing, functional motor evaluations, and clinical severity scores (CSSs), at 12 Cooperative International Neuromuscular Research Group centers. To measure associations, we used linear regression models adjusted for sex, evaluation age, age at onset of weakness, and *D4Z4* repeats.

Results

Among 52 participants (60% female, mean age 22.9 ± 14.7 years), weakness was most pronounced in the shoulder and abdominal musculature. Older enrollment age was associated with greater CSSs ($p = 0.003$). When adjusted for enrollment age, sex, and *D4Z4* repeats, younger age at onset of facial weakness was associated with greater CSSs, slower velocities in timed function tests, and lower MMT scores ($p < 0.05$).

Conclusion

Significant clinical variability was observed in early-onset FSHD. Earlier age at onset of facial weakness was associated with greater disease severity. Longitudinal assessments are needed to determine the rate of disease progression in this population.

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Coinvestigators are listed at links.lww.com/WNL/A340

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Glossary

BMI = body mass index; **CINRG** = Cooperative International Neuromuscular Research Group; **CSS** = clinical severity score; **4SC** = 4-step climb test; **FSHD** = facioscapulohumeral dystrophy; **MMT** = manual muscle testing; **QMT** = quantitative muscle testing; **ROM** = range of motion; **SA** = serratus anterior; **6MWT** = 6-minute walk test; **SS** = stand from supine test; **10MWR** = 10-m walk/run test.

Facioscapulohumeral dystrophy (FSHD) is an autosomal dominant muscular dystrophy with an estimated prevalence of 1 in 8,000 to 15,000.[1,2] FSHD results in progressive asymmetric atrophy and muscle weakness affecting the face and shoulder girdle, followed by involvement of the upper arm, abdominal, and lower limb muscles.[3] The onset of symptoms and disease severity vary considerably, even among individuals in the same family.[4,5] Most people with FSHD develop symptoms during the second or third decade of life, with 20% requiring a wheelchair for mobility as the disease progresses.[6,7]

FSHD is a complex epigenetic disease that is further classified into 2 subtypes.[8,9] Type 1 FSHD (FSHD1) is caused by contraction of the 3.3-kb *D4Z4* repeat array located on chromosome 4q35,[10,11] whereas type 2 FSHD (FSHD2) is associated with mutations of *SMCHD1* in the presence of a disease-permissive 4qA haplotype.[12] Approximately 5% to 10% of FSHD presents as infantile or early-onset FSHD with symptoms and signs of facial weakness before 5 years of age and shoulder weakness by 10 years of age.[13] Early-onset cases are often associated with a smaller number of *D4Z4* repeats and more severe disease phenotypes.[14–17] However, the genotype-phenotype correlation is imprecise, and substantial clinical variability may be seen even among those with very short (<4) *D4Z4* repeats.[18]

Natural history data are a prerequisite for planning FSHD treatment trials. Previous natural history studies of FSHD focused primarily on adult-onset disease.[19,20] The natural history of early-onset FSHD has not been well defined, with most information based on historical or retrospective data. The main objective of this study was to describe the baseline clinical characteristics of a multinational cohort with early-onset FSHD and to provide a comprehensive assessment of natural history with validated outcome measures that will inform the design of therapeutic trials for children and adults with early-onset FSHD.

Methods

This multicenter cross-sectional study was conducted at 12 centers of the Cooperative International Neuromuscular Research Group (CINRG) during 2012 to 2015. Because early-onset FSHD is a rare disease, all eligible patients from the neuromuscular clinics of the participating centers were invited to maximize enrollment. Participants had a genetically confirmed contraction of the *D4Z4* repeat array, ranging from 1 to 10 (10–38 kb) copies on chromosome 4q35. In addition, they met criteria for early-onset FSHD based on symptoms or signs of facial weakness before 5 years of age and/or shoulder girdle weakness before 10 years of age.[13] The age at onset of muscle weakness was based on direct interview with patients and families and review of medical records when available.

