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# Early onset as a marker for disease severity in facioscapulohumeral muscular dystrophy

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## Abstract

### Objective

To assess the relation between age at onset and disease severity in facioscapulohumeral muscular dystrophy (FSHD).

### Methods

In this prospective cross-sectional study, we matched adult patients with FSHD with an early disease onset with 2 sex-matched FSHD control groups with a classic onset; the first group was age matched, and the second group was disease duration matched. Genetic characteristics, muscle performance, respiratory functioning, hearing loss, vision loss, epilepsy, educational level, and work status were compared with the 2 control groups.

### Results

Twenty-eight patients with early-onset FSHD were age ( $n = 28$ ) or duration ( $n = 27$ ) matched with classic-onset patients. Patients with early-onset FSHD had more severe muscle weakness (mean FSHD clinical score 11 vs 5 in the age-matched and 9 in the duration-matched group,  $p < 0.05$ ) and a higher frequency of wheelchair dependency (57%, 0%, and 30%, respectively,  $p < 0.05$ ). In addition, systemic features were more frequent in early-onset FSHD, most important, hearing loss, decreased respiratory function and spinal deformities. There was no difference in work status. Genetically, the shortest D4Z4 repeat arrays (2–3 units) were found exclusively in the early-onset group, and the largest repeat arrays (8–9 units) were found only in the classic-onset groups. De novo mutations were more frequent in early-onset patients (46% vs 4%).

### Conclusions

Patients with early-onset FSHD more often have severe muscle weakness and systemic features. The disease severity is greater than in patients with classic-onset FSHD who are matched for disease duration, suggesting that the progression is faster in early-onset patients.

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## Glossary

**FSHD** = facioscapulohumeral dystrophy; **PBMC** = peripheral blood mononuclear cell.

Facioscapulohumeral dystrophy (FSHD; Online Mendelian Inheritance in Man 158900), one of the most common adult muscle diseases, is a hereditary, progressive muscular dystrophy with a striking disease heterogeneity both between and within families. Consequently, predicting disease severity and progression rate is very challenging in FSHD.

FSHD has historically been divided into 2 clinical subgroups: early-onset FSHD, with facial weakness before the age of 5 years and scapulohumeral weakness before the age of 10 years,<sup>1</sup> and classic FSHD, with a typical onset between 15 and 30 years but often diagnosed throughout the adult lifespan.<sup>2,3</sup> An estimated 7% to 15% of patients with FSHD have the early-onset subtype.<sup>1,4,5</sup> Patients with early-onset FSHD have been described with a more severe disease<sup>1,6,7</sup>; however, what is unclear is whether early-onset FSHD is inherently a more severe, rapidly progressing disease or if these patients are simply more severe as a result of longer disease duration. To the best of our knowledge, no study has systematically attempted to verify this observation. The finding of early onset as a prognostic factor and its underlying causes would facilitate patient counseling, clinical management, and trial readiness.

This study investigates whether patients with an early onset of symptoms are different from patients with a classic onset regarding genotype, hearing loss, vision loss, epilepsy, educational level, muscle and respiratory functioning, and work status.

## Methods

### Patient recruitment

This prospective cross-sectional case-control study was performed at the Radboud University Medical Center, Nijmegen, the Netherlands, between September 2016 and January 2017. Eligible participants had genetically confirmed FSHD1.<sup>1</sup> Early-onset patients (patients who fulfilled the clinical criteria for early-onset FSHD<sup>1</sup>) were recruited via the Dutch national FSHD registry<sup>8</sup> and among the population known at the Neurology Department of the Radboud University Medical Center, a tertiary referral center for patients with FSHD. Participants with classic-onset FSHD were recruited among participants in a large observational cohort study conducted in 2014 to 2015 (n = 203 participants with FSHD, age 18–84 years).<sup>9</sup> Asymptomatic mutation carriers and patients with FSHD2 were excluded. Participants were matched by sex and by age or disease duration.

### Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent, and the Medical Ethics Review Committee region Arnhem-Nijmegen approved the study.

