



Universiteit
Leiden
The Netherlands

Natural history of facioscapulohumeral dystrophy in children: a 2-year follow-up

Dijkstra, J.N.; Goselink, R.J.M.; Alfen, N. van; Groot, I.J.M. de; Pelsma, M.; Stoep, N. van der; ... ; Erasmus, C.E.

Citation

Dijkstra, J. N., Goselink, R. J. M., Alfen, N. van, Groot, I. J. M. de, Pelsma, M., Stoep, N. van der, ... Erasmus, C. E. (2021). Natural history of facioscapulohumeral dystrophy in children: a 2-year follow-up. *Neurology*, 97(21), E2103-E2113.
doi:10.1212/WNL.0000000000012882

Version: Publisher's Version
License: [Creative Commons CC BY-NC-ND 4.0 license](https://creativecommons.org/licenses/by-nc-nd/4.0/)
Downloaded from: <https://hdl.handle.net/1887/3249771>

Note: To cite this publication please use the final published version (if applicable).

Natural History of Facioscapulohumeral Dystrophy in Children

A 2-Year Follow-up

Jildou N. Dijkstra, MD, Rianne J.M. Goselink, MD, PhD, Nens van Alfen, MD, PhD, Imelda J.M. de Groot, MD, PhD, Maaïke Pelsma, MSc, Nienke van der Stoep, PhD, Thomas Theelen, MD, PhD, Baziel G.M. van Engelen, MD, PhD, Nicol C. Voermans, MD, PhD,* and Corrie E. Erasmus, MD, PhD*

Neurology® 2021;97:e2103-e2113. doi:10.1212/WNL.00000000000012882

Correspondence

Dr. Erasmus
corrie.erasmus@
radboudumc.nl

Abstract

Background and Objectives

Data on the natural history of facioscapulohumeral dystrophy (FSHD) in childhood are limited and critical for improved patient care and clinical trial readiness. Our objective was to describe the disease course of FSHD in children.

Methods

We performed a nationwide, single-center, prospective cohort study of FSHD in childhood assessing muscle functioning, imaging, and quality of life over 2 years of follow-up.

Results

We included 20 children with genetically confirmed FSHD who were 2 to 17 years of age. Overall, symptoms were slowly progressive, and the mean FSHD clinical score increased from 2.1 to 2.8 ($p = 0.003$). The rate of progression was highly variable. At baseline, 16 of 20 symptomatic children had facial weakness; after 2 years, facial weakness was observed in 19 of 20 children. Muscle strength did not change between baseline and follow-up. The most frequently and most severely affected muscles were the trapezius and deltoid. The functional exercise capacity, measured with the 6-minute walk test, improved. Systemic features were infrequent and nonprogressive. Weakness-associated complications such as lumbar hyperlordosis and dysarthria were common, and their prevalence increased during follow-up. Pain and fatigue were frequent complaints in children, and their prevalence also increased during follow-up. Muscle ultrasonography revealed a progressive increase in echogenicity.

Discussion

FSHD in childhood has a slowly progressive but variable course over 2 years of follow-up. The most promising outcome measures to detect progression were the FSHD clinical score and muscle ultrasonography. Despite this disease progression, an improvement on functional capacity may still occur as the child grows up. Pain, fatigue, and a decreased quality of life were common symptoms and need to be addressed in the management of childhood FSHD. Our data can be used to counsel patients and as baseline measures for treatment trials in childhood FSHD.

*These authors contributed equally to this work.

From the Departments of Neurology (J.N.D., N.v.A., B.G.M.v.E., N.C.V.) and Rehabilitation (I.J.M.d.G., M.P.), Donders Centre of Neuroscience, Department of Pediatric Neurology (J.N.D., C.E.E.), Amalia Children's Hospital, and Department of Ophthalmology (T.T.), Radboud University Medical Centre, Nijmegen, the Netherlands; Department of Neurology (R.J.M.G.), Jönköping, Region Jönköping County, and Department of Biomedical and Clinical Sciences (R.J.M.G.), Linköping University, Linköping, Sweden; and Department of Clinical Genetics (N.v.d.S.), Leiden University Medical Centre, the Netherlands

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Glossary

COVID-19 = coronavirus disease 2019; **FSHD** = facioscapulohumeral dystrophy; **MFM** = Motor Function Measure; **MRC** = Medical Research Council.

Facioscapulohumeral muscular dystrophy (FSHD) is a slowly progressive muscular dystrophy and one of the most common hereditary muscle diseases, with an estimated prevalence of 12 per 100,000 in the Netherlands.¹ FSHD typically causes progressive, asymmetric weakness of the facial, scapulohumeral, tibial, and axial muscles, with a highly heterogeneous disease severity.²⁻⁴ Type 1 FSHD, responsible for >95% of the FSHD cases, is associated with a contraction of the D4Z4-repeat on chromosome 4q35. In the normal population, this array contains 11 to 100 D4Z4 repeats, whereas in FSHD, there is a contraction of the D4Z4 region to 1 to 10 repeat units, leading to D4Z4 hypomethylation.⁵⁻⁷ In type 2 FSHD, hypomethylation of the D4Z4 repeats is caused by mutations in *SMCHD1* or *DNMT3B* gene.⁵⁻⁷ Both types lead to disease in the setting of a permissive allele, with aberrant *DUX4* expression in skeletal muscle.⁵

The age at symptom onset in FSHD is variable; in approximately one-fifth of all patients, FSHD starts in childhood.^{4,6} Approximately half of the children with FSHD fulfill the criteria of early-onset FSHD, a subgroup defined by facial weakness before the age of 5 years and scapular weakness before the age of 10 years.^{6,8,9} This subgroup is associated with a fewer number of D4Z4 repeats, more extensive muscle weakness, and more systemic features (including hearing loss, retinal abnormalities, epilepsy, intellectual disability, and cardiac arrhythmias) compared to those of similar age and disease duration with classic-onset FSHD.^{6,10-15}

Childhood FSHD is characterized by significant variability in symptoms and clinical disease course. However, so far, only cross-sectional observations are available, and little is known about the natural course in this age group. The rate of disease progression and the presence of systemic features within this population are also unknown.^{16,17} Identification of prognostic factors that can be used in patient care and counseling is needed. Knowledge of the natural history is also required for the design of clinical trials.

In this study, we present the 2-year follow-up of a nationwide prospective cohort study of 28 children diagnosed with FSHD in the Netherlands. Baseline data were reported as the iFocus FSHD study.^{18,19} The primary aim of the current work was to assess the clinical features and natural course of FSHD in childhood in a 2-year follow-up period, to identify prognostic factors of disease severity and progression rate, and to find promising outcome measures that can serve as a base for further clinical trials.