Standard protocol approvals, registrations, and patient consents

The institutional ethics and research review boards at each CINRG site approved the study. Written informed consent was obtained from all participants before study procedures. Physicians and clinical evaluators performed the study evaluations as part of a standardized protocol (appendix e-1, links.lww.com/WNL/A339). All clinical evaluators underwent central training from the lead physical therapist (T.D.) to ensure standardization and reliability of test measures. The extramuscular manifestations will be reported separately.

Baseline health information

Data collected from physicians' assessments included participant demographics, molecular genetic diagnosis from past clinical diagnostic laboratory reports, hand dominance, and standard anamnestic review of medical history, current and past symptoms related to FSHD, current and past use of an assisted mobility device, medication use, and comprehensive physical examination.

Formal motor assessments

Anthropometric measures

Weight and either standing or calculated height were used to calculate body mass index (BMI; in kilograms per meter squared). A calculated height from ulna length was performed for participants unable to stand.[21] The BMI *z* score was calculated from sex-specific World Health Organization growth charts (who.int/growthref/computation.pdf).

Quantitative muscle testing

The CINRG quantitative muscle testing (QMT) system was used to evaluate muscle strength.[22] Muscles were tested according to a standardized protocol developed for this study and informed by prior FSHD natural history studies (appendix e-2, links.lww.com/WNL/A339).[19,20]

Manual muscle testing

The modified Medical Research Council scale was used to assess strength in the major muscle groups.[23,24] Muscles were

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tested bilaterally (when applicable) in standardized positions; the peak side values were used for statistical modeling. Participants with missing manual muscle testing (MMT) scores due to an inability to test the muscle group secondary to disease progression were imputed a score of 1 as a conservative estimation of muscle strength for modeling only. MMT scores were converted to a linear measure for modeling and summation based on previous research.[20] Muscle group measures and total scores were calculated by summing all peak muscle scores within the muscle group and overall, respectively.

Timed function assessments

The maximum distance walked in 6 minutes (6MWT) was recorded in meters; tests for time to walk/run 10 m (10MWR), to climb 4 stairs (4SC), and to stand from supine (SS) were performed on ambulatory participants ≥4 years of age. Results from the timed function assessments were converted to velocity measures. Individuals who were nonambulatory and unable to perform the timed function assessments were assigned a velocity of zero for statistical modeling.

Functional motor evaluations

The Brooke upper extremity and the Vignos lower extremity scales were used for functional assessments.[23,25] Both scales were dichotomized for statistical modeling as high function (scores of 1 or 2), and low function (scores of ≥3).

Range of motion

Active and passive range of motion (ROM) of the shoulder, elbow, knee, and ankle joints was measured bilaterally and recorded in degrees.[26] The peak-side ROM was used for statistical modeling.

Clinical severity score

This FSHD global impairment measure assesses facial, shoulder girdle, upper limb, distal leg, pelvic girdle, and abdominal muscles to determine disease severity.[27]

Statistical analysis

Descriptive statistics, including mean ± SD or median (interquartile range), were used to summarize the clinical characteristics of study participants. For all measures conducted bilaterally, the side-to-side values (peak [i.e., strongest] vs nonpeak and dominant vs nondominant) were compared by use of paired *t* test or Wilcoxon signed-rank sum test. Timed functional assessments from the 6MWT, 10MWR, 4SC, and SS were converted to velocities to allow nonambulatory patients to be included in the statistical analysis of these variables. The effect of clinical characteristics, including age at enrollment, sex, number of *D4Z4* repeats, and age at onset of facial or shoulder weakness on motor outcomes, was examined separately with regression analysis; those characteristics associated with outcomes at a value of $p < 0.10$ were considered for inclusion in multivariable analyses. It was decided a priori to further examine the association between *D4Z4* repeat size and clinical characteristics; the number of *D4Z4* repeats was modeled as a continuous independent variable with each of the motor outcomes as the dependent variable in separate models adjusted for sex, evaluation age, and age at onset of muscle weakness. Similarly, to assess the relationship between motor outcomes and age at disease onset, age at first onset of either facial or shoulder girdle weakness was modeled as a continuous variable adjusted for sex, age at assessment, and number of D4Z4 repeats. Data were analyzed with SAS (version 9.2, SAS Institute Inc, Cary, NC). All statistical tests were 2 sided; a value of $p < 0.05$ was considered significant.