### Clinical assessment

Age at onset was retrieved from the medical file to minimize the effect of recall bias. If this was not available, a patient-reported age at onset was used. Information on hearing difficulties, visual problems, cardiac abnormalities, respiratory abnormalities, CNS complications, educational level, and work status was obtained from medical files and patient questionnaires. Clinical assessments were performed at the outpatient clinic of the Radboud University Medical Center and included manual muscle testing (shoulder external rotators, elbow flexors, knee extensors, foot dorsiflexors, and foot plantar flexors), the FSHD clinical score (range 0–15, 0 = unaffected, 15 = severe involvement of facial, upper limb, leg, scapular and pelvic girdle, and abdominal muscles<sup>10</sup>), and visual inspection of the spine (scoliosis and/or lumbar hyperlordosis classified as normal/mild/severe). Respiratory function was assessed with a handheld spirometer with a face mask (MicroLoop, MicroMedical, Chatham, IL), and the percentage of expected forced vital capacity (based on sex and height) was reported.

### Genetic analysis

Genetic analysis of peripheral blood mononuclear cells (PBMCs) was performed at the Department of Human Genetics of the Leiden University Medical Center, the Netherlands, and consisted of pulsed field gel electrophoresis for the sizing of the D4Z4 repeats on chromosomes 4 and 10, haplotype analysis by hybridization of pulsed field gel electrophoresis blots with probes A and B in combination with PCR-based simple sequence length polymorphism analysis,<sup>11,12</sup> and methylation analysis of the D4Z4 repeat at the *FseI* restriction site in the proximal unit of the D4Z4 array.<sup>13,14</sup> Methylation values are expressed as the Delta1 score, that is, the observed methylation minus the predicted methylation based on the D4Z4 repeat size.<sup>15</sup>

### Statistics

All eligible participants with early-onset FSHD were invited for participation and after inclusion were matched with classic-onset patients 2 times in a 1:1 way. Descriptive statistics were applied to describe patient characteristics, with continuous data reported as mean  $\pm$  SD. For comparing motor scores between 2 groups, 2-tailed *t* tests were used for numerical data, and the Fisher exact test was used for categorical data. The primary aim was to investigate whether early onset is a risk factor for more severe disease that is independent of current age or disease duration. We therefore compared the early-onset group with both control groups separately (comparing group 1 with group 2 and group 1 with group 3) and did not adjust for 3 group analyses. The Pearson correlation coefficient was calculated for correlations between genotype and phenotype.

After data analysis, a subdivision in the early-onset group was suspected; therefore, additional subgroup analyses were performed on patients with an onset before the age of 8 years and onset between 8 and 10 years. We performed linear regression analyses to compare age at onset with disease severity. Relations with values of  $p < 0.05$  were considered statistically significant. Statistical analyses were performed with GraphPad Prism.<sup>16</sup>

### Data availability

The data from this study cannot be made publicly available because no patient approval has been obtained for sharing coded data. Output of statistical analyses (GraphPad Prism) will be made available on reasonable request.

## Results

### Demographics

A total of 62 patients with early-onset FSHD were identified; 28 participated. The exclusion reasons for the other 34 patients were as follows: 1 had died, 4 had FSHD type 2, 12 could not be contacted, and 17 were not able to come to the study location or refused participation. The participants were matched with 28 age- and sex-matched patients with classic-onset FSHD and with 27 duration- and sex-matched patients with classic-onset FSHD (figure 1, demographics given in table 1). In the early-onset group, age at onset was stated in the medical file in 12 of 28 patients and was similar to the patient-reported age at onset in 10 patients. In the other 2 patients, the age at onset was 2 and 3 years earlier than reported by the patient.

### Muscle weakness

The patients with early-onset FSHD had more severe muscle weakness defined by the FSHD clinical score, the Medical Research Council sum score, and the percentage of wheelchair dependency (table 1 and figure 2). In the early-onset group, the frequency of wheelchair dependency was higher; it occurred at an earlier age and after shorter disease duration. The early-onset population had a smaller variability in the severity of muscle weakness. There was a ceiling effect in the FSHD clinical score, mostly in the early-onset group, for wheelchair-dependent patients.