Methods

Patients and Design

This is a prospective cohort study of FSHD in childhood. The iFocus FSHD study cohort includes 28 children with

genetically confirmed type 1 FSHD who were 0 to 17 years of age and living in the Netherlands, of whom 1 patient was asymptomatic at baseline. A detailed protocol and description of the baseline characteristics can be found elsewhere.^{18,19}

Clinical Assessments

Clinical assessment of the patients was performed by the same examiners at study initiation and after 2 years of follow-up. The follow-up measurements took place from March 2018 until March 2020. All assessments were performed as a part of this study. The study visit took ≈4 hours, including a lunch break. When patients were unable to visit the study site, information was obtained by a phone interview with the patient or a parent, supplemented with information from the electronic health record, including a recent evaluation by the participant's pediatric neurologist or rehabilitation physician. A full description of the study procedures can be found in the published protocol.¹⁸

In brief, the clinical phenotype of each participant was assessed by the Motor Function Measure (MFM)²⁰; the shoulder dimension of the Performance of the Upper Limb module^{21,22}; manual muscle force testing with the Medical Research Council (MRC) sum score from the trapezius, deltoid, biceps brachii, finger flexors, quadriceps femoris, tibialis anterior, and gastrocnemius muscle on both sides²³; and testing motor performance with the 6-minute walk test.²⁴ The MFM assesses proximal, distal, and axial motor functions and has been developed for the broad spectrum of neuromuscular diseases.²⁰ A short form is validated for the use in children 2 to 7 years of age.²⁵ The Performance of the Upper Limb scale was developed to measure upper limb function in patients with Duchenne muscular dystrophy. Weakness is tested through 3 domains: shoulder, mid, and distal, of which the shoulder domain is relevant for the FSHD population (minimal score 0, maximum score 16).²² Results of the 6-minute walk test were expressed as a z score (the number of SDs from the mean for sex and age in healthy individuals).²⁶ In addition, the FSHD clinical score (an evaluation scale that assesses the strength and functionality of 6 different groups of muscles typically involved in FSHD; total score ranges from 0 when no symptoms are present to a maximum of 15)²⁷ and (age-corrected) FSHD clinical severity scale (a score ranging from 0–10 that evaluates the extent of weakness in FSHD, considering the descending spread of symptoms)^{28,29} were scored. The burden of disease on quality of life was assessed by asking about the presence and location of pain, evaluating fatigability (NeuroQoL fatigue domain³⁰), and scoring the Kidscreen questionnaire.³¹ These questionnaires were completed by children ≥8 years of age; if participants were younger, their caregivers were asked to complete these forms.

Information about (para)medical treatments was obtained from an interview with the patient and/or parent and concerned the doctors and therapists involved in the treatment and the frequency of these visits. Muscle imaging was performed with muscle ultrasonography, with visual grading according to the Heckmatt scale (a 4-point visual grading scale to classify muscle intensity, ranging from 1 for normal ultrasound appearance to 4 for very strongly increased echogenicity) and quantitative gray scale analysis to determine echogenicity of the bilateral trapezius, biceps brachii, rectus abdominis, rectus femoris, and tibialis anterior muscles.³² Gray scale results were expressed as a *z* score, that is, the number of SDs from the mean, after comparing the echogenicity to a muscle-specific reference value. Patients were screened for systemic disease features with ophthalmologic screening, including a fundoscopy and visual acuity testing by an ophthalmologist, tone- and speech audiometry by an audiometrist, an ECG, and observation of possible spinal deformities.

Statistical Analyses

Statistical analyses were performed with SPSS version 25 (IBM SPSS Inc, Chicago IL). Continuous parametric variables were expressed as mean and SDs, whereas continuous nonparametric variables were expressed as median and interquartile ranges. Categorical data were given as a percentage. The Kolmogorov-Smirnov test was used for testing normality assumptions in the distribution of the data. For continuous variables with a normal distribution, a paired *t* test was performed to test a mean difference between baseline and the 2-year follow-up. The Wilcoxon signed-rank test was performed to compare nonparametric continuous variables, and the McNemar test was used for comparing paired categorical data. For comparison between the early-onset and classic-onset groups at the 2-year follow-up, the Mann-Whitney *U* test was used for nonparametric continuous variables, the independent *t* test was used for continuous variables with a normal distribution, and the Fisher exact test was used for categorical variables. Linear mixed models were applied to analyze differences in disease progression. The continuous variable of the FSHD clinical score was used as the primary outcome, whereas the repeat length (divided into categories of 1–3, 4–6, and 7–10 D4Z4 repeat units), age at baseline, and sex were used as the fixed-effect predictors. The level of statistical significance was set at ≤ 0.05 .

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol has been approved by the Medical Review Ethics Committee region Arnhem-Nijmegen (NLS53213.091.15). Written consent for study participation was provided by parents/legal guardians of all participants and by participants 12 to 18 years of age.^{18,19}

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

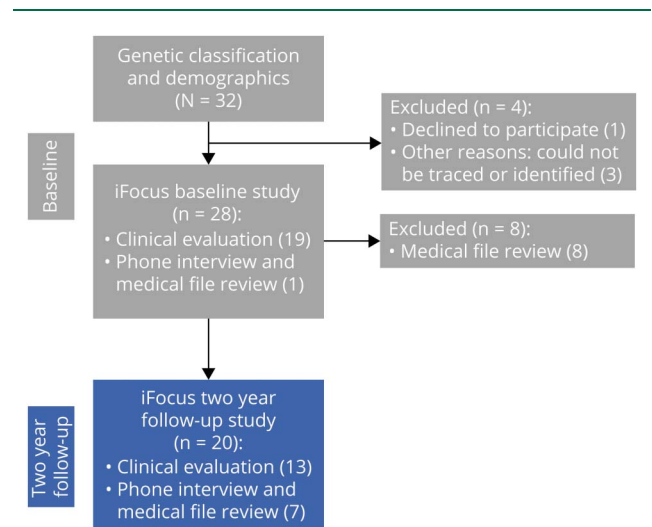
Results

Demographics and Genetic Characteristics

Of the 28 participants in the baseline study, a total of 20 children from 17 families, including 3 sibling pairs, could be included for this follow-up study. Thirteen of them were clinically examined at the study location. An electronic health record review combined with a telephone interview was performed in 7 participants; 2 of them could not be examined at the study location because of the coronavirus disease 2019 (COVID-19) pandemic restrictions; the other 5 were unable to visit for other reasons, mainly because of the added burden of a hospital visit (Figure 1). Participants were very cooperative; all of them gave permission to approach them again for future study visits.

The demographic and genetic characteristics of the cohort of 20 children who completed the 2-year follow-up are shown in Table 1. We observed a significant correlation between mean number of units in the pathogenic D4Z4 repeat and the age at onset, with a lower number of D4Z4 units associated with a younger age at onset ($r = 0.498$, $p = 0.015$). No significant correlation between the number of D4Z4 repeats and disease severity as measured by the FSHD clinical score and clinical severity scale was found at either baseline or follow-up. In addition, no correlation between the age at onset and disease severity (FSHD clinical score and clinical severity scale) was found.