Results

The baseline characteristics of the 52 participants with early-onset FSHD are described in table e-1 (links.lww.com/WNL/A338). The average age at enrollment was 22.9 (SD 14.7, range 3.0–56.8) years. The mean *D4Z4* fragment size was 17.6 (SD 6.8) kb, or 3.4 (SD 2.1) repeats. Missing values in the functional motor evaluation were mostly related to disease progression; it was rarely caused by equipment malfunction or scheduling conflict. One participant declined motor assessment because of young age.

Summary of functional motor assessments

Brooke and Vignos functional grade

Twenty-five participants had good (Brooke grade 1 or 2) shoulder function, while the remaining 50% had moderate to severe impairment (31% grade 3, 4% grade 4, and 14% grade 5). Most (55%) participants could walk and climb stairs independently (Vignos grade 1); 24% could walk with assistance (18% grade 2, 4% grade 3, 0% grade 4 or 5, 2% grade 6), and 21% were wheelchair dependent (grade 7).

Range of motion

Passive ROM was preserved in most joints tested; minimal limitation in knee extension (mean −2.0°, SD 12.5°) was noted. Active ROM was reduced in the upper extremity, with a mean passive to active ROM difference of 25.2° for elbow flexion (150.3° vs 125.0°), 53.4° for shoulder abduction (167.6° vs 114.2°), and 57.9° for shoulder flexion (163.7° vs 105.8°), respectively, on the peak side.

Quantitative muscle test

QMT measurements of strength revealed relative weakness of shoulder abduction and adduction, elbow flexion, and knee extension. Side-to-side asymmetry in muscle strength was noted; the peak to nonpeak QMT scores for each muscle group, including hand grip, shoulder abductors and adductors, elbow flexors and extensors, and knee extensors and flexors, were all different ($p < 0.0001$); this was unrelated to hand dominance (appendix e-3, links.lww.com/WNL/A339).

Manual muscle test

The distribution of muscle strength by MMT revealed the most prevalent muscle weakness in the shoulder and

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abdominal musculature. Similar to QMT, there was a difference ($p < 0.05$) in the mean peak and nonpeak MMT values in all muscle groups (appendix e-4, links.lww.com/WNL/A339).

Timed function assessments

Seventy-six percent of participants could stand unsupported, and most were able to perform timed function assessments (appendix e-2, links.lww.com/WNL/A339). The mean distance for the 6MWT was 489.6 (SD 163.2) m, with a mean 10MWR time of 6.2 (SD 5.1) seconds, a mean 4SC time of 3.9 (SD 4.1) seconds, and a mean SS time of 4.5 (SD 3.4) seconds. The mean velocity was 1.0 (SD 0.7) m/s for the 6MWT, 1.7 (SD 1.4) m/s for the 10MWR, 0.3 (SD 0.3) per second for the 4SC, and 0.2 (SD 0.2) per second for SS test.

Clinical severity score

The mean clinical severity score (CSS) was 7.1 (SD 4.1, range 1–15). According to the CSS grades (appendix e-5, links.lww.com/WNL/A339), 48 (100%) had scapular girdle involvement, 6 (12%) had preserved facial movements, 5 (10%) had preserved upper limb function, 18 (38%) had normal distal leg movement, 21 (44%) had no pelvic girdle involvement, and 16 (36%) had a negative Beevor sign.[28] For participants (n = 7) who could not undergo testing of the Beevor sign, the CSS was rescaled to 14 (total score without abdominal muscle domain × 15/14) for modeling purpose only. No material differences were noted when findings from the imputed scores were compared to the subset with complete values.