### Systemic features

CNS complications such as hearing loss, vision loss, and epilepsy are summarized in table 2. Hearing loss was diagnosed between the ages of 1 and 36 years (mean 9 years) in the 5 patients in the early-onset group and at a mean age of 12 years for the patients in the duration-matched group. Hearing loss consisted of bilateral high-frequency loss, and 4 of 5 (80%) of the patients in the early-onset group required hearing aids. Vision loss was found in 1 early-onset patient in whom Coats syndrome was diagnosed. Idiopathic epilepsy without structural brain abnormalities on imaging was found in 2 patients with early-onset FSHD. Intellectual disability was not observed in any of the patients, and there was no difference in mean educational level, although more patients received specialized education in the early-onset group (5 vs 2 patients). Complications of severe axial weakness such as spinal deformities and respiratory complications were more frequent in the early-onset group. Five patients needed nocturnal noninvasive ventilation starting at a mean age of 46 years. All 5 were wheelchair dependent and had severe axial weakness.

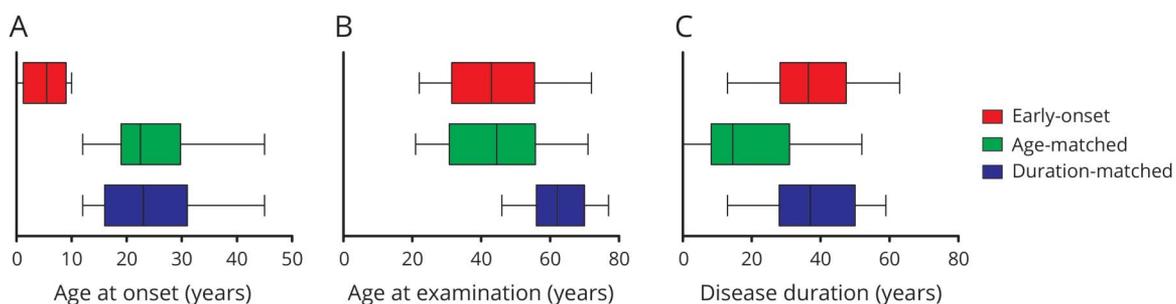
### Genetic characteristics

The mean number of D4Z4 repeat units of the disease allele in the early-onset patients was significantly lower than in the classic-onset patients (3.6 vs 6.2 units, table 1). The methylation value, as measured by the Delta1 score, did not significantly differ between the groups. All patients with very short repeat array sizes (2–3 units) had an early disease onset, and all patients with large repeat array sizes (8–9 units) had a classic age at onset (figure 3). Systemic features were seen mostly in patients with short repeats (2–3 units) but occurred in patients with 5 to 8 units as well. Somatic mosaicism for the D4Z4 repeat array contraction was found in 2 patients: 1 early-onset patient had a repeat array size of 2 units in 40% of PBMCs and a normal repeat array size (14 units) in 60%; the classic-onset patient had 8 units in 90% of PBMCs and 7 units in 10%.

### Correlating age at onset with disease severity

In the early-onset group, the age at onset had a bimodal distribution, with a peak of onset between 0 and 2 years and between 8 and 10 years (figure 3). Patients 0 to 7 years of age at onset were clinically more homogeneous with pronounced

**Figure 1** Group characteristics



**Table 1** Clinical and genetic characteristics of patients with early-onset and classic-onset (age matched or duration matched) FSHD