Figure 1 Flow Diagram of Patient Inclusion in Previously Published Baseline Study (Gray) and Current 2-Year Follow-up Study (Blue)



The 8 children for whom only an electronic health record review had been performed at baseline were not invited for follow-up. However, their baseline characteristics, including the mean age at time of baseline examination, age at onset of symptoms, age at time of diagnosis, sex, and mean number of D4Z4 repeats, were similar to those of the group of children who were included in this follow-up study.

Table 1 Demographic and Genetic Characteristics in Current 2-Year Follow-up Study

Demographics	Value	Mean	Range	SD
Age at baseline examination, y	20	10.8	2 to 17	4.6
Male sex, n (%)	8 (40)			
D4Z4 ^a repeat units, n	20	5.1	2 to 10	2.2
Delta 1 methylation, % ^b	13	-7.2	-13 to 5	5.3
Hereditary pattern, n/total (%)				
Maternal AD	10/20 (50)			
Paternal AD	7/20 (35)			
Sporadic (de novo mutations)	3/20 (15)			
Mosaic inheritance, n/total (%)	0/16 (0)			
Onset type, n/total (%)				
Early onset	8/20 (40)			
Classic onset	10/20 (50)			
Too young for classification	1/20 (5)			
Asymptomatic	1/20 (5)			
Age at symptom onset, y	19 ^c	6.9	1–16	5.1
Age at diagnosis, y	20	9.5	0–17	5.1

Abbreviation: AD = autosomal dominant.

^a Mean number of units within the pathogenic D4Z4 repeat.

^b The observed methylation minus the predicted methylation based on the D4Z4 repeat size.

^c One child was from a family with facioscapulohumeral dystrophy and had been tested and diagnosed asymptotically.

Clinical Characteristics and Changes Over 2 Years

Muscle Function

At baseline, 15 of 20 patients (75%) had facial weakness; 2 years later, this had increased to 19 of 20 (95%). One child developed new scapular weakness during follow-up; a total of 6 of 15 patients had functional impairment of the shoulder or arm after 2 years. The mean MRC sum score of the group did not change between baseline and follow-up and varied between 60 and 70 (median 69, maximum score 70). The most frequently and most severely affected muscles were the trapezius and deltoid, but we also observed weakness of the biceps brachii, quadriceps, tibialis anterior, and gastrocnemius muscles. The mean clinical severity scale was stable over the 2-year period, despite variability between individuals. The mean FSHD clinical score increased from 2.1 to 2.8 (range 1–8, $p = 0.003$). The mean result of the 6-minute walk test and MFM showed a tendency toward an increase, but this did not reach statistical significance. Despite better test scores during follow-up, the 6-minute walk distance was on average still below the mean for sex and age (mean -1.3 SDs, range -2.7 to 0.2 , SD 1.0), and a large variability between patients was

observed. During follow-up, 11 of 20 patients (55%) were given physical therapy compared to 8 of 20 (40%) at baseline.

All muscle measurements are summarized in Table 2. Figure 2 displays the change in FSHD clinical score, MFM, the 6-minute walk test, and the quantitative muscle ultrasonography results of individual patients over the course of 2 years.

Muscle Imaging

Visual muscle ultrasound grading from 14 children at baseline and 9 children at follow-up showed a mean Heckmatt score of 1.4 and 1.6, respectively. Quantitative muscle ultrasound showed an increase in the mean z scores from 1.0 to 2.1 after 2 years (Table 2).

The visual grading correlated moderately to strongly with the quantitative score (baseline $r = 0.55$, $p = 0.02$; 2-year follow-up $r = 0.88$, $p = 0.001$). Figure 3A shows mean z score per muscle at the 2-year follow-up. All clinically affected muscles had an increased echogenicity except for the rectus abdominis. Three patients with an increased lumbar lordosis, considered to be a sign of weakness of the abdominal muscles in FSHD,⁴ did not have an increased echo intensity of the bilateral rectus abdominis. In addition, spinal and hip girdle muscle weakness contributes to postural instability in FSHD.³³ These muscles were not evaluated by muscle ultrasound. Not all muscles with an increased echogenicity were clinically affected. We found a negative correlation between the mean quantitative gray scale analysis z score and the MRC sum score ($r = -0.74$, $p = 0.01$). Disease severity as measured by the FSHD clinical score demonstrated a trend toward a positive correlation with the mean z scores, but this did not reach statistical significance ($r = 0.51$, $p = 0.07$). One child showed a deterioration on muscle ultrasound with a z score increase of 1.06 but no clinical changes as measured by the FSHD clinical score. Figure 2D shows the changes in mean echogenicity in individual patients over the course of 2 years and demonstrates the variability in progression. Figure 3, B and C shows the distribution of the measured muscles at baseline and at follow-up by visual (Heckmatt score) and quantitative (z score) analysis.

Systemic Features

The presence of systemic features is shown in Table 3.

Vision

None of the children or parents reported vision loss. Despite normal visual acuity, retinal abnormalities were frequently observed on fundoscopy in 6 of 8 patients tested. Retinal changes consisted of mild tortuosity of the retinal arteries. The degree of retinal abnormalities did not change over 2 years. Coats disease with retinal detachment was not observed.

Hearing

One child reported hearing problems, and in 2 children (12.5%), a hearing loss was detected by audiometry. One

Table 2 Clinical and Imaging Characteristics at Baseline and 2-Year Follow-up

	No. of participants (at baseline—2-y follow-up)	Baseline scoring	2-y follow-up scoring	p Value
Motor functioning, n/total (%)				
Facial weakness^a	20–20	15/20 (75)	19/20 (95)	0.13 ^d
No weakness		5 (25)	1 (5)	
Moderate weakness		12 (60)	15 (75)	
Severe weakness		3 (15)	4 (20)	
Scapular weakness,^b n/total (%)	15–15	5/15 (33)	6/15 (40)	1.00 ^d
MRC sum score (0–70), median (IQR)	18–18	70 (2)	69 (4)	0.30 ^e
Clinical severity scale (0–10), mean ± SD (range)	20–20	2.2 ± 1.5 (0–6)	2.6 ± 1.8 (0–6)	0.18 ^f
FSHD clinical score (0–15), mean ± SD (range)	20–20	2.1 ± 1.7 (0–6)	2.8 ± 1.9 (0–8)	0.003 ²
6-min walk test score, No. of SDs, mean ± SD	13–12	–2.1 ± 1.5	–1.3 ± 1.0	0.07 ^f
Motor Function Measure score, median (IQR), %	16–16	99 (1.8)	100 (0.8)	0.11 ^e
Muscle imaging				
MUS score (z score)^c (mean ± SD)	14–9	1.0 ± 1.4	2.1 ± 2.0	0.02 ^f
Heckmatt score (1–4) (mean ± SD)	14–9	1.4 ± 0.4	1.6 ± 0.4	0.07 ^f

Abbreviations: FSHD = facioscapulohumeral dystrophy; MRC = Medical Research Council; MUS = muscle ultrasound.