Bivariate analyses

Older age at enrollment was associated with greater disease severity, as determined by higher CSSs ($p = 0.003$), and slower timed function assessment velocities (appendix e-6, links.lww.com/WNL/A339). Furthermore, younger age at onset of facial weakness was associated with slower velocities, higher CSSs, and more impaired Brooke functional grade (all $p < 0.05$, table e-2, links.lww.com/WNL/A338). In contrast, the age at onset of shoulder weakness was not associated with any motor functional measures. There was no association between the number of *D4Z4* repeats, sex, race, BMI, and motor performance. However, being underweight was associated with lower QMT and MMT scores for some muscle groups; in addition, participants with ≤4 *D4Z4* repeat units had higher CSS values (indicating greater disease severity) compared to those with >4 repeats (data not shown).

Multivariate analysis

After adjustment for age at enrollment, sex, and *D4Z4* repeats, younger age at onset of facial weakness was associated with greater CSS, slower velocities in timed function assessments, and lower MMT scores (all $p < 0.05$) (table e-3, links.lww.com/WNL/A338). Each 1-year increase in age at onset of facial weakness was associated with a 0.7-point decline in the CSS and an increase in mean total MMT score of 2.6. Similarly, the odds for higher Brooke and Vignos grades (indicating lower function) were reduced by 42% and 39%, respectively, with later-onset facial weakness (table e-3). There were no associations between age at onset of shoulder weakness and either disease severity or motor performance (all $p > 0.05$, data not shown). Participants with ≤4 *D4Z4* repeat units did not have higher CSSs compared to those with >4 repeats after accounting for sex and age at onset of facial weakness.

Discussion

Facial weakness is often the first presenting sign of FSHD, especially in the early-onset form. We identified an association between age at onset of facial weakness and motor performance in early-onset FSHD. Earlier onset of facial weakness correlated with greater disease severity after adjustment for age at enrollment and other baseline characteristics. Because the timing of facial weakness may predict disease severity, it is clinically meaningful to capture the age at onset of facial weakness accurately. Detailed prospective history and physical examination would be ideal; if not available, family photographs can be reviewed to help reduce recall bias in retrospective reports. However, as observed in our study, facial weakness can be mild or absent in ≈10% of individuals with genetically confirmed FSHD, thus limiting the generalizability of facial weakness onset age as an early predictor of disease severity.

Because FSHD is a progressive myopathy, older participants in this early-onset cohort had more prominent muscle weakness with loss of independent ambulation beginning in the second decade. Among the 36 patients who were able to complete the 6MWT, their mean *z* score for the total distance was −1.98 (SD 1.91) compared with reference data from healthy age- and sex-matched controls[29]; 41.7% had 6MWT distance at ≥2 SDs below the mean, and the frequency increased by age (11.1% at 3–9 years, 50% at 10–19 years, and 54.5% at 20–59 years of age). Because most participants could walk independently, we could not determine the association between age at onset of wheelchair dependency and number of *D4Z4* repeats, as previously reported.[7] In another FSHD study, female patients were comparatively stronger with lower disease severity compared to male patients[30]; we did not find this association in our study.

Overall, there was substantial clinical variability among participants with early-onset disease. The disease heterogeneity of FSHD among patients with 1 to 3 *D4Z4* repeats was recently highlighted by data from the Italian FSHD Registry; neither age at onset nor size of repeats was associated with disease severity.[18] Instead, higher (61%) de novo rates were found among index cases in the Italian cohort with short *D4Z4* repeats, and 55% of the de novo cases had early- (<10 years) onset disease. Furthermore, consistent with our study, facial weakness was the most common sign in most de novo cases, and their risk of motor impairment increased from 65%

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by 10 years of age to 98% by 20 years of age; however, their long-term outcome did not differ from later-onset cases.[18] In other series of infantile FSHD, most affected individuals had short *D4Z4* repeats (<15–20 kb) and early-onset disease (<10 years), but exceptions were noted.[31] Other large studies have similarly shown variable disease expressivity, penetrance, and genotype-phenotype correlations in FSHD.[30,32–34]

Because individuals with early-onset FSHD are at risk of more rapid progression, prompt diagnosis based on recognition of the pattern of muscle involvement, extramuscular features, and genetic confirmation is critical.[15] The rate of disease progression will require longitudinal studies. Because early-onset FSHD is uncommon, clinical trial recruitment of a clinically homogeneous cohort with similar age, sex, symptom onset, and *D4Z4* repeats will be challenging. It may be necessary to adjust for the effects of these factors on disease severity and motor performance. Recently, a second genetic form of FSHD2 was identified with mutations of *DNMT3B*; the mutations alter the degree of chromatin hypomethylation without contraction of *D4Z4* repeats.[35] A new comprehensive clinical evaluation form was proposed for uniform characterization of the disease phenotype, stratification for clinical trials, and identification of other genetic and epigenetic modifiers of FSHD.[32]

The cross-sectional design provides a comprehensive description of a relatively large cohort of early-onset FSHD. We detected early muscle weakness using a comprehensive panel of motor assessments. Conversion of timed function assessments to velocities enabled the inclusion of individuals with advanced disease progression by imputing a velocity score of zero.

One limitation was that historical, self-reported onset of symptoms is subject to recall bias, especially when disease recognition is delayed. The inclusion of a concurrent age- and sex-matched healthy control group to provide direct comparison of percentage predicted motor performance would have been beneficial. The genetic data were collected from multiple laboratories using varying methodologies; haplotyping of the disease-permissive 4qA allele was rarely specified, and therefore, it was not analyzed. Other disease modifiers such as *SMCHD1* are presently unknown, and parental genetics studies were not available to confirm familial or de novo mutations.

Even though the CSS is a descriptive measure of muscle involvement in FSHD, it was only weakly associated with age at onset and functional motor outcomes. A ceiling effect was also noted among those with advanced disease. Despite the fact that the serratus anterior (SA) is the second most severely affected muscle in FSHD,[36,37] 17 participants in our study appeared to have preserved SA function on the basis of clinical assessments. Muscle MRI data could enhance the determination of SA sparing as part of the clinical heterogeneity of FSHD or confirm whether other shoulder girdle stabilizers such as the pectoral muscles were able to compensate for SA weakness. Furthermore, we recommend additional functional measures such as the Performance of Upper Limb to more effectively assess shoulder girdle function and endurance in FSHD studies.[38]

Natural history studies provide essential data for the design of clinical trials. Because effort-dependent functional motor assessments can be challenging to measure across the life span of a progressive disease, other outcome measures such as serum biomarkers and muscle imaging studies could serve as surrogates of disease progression.[39,40] Further longitudinal studies of early-onset FSHD will help determine the rate of clinical progression in FSHD subgroups and identify sensitive and reliable outcome measures.

Author contributions

Jean K. Mah designed the study, facilitated data collection, interpreted data, wrote and revised the manuscript. Jia Feng contributed to design of the study, analyzed data, performed statistical analysis, and revised the manuscript. Marni B. Jacobs analyzed data, performed statistical analysis, and revised the manuscript. Tina Duong contributed to design of the study, facilitated data collection, and revised the manuscript. Kate Carroll, Katy de Valle, Cara L. Carty, and Lauren P. Morgenroth facilitated data collection, interpreted data, and revised the manuscript. Michela Guglieri, Monique M. Ryan, Paula R. Clemens, Mathula Thangarajh, Richard Webster, Edward Smith, Anne M. Connolly, Craig M. McDonald, Peter Karachunski, Mar Tulinius, and Amy Harper facilitated data collection and revised the manuscript. Avital Cnaan and Yi-Wen Chen contributed to design of the study and revised the manuscript.