^a Based on ≥1 points on the facial weakness domain of the FSHD clinical score.

^b Based on a score of ≤15 on the Performance of the Upper Limb shoulder module.

^c Mean z score of the quantified echogenicity per muscle measured by MUS.

^d McNemar test.

^e Wilcoxon signed-rank test.

^f Paired t test.

child had a conductive hearing deficit at baseline and a normal audiometry during follow-up. There were no patients with a newly diagnosed hearing deficit on follow-up.

Cardiac Function

No changes were observed in the frequency of abnormalities seen on the ECG. We found a right-axis deviation without clinical consequences in 1 child.

Skeletal Features

The percentage of children with lumbar hyperlordosis showed an increase from 35% to 53% over 2 years, but this change was not found to be statistically significant (Table 3). At baseline, a mild scoliotic posture was seen in 2 participants; however, this was no longer observed during the neurologic examination at the 2-year follow-up visit.

Speaking and Swallowing

Bulbar dysarthria was found in 25% of children on baseline, and its occurrence increased to 50% after the 2-year follow-up. All children with severe facial weakness had dysarthric speech. No changes were observed in the number of children with swallowing difficulties over time.

Central Nervous System

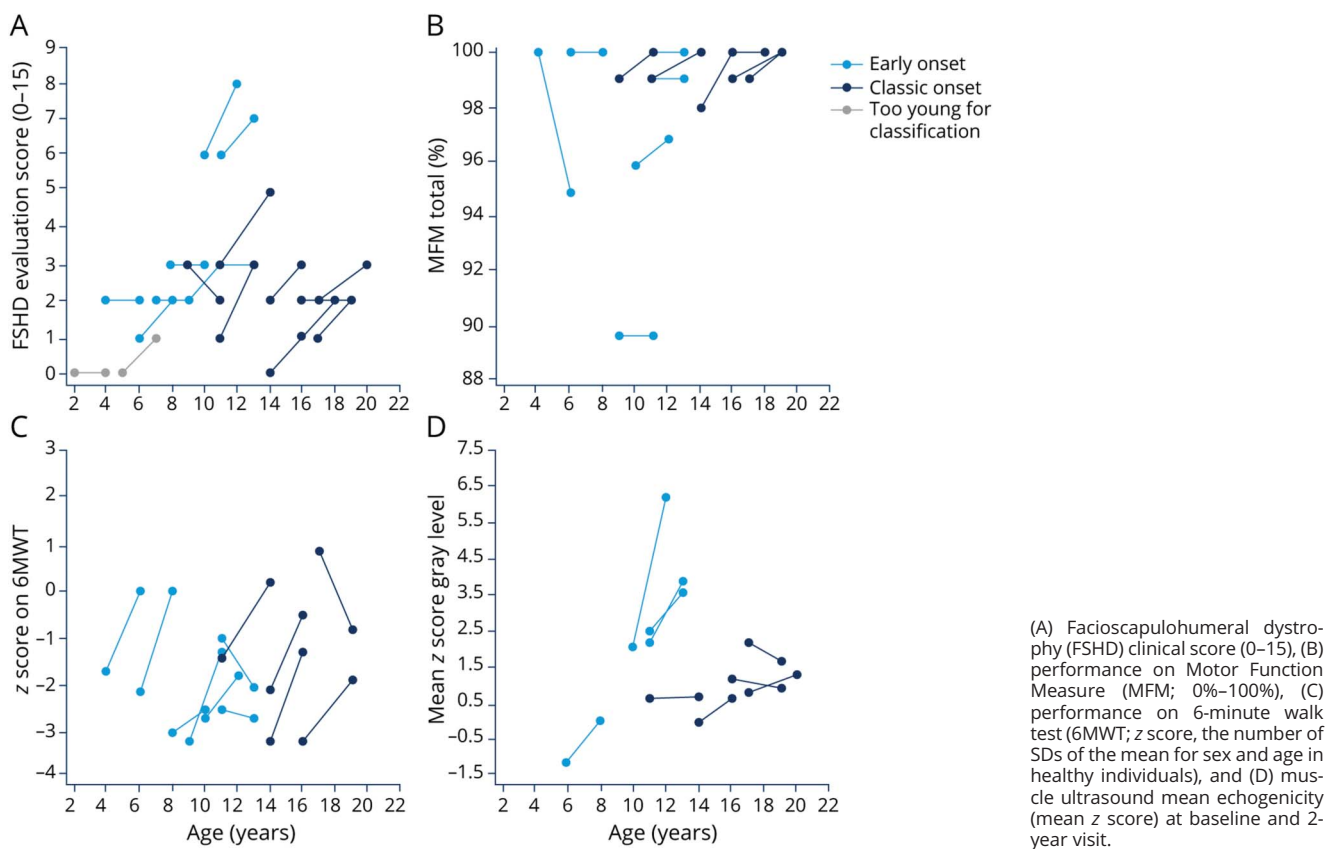
None of the participants had an intellectual disability or developmental impairment. One child was diagnosed with dyslexia, and 1 child had psychological support to deal with anxiety. Seventeen of 20 children (85%) attended regular education. None of the participants had or developed epilepsy.

Pain, Fatigue, and Quality of Life

Pain and fatigue were frequently reported, and their occurrence increased during the 2-year follow-up (75% and 70%, respectively). The location of pain was mainly the lower legs (53%) but also in the scapular region (27%) and lower back (20%). The pain was typically induced by muscle exercise and exertion. The NeuroQoL fatigue questionnaire showed that the children experienced more fatigue compared to healthy children, both at baseline and after the 2-year follow-up. The mean z score did not increase during follow-up (Table 3).

Quality of life was lower in children with FSHD compared to their healthy peers. Low scores were found especially in the domains of physical well-being and social acceptance. Overall, there was no difference in quality of life at baseline and after 2 years. On follow-up there was a significant improvement of the scores in the domains of parent relation and home life and of school environment. Details are shown in Table 3.

Figure 2 Muscle Function and Imaging in Individual Patients Over 2 Years



(A) Facioscapulohumeral dystrophy (FSHD) clinical score (0-15), (B) performance on Motor Function Measure (MFM; 0%-100%), (C) performance on 6-minute walk test (6MWT; z score, the number of SDs of the mean for sex and age in healthy individuals), and (D) muscle ultrasound mean echogenicity (mean z score) at baseline and 2-year visit.