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Disclosure

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References

1. Mostacciuolo ML, Pastorello E, Vazza G, et al. Facioscapulohumeral muscular dystrophy: epidemiological and molecular study in a north-east Italian population sample. Clin Genet 2009;75:550–555.
2. Deenen JC, Arnts H, van der Maarel SM, et al. Population-based incidence and prevalence of facioscapulohumeral dystrophy. Neurology 2014;83:1056–1059.
3. Sacconi S, Salviati L, Desnuelle C. Facioscapulohumeral muscular dystrophy. Biochim Biophys Acta 2015;1852:607–614.
4. Lemmers RJ, Goeman JJ, van der Vliet PJ, et al. Inter-individual differences in CpG methylation at D4Z4 correlate with clinical variability in FSHD1 and FSHD2. Hum Mol Genet 2015;24:659–669.
5. Jones TI, King OD, Himeda CL, et al. Individual epigenetic status of the pathogenic D4Z4 macrosatellite correlates with disease in facioscapulohumeral muscular dystrophy. Clin Epigenetics 2015;7:37.
6. Padberg GW, Lunt PW, Koch M, Fardeau M. Diagnostic criteria for facioscapulohumeral muscular dystrophy. Neuromuscul Disord 1991;1:231–234.
7. Statland JM, Tawil R. Risk of functional impairment in facioscapulohumeral muscular dystrophy. Muscle Nerve 2014;49:520–527.
8. van der Maarel SM, Frants RR. The D4Z4 repeat-mediated pathogenesis of facioscapulohumeral muscular dystrophy. Am J Hum Genet 2005;76:375–386.
9. Himeda CL, Jones TI, Jones PL. Facioscapulohumeral muscular dystrophy as a model for epigenetic regulation and disease. Antioxid Redox Signal 2015;22:1463–1482.
10. Wijmenga C, Frants RR, Brouwer OF, Moerer P, Weber JL, Padberg GW. Location of facioscapulohumeral muscular dystrophy gene on chromosome 4. Lancet 1990;336:651–653.
11. van Deutekom JC, Wijmenga C, van Tienhoven EA, et al. FSHD associated DNA rearrangements are due to deletions of integral copies of a 3.2 kb tandemly repeated unit. Hum Mol Genet 1993;2:2037–2042.
12. Lemmers RJ, Tawil R, Petek LM, et al. Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. Nat Genet 2012;44:1370–1374.
13. Brouwer OF, Padberg GW, Wijmenga C, Frants RR. Facioscapulohumeral muscular dystrophy in early childhood. Arch Neurol 1994;51:387–394.
14. Chen TH, Lai YH, Lee PL, et al. Infantile facioscapulohumeral muscular dystrophy revisited: expansion of clinical phenotypes in patients with a very short EcoRI fragment. Neuromuscul Disord 2013;23:298–305.
15. Tawil R, Kissel JT, Heatwole C, Pandya S, Gronseth G, Benatar M. Evidence-based guideline summary: evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology 2015;85:357–364.
16. Jardine PE, Koch MC, Lunt PW, et al. De novo facioscapulohumeral muscular dystrophy defined by DNA probe p13e-11 (D4F104S1). Arch Dis Child 1994;71:221–227.
17. Klinge L, Eagle M, Haggerty ID, Roberts CE, Straub V, Bushby KM. Severe phenotype in infantile facioscapulohumeral muscular dystrophy. Neuromuscul Disord 2006;16:553–558.
18. Nikolic A, Ricci G, Sera F, et al. Clinical expression of facioscapulohumeral muscular dystrophy in carriers of 1-3 D4Z4 reduced alleles: experience of the FSHD Italian national registry. BMJ Open 2016;6:e007798.
19. Tawil R, McDermott MP, Mendell JR, Kissel J, Griggs RC. Facioscapulohumeral muscular dystrophy (FSHD): design of natural history study and results of baseline testing: FSH-DY group. Neurology 1994;44:442–446.
20. A prospective, quantitative study of the natural history of facioscapulohumeral muscular dystrophy (FSHD): implications for therapeutic trials: the FSH-DY Group. Neurology 1997;48:38–46.