Differences in Early-Onset and Classic-Onset Type

The differences between children with an early-onset and classic-onset type are listed in Table 4. Two of the 20 children were too young to determine their specific phenotype and were excluded from this analysis. Patients with early-onset FSHD had a shorter number of units within the pathogenic D4Z4 repeat compared to classic-onset patients, as expected. Patients with an early-onset type were significantly younger than patients in the classic-onset group. Motor functioning after 2 years as measured by MRC sum score, FSHD score, clinical severity scale, and 6-minute walking test did not differ significantly between these subgroups. The age-adjusted clinical severity scale score was higher in the early-onset subgroup ($p = 0.02$). No significant difference in disease progression was found between the 2 onset types, with a mean change in FSHD clinical score of 0.63 points in the early-onset subgroup and 0.80 in the classic-onset subgroup ($p = 0.65$).

The visual and quantified muscle echogenicity tended to be higher in early-onset patients, but these changes did not reach statistical significance ($p = 0.11$ and $p = 0.07$). During follow-up, early-onset patients showed a bigger mean echogenicity change compared to classic-onset patients: in early-onset patients, an increase in mean z score of 2.0 ± 1.4 was seen compared to an increase of 0.1 ± 0.5 in the classic-onset

subgroup ($p = 0.02$). The presence of pain, fatigue, and systemic features did not vary significantly between the 2 groups, although hearing abnormalities were observed only in the children with early-onset FSHD who had a D4Z4 repeat size of 2 units.

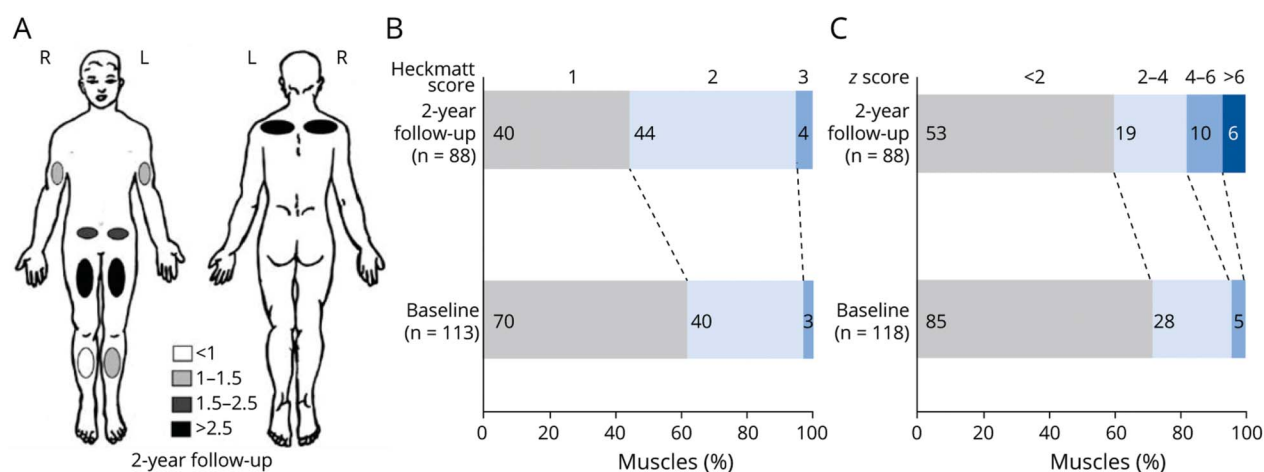
Determinants of Disease Progression

The rate of disease progression in 2 years as measured by the change of FSHD clinical score was not influenced by sex, current age, the number of D4Z4 repeats, or the mean echogenicity z score at baseline.

Discussion

This 2-year follow-up study in children with FSHD clinically showed mild progression of facial weakness, pain and fatigue, and lumbar hyperlordosis. This was reflected by an increase of disease severity as measured by the FSHD clinical score. As in adults, the disease course was variable. The muscle ultrasound abnormalities increased over 2 years and correlated with disease severity. The early-onset subtype had shorter D4Z4 repeats and a more severe phenotype as indicated by a higher age-corrected clinical severity score, more ultrasound abnormalities, and a higher prevalence of hearing and retinal abnormalities.

Figure 3 Muscle Ultrasound Results



(A) Mean z score of quantitative muscle ultrasound measuring echogenicity. This shows the combined muscle ultrasound measurements of 9 participants at the 2-year follow-up. (B) Distribution of the measured muscles at baseline and follow-up by qualitative analysis using Heckmatt scores and (C) by quantitative analysis using z scores.

While the clinical scores indicated disease progression, the actual changes were limited. The FSHD clinical score, a sum score of 6 independent sections that describes strength and functionality of several muscle regions, was the only motor function outcome measurement that showed a significant deterioration. The children's performance on functional exercise tests improved over 2 years, although it was still below the average performance for healthy peers. This most likely indicates the delayed but still ongoing motor development in children with FSHD compared to healthy children, which is in line with observations in patients with Duchenne muscular dystrophy that a delay in gross motor development is seen in one-third of children.³⁴ Physical therapy and functional training might also improve functional capacities,³⁵ but we did not find a relationship between attending physical therapy and improvement. This result might also point to limitations of the 6-minute walk test: its result is affected by the effort of the child. It gives us an estimate of the child's functional status but does not assess the mechanism of exercise intolerance.³⁶ The improvement found emphasizes the importance of natural history studies to ensure correct implementation of these outcome measurements in future clinical trials in children.

The prevalence and severity of facial weakness, dysarthria, and swallowing difficulties increased during follow-up. All children with severe facial weakness also had a dysarthric speech. The swallowing difficulties were mild, with a score of 7 on the Neuromuscular Disease Swallowing Status Scale, which indicates that the person is totally orally fed without difficulties but avoids more difficult-to-eat foods. The prevalence of these symptoms was higher than in the adult population, and no difference between children with a classic-onset or early-onset type was found, suggesting that orofacial function improves during the normal development in childhood.³⁷ The low

prevalence of systemic features found in this cohort, which did not increase after the 2-year follow-up, is similar to what is seen in the adult population with classic FSHD.³⁸⁻⁴⁰

Our studied cohort confirmed the previous finding that muscle ultrasound is correlated with disease severity and a responsive biomarker for FSHD disease progression.⁴¹ Ultrasound was previously shown to have a sensitivity similar to that of quantitative MRI.⁴² Visual grading correlated with quantified muscle ultrasound; both could be used in evaluating muscle ultrasound abnormalities in children.

In a comparison of the subgroups defined by onset type, after 2 years of follow-up, patients with an early-onset subtype were deteriorating faster in mean echogenicity than patients with a classic-onset type. On the other hand, the progression on the FSHD clinical score did not differ, suggesting that muscle ultrasound abnormalities precede clinical deterioration and thus seem to be a reliable biomarker. This resembles the finding in patients with Duchenne muscular dystrophy that muscle echogenicity of patients already deviates from that of healthy controls in an early stage and is of great importance in the early detection of muscle functioning impairments.⁴³

Pain, fatigue, and a decreased quality of life appear to be major problems in childhood, with a prevalence similar to that in the adult population.⁴⁴⁻⁴⁶ The current study reports an even higher proportion of children experiencing pain compared to another recent study on FSHD in childhood (83% vs 61%), despite the fewer patients with systemic features or loss of ambulation in our cohort.¹² This difference could be explained by the different approach to exploring the presence of pain in the current study. We consciously asked for the presence of pain without the use of a pain scale, thus including all levels and patient perceptions of pain. Another possible

Table 3 Systemic Features, Pain, Fatigue, and Quality of Life at Baseline and 2-Year Follow-up

	No. of participants (at baseline—2-y follow-up)	Baseline scoring	2-y Follow-up scoring	p Value
Systemic features, n/total (%)				
Hearing loss ^a	18–16	3/18 (17)	2/16 (12.5)	1.00 ^e
Vision loss	20–12	0/18 (0)	0/12 (0)	1.00 ^e
Retinal abnormalities ^b	11–8	8/11 (73)	6/8 (75)	1.00 ^e
Cardiac abnormalities ^c	15–13	3/15 (20)	1/13 (8)	1.00 ^e
Assisted ventilation	20–20	0/20 (0)	0/20 (0)	1.00 ^e
Lumbar hyperlordosis	20–19	7/20 (35)	10/19 (53)	0.38 ^e
Dysarthria	20–20	5/20 (25)	10/20 (50)	0.13 ^e
Swallowing difficulties ^d	20–20	5/20 (25)	7/20 (35)	0.69 ^e
Intellectual disability	20–20	0/20 (0)	0/20 (0)	1.00 ^e
Epilepsy	20–20	0/20 (0)	0/20 (0)	1.00 ^e
Pain and quality of life				
Pain, n/total (%)	20–20	12/20 (60)	15/20 (75)	0.51 ^e
Fatigue, n/total (%)	20–20	12/20 (60)	14/20 (70)	0.69 ^e
NeuroQoL 8-item fatigue bank score, mean SD	10–11	1.1	1.0	0.37 ^g
Kidscreen total score, mean SD	9–11	–0.9	–0.7	0.13 ^g
Kidscreen subdomain scores, mean SD				
Physical well-being	9–11	–1.5	–2.0	0.14 ^g
Psychological well-being	9–11	–1.0	–0.4	0.20 ^g
Autonomy	9–11	–0.7	–0.4	0.40 ^f
Parent relation and home life	9–11	–0.8	0.2	0.04 ^g
Financial resources	9–11	–0.7	–0.3	0.21 ^f
Social support and peers	9–11	–0.8	–0.9	0.27 ^g
School environment	9–11	–0.7	–0.1	0.03 ^g
Social acceptance	9–11	Insufficient numbers or replies	–1.6	

^a Based on audiometry abnormalities.

^b Defined as mild or severe tortuosity of retinal arteries in at least 1 eye measured by fundoscopy.

^c Based on ECG abnormalities.

^d Based on a score of ≤ 7 on the Neuromuscular Disease Swallowing Status Scale.

^e McNemar test.

^f Wilcoxon signed-rank test.

^g Paired *t* test.

explanation is that the children in our cohort experience more pain secondary to exercise because of their maintained ambulation. The high prevalence of pain and fatigue in children with FSHD is a reason for concern, especially when we take into account the correlation between age and fatigue severity,⁴⁵ with increasing age leading to a further deterioration of the quality of life.⁴⁴ For children, this could have a substantial effect on participation in school and sports and their professional development. We suggest placing more focus on the management of pain and fatigue to ameliorate physical impairment and to optimize the child's abilities.

A strength of this nationwide study is that it provided information about the full spectrum of FSHD in childhood. However, our study also has some limitations. First, the small number of participants makes it hard to determine correlations. This could be addressed by an even more encompassing international study or prospective data collection initiative for patients with FSHD. Second, FSHD in childhood appears to be a slowly progressive disease, so a 2-year follow-up is a short period to evaluate clinically relevant changes. A longer follow-up period is expected to provide further information about the natural history and support longer running treatment trials. Last, missing data were caused by

Table 4 Comparison of Motor Functioning and Systemic Complications Between Early-Onset and Classic Onset FSHD After 2-Year Follow-up

	Early onset (n = 8)	Classic onset (n = 10)	p Value
Demographics			
Age at baseline examination, y	8.3 ± 2.5	14.2 ± 2.9	<0.001 ^c
Age at 2-y follow-up, y	10.3 ± 2.5	16.4 ± 3.0	<0.001 ^c
Age at onset of symptoms, y	2.8 ± 2.2	10.5 ± 4.2	0.01 ^b
D4Z4, ^d mean ± SD	3.8 ± 2.2	6.4 ± 1.7	0.02 ^b
Motor functioning			
MRC sum score (0–70), mean ± SD	66.7 ± 3.9	69.0 ± 1.4	0.17 ^b
CSS score (0–10), mean ± SD	3.1 ± 2.0	2.7 ± 1.8	0.70 ^b
Age-corrected CSS score (0–2000), mean ± SD	288 ± 131	168 ± 112	0.02 ^b
FSHD clinical score (0–15), mean ± SD	3.0 ± 1.9	2.5 ± 1.1	0.27 ^b
6-min walk test score, No. of SDs, mean ± SD	–1.5 ± 1.1	–1.0 ± 0.9	0.40 ^c
Motor Function Measure score, mean ± SD	97.2 ± 3.9	100 ± 0	0.06 ^b
Muscle imaging			
MUS score (z score), mean ± SD ^e	3.4 ± 2.5 (n = 4)	1.1 ± 0.4 (n = 5)	0.07 ^c
Heckmatt score (1–4), mean ± SD	1.9 ± 0.6 (n = 4)	1.4 ± 0.1 (n = 5)	0.11 ^c
ΔMUS ^f score (z score), mean ± SD ^e	2.0 ± 1.4 (n = 4)	0.1 ± 0.5 (n = 5)	0.02 ^c
Pain, fatigue, and systemic features, n/total (%)			
Pain	7/8 (87.5)	8/10 (80)	0.59 ^a
Fatigue	7/8 (87.5)	7/10 (70)	0.38 ^a
Hearing abnormalities	2/7 (28.6)	0/9 (0)	0.18 ^a
Retinal abnormalities	3/3 (100)	3/5 (60)	0.36 ^a
Lumbar hyperlordosis	4/8 (50)	5/10 (50)	0.68 ^a
Swallowing difficulties	2/8 (25)	4/10 (40)	0.43 ^a
Dysarthria	5/8 (62.5)	4/10 (40)	0.32 ^a

Abbreviations: FSHD = facioscapulohumeral dystrophy; CSS = clinical severity scale; MRC = Medical Research Council; MUS = muscle ultrasound.