21. Gauld LM, Kappers J, Carolin JB, Robertson CF. Height prediction from ulna length. Dev Med Child Neurol 2004;45:475–480.
22. Escolar DM, Henricson EK, Mayhew J, et al. Clinical evaluator reliability for quantitative and manual muscle testing measures of strength in children. Muscle Nerve 2001;24:787–793.
23. Brooke MH, Griggs RC, Mendell JR, Fenichel GM, Shumate JB, Pellegrino RJ. Clinical trial in Duchenne dystrophy, I: the design of the protocol. Muscle Nerve 1981;4:186–197.
24. Lord JP, Portwood MM, Fowler WM, Lieberman JS, Carson R. Upper vs lower extremity functional loss in neuromuscular disease. Arch Phys Med Rehabil 1987;68:8–9.
25. Vignos PJ, Spencer GE, Archibald KC. Management of progressive muscular dystrophy in childhood. JAMA 1963;184:89–96.
26. Johnson ER, Fowler WM, Lieberman JE. Contractures in neuromuscular disease. Arch Phys Med Rehab 1992;73:807–810.
27. Lamperti C, Fabbri G, Vercelli L, et al. A standardized clinical evaluation of patients affected by facioscapulohumeral muscular dystrophy: the FSHD clinical score. Muscle Nerve 2010;42:213–217.
28. Mathys J, De Marchis GM. Teaching video neuroimages: Beevor sign: when the umbilicus is pointing to neurologic disease. Neurology 2013;80:e20.
29. McKay MJ, Baldwin JN, Ferreira P, Simic M, Vanicek N, Burns J; 1000 Norms Project Consortium. Reference values for developing responsive functional outcome measures across the lifespan. Neurology 2017;88:1512–1519.
30. Tonini MM, Passos-Bueno MR, Cerqueira A, Matioli SR, Pavanello R, Zatz M. Asymptomatic carriers and gender differences in facioscapulohumeral muscular dystrophy (FSHD). Neuromuscul Disord 2004;14:33–38.
31. Goselink RJ, Schreuder TH, Mul K, et al. Facioscapulohumeral dystrophy in children: design of a prospective, observational study on natural history, predictors and clinical implications (iFocus FSHD). BMC Neurol 2016;16:138.
32. Sakellariou P, Kekou K, Fryssira H, et al. Mutation spectrum and phenotypic manifestation in FSHD Greek patients. Neuromuscul Disord 2012;22:339–349.
33. Ricci G, Scionti I, Sera F, et al. Large scale genotype-phenotype analyses indicate that novel prognostic tools are required for families with facioscapulohumeral muscular dystrophy. Brain 2013;136:3408–3417.
34. Ricci G, Ruggiero L, Vercelli L, et al. A novel clinical tool to classify facioscapulohumeral muscular dystrophy phenotypes. J Neurol 2016;263:1204–1214.
35. van den Boogaard ML, Lemmers RJ, Balog J, et al. Mutations in DNMT3B modify epigenetic repression of the D4Z4 repeat and the penetrance of facioscapulohumeral dystrophy. Am J Hum Genet 2016;98:1020–1029.
36. Tasca G, Monforte M, Iannaccone E, et al. Upper girdle imaging in facioscapulohumeral muscular dystrophy. PLoS One 2014;9:e100292.
37. Gerevini S, Scarlato M, Maggi L, et al. Muscle MRI findings in facioscapulohumeral muscular dystrophy. Eur Radiol 2016;26:693–705.
38. Mayhew A, Mazzone ES, Eagle M, et al. Development of the performance of the upper limb module for Duchenne muscular dystrophy. Dev Med Child Neurol 2013;55:1038–1045.
39. Petek LM, Rickard AM, Budech C, et al. A cross sectional study of two independent cohorts identifies serum biomarkers for facioscapulohumeral muscular dystrophy (FSHD). Neuromuscul Disord 2016;26:405–413.
40. Tawil R, Padberg GW, Shaw DW, van der Maarel SM, Tapscott SJ; FSHD Workshop Participants. Clinical trial preparedness in facioscapulohumeral muscular dystrophy: clinical, tissue, and imaging outcome measures 29–30 May 2015, Rochester, New York. Neuromuscul Disord 2016;26:181–186.