^a Fisher exact test, 1-sided *p* value.

^b Mann-Whitney *U* test.

^c Independent *t* test.

^d Mean number of units within the pathogenic D4Z4 repeat.

^e Mean z score of the quantified echogenicity per muscle measured by MUS.

^f Change in mean z score of the quantified echogenicity during 2 years of follow-up.

COVID-19 and by the substantial proportion of patients or their parents who preferred not to visit the study center and participated by a phone interview and chart review only.

The slowly progressive course of childhood FSHD offers the opportunity for a future drug trial to delay or thwart this progression rate. According to our results, the most promising outcome measures for analyzing the effects of future therapeutics are the FSHD clinical score and muscle ultrasound. We expect to further define the natural history and course in a subsequent 5-year follow-up study of this cohort.

Acknowledgment

The authors thank all the patients, parents, and sponsors for their time and effort in this study. In addition, they acknowledge the following people who have contributed to the study: Merel Jansen, Henny Janssen, Richard Lemmers, Silvère van der Maarel, Sander Pagen, Wilma Raijmann, Tim Schreuder, and Vivian Schreur.

Study Funding

The study is externally funded by a major funding body (charitable foundation Prinses Beatrix Spierfonds/Spiereen voor Spieren, W.OR14.22 to C.E.E. and B.G.M.v.E.).

Disclosure

J.N. Dijkstra and R.J.M. Goselink report no disclosures relevant to the manuscript. N. van Alfen consults for Dynacure and provides editorial duties for Wiley Inc; all fees are paid to her employer. I.J.M. De Groot, M. Pelsma, N. Van der Stoep, and T. Theelen report no disclosures relevant to the manuscript. B.G.M. Van Engelen received grants from Global FSH, Stichting Spieren voor Spieren, Prinses Beatrix Spierfonds, and Dutch FSHD foundation. N.C. Voermans and C.E. Erasmus report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* June 9, 2021. Accepted in final form September 24, 2021.

Appendix Authors

Name	Location	Contribution
Jildou N. Dijkstra, MD	Department of Neurology, Donders Centre of Neuroscience, Radboud University Medical Centre, Nijmegen, the Netherlands; Department of Pediatric Neurology, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Rianne J.M. Goselink, MD, PhD	Department of Neurology, Jönköping, Region Jönköping County, and Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Nens van Alfen, MD, PhD	Department of Neurology, Donders Centre of Neuroscience, Radboud University Medical Centre, Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Imelda J.M. de Groot, MD, PhD	Department of Rehabilitation, Donders Centre for Neuroscience, Radboud University Medical Centre, Nijmegen, the Netherlands	Study concept or design
Maaïke Pelsma, MSc	Department of Rehabilitation, Donders Centre for Neuroscience, Radboud University Medical Centre, Nijmegen, the Netherlands	Major role in the acquisition of data
Nienke van der Stoep, PhD	Department of Clinical Genetics, Leiden University Medical Centre, the Netherlands	Major role in the acquisition of data; analysis or interpretation of data
Thomas Theelen, MD, PhD	Department of Ophthalmology, Radboud University Medical Centre, Nijmegen, the Netherlands	Major role in the acquisition of data
Baziel G.M. van Engelen, MD, PhD	Department of Neurology, Donders Centre of Neuroscience, Radboud University Medical Centre, Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Nicol C. Voermans, MD, PhD	Department of Neurology, Donders Centre of Neuroscience, Radboud University Medical Centre, Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Corrie E. Erasmus, MD, PhD	Department of Pediatric Neurology, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; Analysis or interpretation of data

References

- Deenen JC, Arnts H, van der Maarel SM, et al. Population-based incidence and prevalence of facioscapulohumeral dystrophy. *Neurology*. 2014;83(12):1056-1059.
- Tawil R, van der Maarel SM, Tapscott SJ. Facioscapulohumeral dystrophy: the path to consensus on pathophysiology. *Skelet Muscle*. 2014;4:12.
- Sacconi S, Salviati L, Desnuelle C. Facioscapulohumeral muscular dystrophy. *Biochim Biophys Acta*. 2015;1852(4):607-614.
- Mul K, Lassche S, Voermans NC, Padberg GW, Horlings CG, van Engelen BG. What's in a name? The clinical features of facioscapulohumeral muscular dystrophy. *Pract Neurol*. 2016;16(3):201-207.
- Himeda CL, Jones PL. The genetics and epigenetics of facioscapulohumeral muscular dystrophy. *Annu Rev Genomics Hum Genet*. 2019;20:265-291.
- Mah JK, Chen YW. A pediatric review of facioscapulohumeral muscular dystrophy. *J Pediatr Neurol*. 2018;16(4):222-231.
- de Greef JC, Lemmers RJ, van Engelen BG, et al. Common epigenetic changes of D4Z4 in contraction-dependent and contraction-independent FSHD. *Hum Mutat*. 2009;30(10):1449-1459.
- Brouwer OF, Padberg GW, Wijmenga C, Frants RR. Facioscapulohumeral muscular dystrophy in early childhood. *Arch Neurol*. 1994;51(4):387-394.
- Dorobek M, van der Maarel SM, Lemmers RJ, et al. Early-onset facioscapulohumeral muscular dystrophy type 1 with some atypical features. *J Child Neurol*. 2015;30(5):580-587.
- Goselink RJM, Mul K, van Kernebeek CR, et al. Early onset as a marker for disease severity in facioscapulohumeral muscular dystrophy. *Neurology*. 2019;92(4):e378-e385.
- Goselink RJM, Voermans NC, Okkensen K, et al. Early onset facioscapulohumeral dystrophy: a systematic review using individual patient data. *Neuromuscul Disord*. 2017;27(12):1077-1083.
- Steel D, Main M, Manzur A, Muntoni F, Munot P. Clinical features of facioscapulohumeral muscular dystrophy 1 in childhood. *Dev Med Child Neurol*. 2019;61(8):964-971.
- Trevisan CP, Pastorello E, Tomelleri G, et al. Facioscapulohumeral muscular dystrophy: hearing loss and other atypical features of patients with large 4q35 deletions. *Eur J Neurol*. 2008;15(12):1353-1358.
- 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(4):298-305.
- Funakoshi M, Goto K, Arahata K. Epilepsy and mental retardation in a subset of early onset 4q35-facioscapulohumeral muscular dystrophy. *Neurology*. 1998;50(6):1791-1794.
- Mah JK, Feng J, Jacobs MB, et al. A multinational study on motor function in early-onset FSHD. *Neurology*. 2018;90(15):e1333-e1338.
- Goselink RJM, van Kernebeek CR, Mul K, et al. A 22-year follow-up reveals a variable disease severity in early-onset facioscapulohumeral dystrophy. *Eur J Paediatr Neurol*. 2018;22(5):782-785.
- Goselink RJ, Schreuder TH, Mul K, et al. Facioscapulohumeral dystrophy in children: design of a prospective, observational study on natural history, predictors and clinical impact (iFocus FSHD). *BMC Neurol*. 2016;16:138.
- Goselink RJM, Schreuder THA, van Alfen N, et al. Facioscapulohumeral dystrophy in childhood: a nationwide natural history study. *Ann Neurol*. 2018;84(5):627-637.
- Bérard C, Payan C, Hodgkinson I, Fermanian J, MFM Collaborative StudyGroup. A Motor Function Measure for neuromuscular diseases: construction and validation study. *Neuromuscul Disord*. 2005;15(7):463-470.
- Pane M, Mazzone ES, Fanelli L, et al. Reliability of the performance of upper limb assessment in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2014;24(3):201-206.
- 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(11):1038-1045.
- Vanhoutte EK, Faber CG, van Nes SI, et al. Modifying the Medical Research Council grading system through Rasch analyses. *Brain* 2012;135(pt 5):1639-1649.

24. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166(1):111-117.
25. de Lattre C, Payan C, Vuillerot C, et al. Motor Function Measure: validation of a short form for young children with neuromuscular diseases. *Arch Phys Med Rehabil.* 2013;94(11):2218-2226.
26. Geiger R, Strasak A, Trembl B, et al. Six-minute walk test in children and adolescents. *J Pediatr.* 2007;150(4):395-399, 399.e1-399.e2.
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(2):213-217.
28. Ricci E, Galluzzi G, Deidda G, et al. Progress in the molecular diagnosis of facioscapulohumeral muscular dystrophy and correlation between the number of KpnI repeats at the 4q35 locus and clinical phenotype. *Ann Neurol.* 1999;45(6):751-757.
29. van Overveld PG, Enthoven L, Ricci E, et al. Variable hypomethylation of D4Z4 in facioscapulohumeral muscular dystrophy. *Ann Neurol.* 2005;58(4):569-576.
30. Gordijn M, Suzanne Gordijn M, Cremers EM, Kaspers GJ, Gemke RJ. Fatigue in children: reliability and validity of the Dutch PedsQL™ multidimensional fatigue scale. *Qual Life Res.* 2011;20(7):1103-1108.
31. Ravens-Sieberer U, Gosch A, Rajmil L, et al. KIDSCREEN-52 quality-of-life measure for children and adolescents. *Expert Rev Pharmacoecon Outcomes Res.* 2005;5(3):353-364.
32. Wijntjes J, van Alfen N. Muscle ultrasound: present state and future opportunities. *Muscle Nerve.* 2021;63(4):455-466.
33. Rijken NH, van der Kooi EL, Hendriks JC, et al. Skeletal muscle imaging in facioscapulohumeral muscular dystrophy, pattern and asymmetry of individual muscle involvement. *Neuromuscul Disord.* 2014;24(12):1087-1096.
34. Sarrazin E, von der Hagen M, Schara U, von Au K, Kaindl AM. Growth and psychomotor development of patients with Duchenne muscular dystrophy. *Eur J Paediatr Neurol.* 2014;18(1):38-44.
35. Voet NB, van der Kooi EL, van Engelen BG, Geurts AC. Strength training and aerobic exercise training for muscle disease. *Cochrane Database Syst Rev.* 2019;12(7):CD003907.
36. Reybrouck T. Clinical usefulness and limitations of the 6-minute walk test in patients with cardiovascular or pulmonary disease. *Chest.* 2003;123(2):325-327.
37. Mul K, Berggren KN, Sills MY, et al. Effects of weakness of orofacial muscles on swallowing and communication in FSHD. *Neurology.* 2019;92(9):e957-e963.
38. Trevisan CP, Pastorello E, Ermani M, et al. Facioscapulohumeral muscular dystrophy: a multicenter study on hearing function. *Audiol Neurootol.* 2008;13(1):1-6.
39. Fitzsimons RB, Gurwin EB, Bird AC. Retinal vascular abnormalities in facioscapulohumeral muscular dystrophy: a general association with genetic and therapeutic implications. *Brain.* 1987;110(pt 3):631-648.
40. Goselink RJM, Schreur V, van Kernebeek CR, et al. Ophthalmological findings in facioscapulohumeral dystrophy. *Brain Commun.* 2019;1(1):fz023.
41. Goselink RJM, Schreuder THA, Mul K, et al. Muscle ultrasound is a responsive biomarker in facioscapulohumeral dystrophy. *Neurology.* 2020;94(14):e1488-e1494.
42. Janssen BH, Pillen S, Voet NB, Heerschap A, van Engelen BG, van Alfen N. Quantitative muscle ultrasound versus quantitative magnetic resonance imaging in facioscapulohumeral dystrophy. *Muscle Nerve.* 2014;50(6):968-975.
43. Janssen MMHP, Harlaar J, Koopman B, de Groot IJM. Dynamic arm study: quantitative description of upper extremity function and activity of boys and men with Duchenne muscular dystrophy. *J Neuroeng Rehabil.* 2017;14(1):45.
44. Padua L, Aprile I, Frusciantè R, et al. Quality of life and pain in patients with facioscapulohumeral muscular dystrophy. *Muscle Nerve.* 2009;40(2):200-205.
45. Kalkman JS, Schillings ML, van der Werf SP, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. *J Neurol Neurosurg Psychiatry.* 2005;76(10):1406-1409.
46. Jensen MP, Hoffman AJ, Stoelb BL, Abresch RT, Carter GT, McDonald CM. Chronic pain in persons with myotonic dystrophy and facioscapulohumeral dystrophy. *Arch Phys Med Rehabil.* 2008;89(2):320-328.

Neurology®

Natural History of Facioscapulohumeral Dystrophy in Children: A 2-Year Follow-up

Jildou N. Dijkstra, Rianne J.M. Goselink, Nens van Alfen, et al.

Neurology 2021;97:e2103-e2113 Published Online before print October 21, 2021

DOI 10.1212/WNL.0000000000012882

This information is current as of October 21, 2021

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/97/21/e2103.full
References	This article cites 46 articles, 8 of which you can access for free at: http://n.neurology.org/content/97/21/e2103.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): All Pediatric http://n.neurology.org/cgi/collection/all_pediatric Muscle disease http://n.neurology.org/cgi/collection/muscle_disease Natural history studies (prognosis) http://n.neurology.org/cgi/collection/natural_history_studies_prognosis
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