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FULL-LENGTH ARTICLE NPub.org/rwgtpf

A multinational study on motor function in early-onset FSHD

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Study question

What is the relationship between age at onset and motor impairment severity in patients with early-onset facioscapulohumeral muscular dystrophy (FSHD)?

Summary answer

Earlier ages at onset of facial weakness are associated with greater motor impairment severities in patients with early-onset FSHD.

What is known and what this paper adds

FSHD is a complex epigenetic disease, and most natural history studies have examined adult-onset FSHD. This study characterizes the natural history of early-onset FSHD with a focus on the clinical associations of age at onset of muscle weakness with disease severity.

Participants and setting

This study enrolled 52 participants (60% female; mean age, 22.9 ± 14.7 years) with early-onset FSHD from 12 multinational centers in United States, Canada, Europe, and Australia belonging to the CINRG research network between 2012 and 2015. Early-onset FSHD was defined as developing facial weakness before 5 years of age, shoulder girdle weakness before 10 years of age, or both. All patients had 1–10 copies of the *D4Z4* repeat array.

Design, size, and duration

This study is a cross-sectional natural history study. The age at onset was determined by interviewing patients and their families and reviewing medical records. The participants completed a battery of standardized outcome measures assessing strength and motor function. These included manual muscle testing, timed function tests, FSHD Clinical Severity Score determinations and quantitative muscle testing.

Primary outcomes

The primary outcome was the association between age at onset and motor assessment results, as determined via regression modeling with adjustments for various demographic and clinical variables.

Main results and the role of chance

Younger ages at onset of facial weakness were associated with greater Clinical Severity Scores, slower velocities in timed function assessments, and lower manual muscle test scores (all $p < 0.05$). No such associations were detected for ages at onset of shoulder weakness.

Table Age at onset of facial weakness and motor outcome; results from multivariable models[a]

	Age at onset of facial weakness, y		
Motor Function Assessment	**Beta (SE)**	***p* Value**	**R^2**
MMT Total Score (based on peak value)	2.56 (0.83)	**0.004**	0.39
Velocity of Timed Function Tests			
10 m run/walk (m/s)	0.24 (0.06)	**0.0002**	0.44
4 stairs climb (task/s)	0.05 (0.01)	**0.0004**	0.43
Rise from floor (rising velocity)	0.04 (0.01)	**0.0002**	0.44
6 min walking test (m/s)	0.12 (0.03)	**0.0005**	0.40
Total Clinical Severity Score	−0.69 (0.19)	**0.0007**	0.49

[a]Results based on linear regression for continuous variables and logistic regression for categorical variables, adjusted for age at enrollment, gender, and number of D4Z4 repeats.
Numbers in bold significant at $p < 0.05$.
Excerpted from table e-3.

Bias, confounding, and other reasons for caution

Recall bias might have influenced the reported age at onset of symptoms. There was no healthy control group for motor performance comparisons. The genetic data were collected from clinical chart review from multiple laboratories using different methodologies.

Generalizability to other populations

Facial weakness is mild or absent in ~10% of patients with genetically confirmed FSHD. This limits the generalizability of age at onset of facial weakness as a predictor of disease severity.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

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