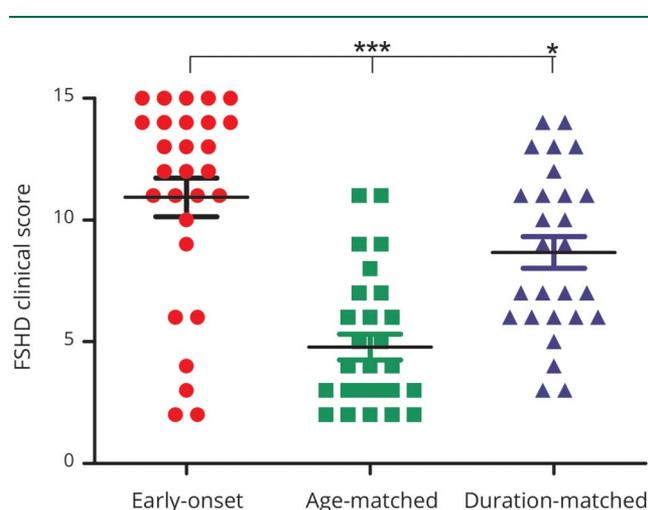
	Early-onset FSHD	Age-matched classic-onset FSHD	Duration-matched classic-onset FSHD
<b>Demographics</b>			
Participants, n	28	28	27
Male, %	46	46	44
Age at examination, mean ± SD, y	43 ± 15	44 ± 15	63 ± 8
Age at disease onset, mean ± SD, y	6 ± 3.7	24 ± 7.7	25 ± 9.6
Age at diagnosis, mean ± SD, y	13 ± 6	32 ± 14	37 ± 13
Disease duration from onset, mean ± SD, y	38 ± 14.4	20 ± 14.5	38 ± 14.8
<b>Clinical history</b>			
FSHD clinical score (0-15), mean ± SD	10.8 ± 4.2	4.8 ± 2.8 <sup>a</sup>	8.7 ± 3.4 <sup>a</sup>
Medical Research Council sum score (0-50), mean ± SD	31 ± 10	43 ± 5 <sup>a</sup>	36 ± 7
Wheelchair dependency, %	57	0 <sup>a</sup>	30 <sup>a</sup>
Mean age at wheelchair dependency, mean ± SD, y	31 ± 17	— <sup>a</sup>	58 ± 6
Disease duration at wheelchair dependency, mean ± SD, y	26 ± 15	— <sup>a</sup>	39 ± 7
<b>Genetic characteristics</b>			
D4Z4 repeats, mean ± SD (range), units	3.6 ± 1.3 (2-7)	6.2 ± 1.4 (4-9) <sup>a</sup>	6.3 ± 1.3 (3-9) <sup>a</sup>
De novo mutations, n (%)	13 (46)	3 (11) <sup>a</sup>	3 (11) <sup>a</sup>
Mosaic mutations, n (%)	1 (4)	1 (4)	2 (7)
Methylation, Delta1 score, mean ± SD (range)	-0.5 ± 14 (-34 to 18)	-2.2 ± 10 (-23 to 17)	-3.8 ± 7 (-20 to 40)

Abbreviation: FSHD = facioscapulohumeral dystrophy.

Delta1 score is the observed methylation minus the predicted methylation based on the D4Z4 repeat size.

<sup>a</sup> Significantly different from early-onset FSHD,  $p < 0.05$ .

**Figure 2** FSHD clinical score from early-onset patients compared with the 2 control groups



Mean facioscapulohumeral dystrophy (FSHD) clinical score is significantly higher in the early-onset group than in both control groups (\*\*\*)  $p < 0.0001$ , \*  $p = 0.03$ .

muscle weakness (FSHD clinical scores 9–15) and with more frequent systemic features. Patients with an onset age between 8 and 10 years were genetically and clinically more heterogeneous, with 5 having a mild clinical severity (FSHD clinical scores 2–6, wheelchair at a later age or lasting ambulant, rarely systemic features) and more frequently familial cases (table 3).

We assessed the correlation between age at onset and clinical severity using the age-corrected clinical severity score. In the early-onset group, age at onset accounted for 43% ( $R^2 = 0.43$ ,  $p < 0.0001$ ) of the variability in the age-adjusted clinical severity score compared to 24% ( $R^2 = 0.24$ ,  $p < 0.0001$ , figure 4) in the total cohort.

## Discussion

This study shows that disease severity is related to age at symptom onset in FSHD. Patients with an early age at onset have more severe muscle weakness and more frequently systemic features compared to both age-matched and duration-matched patients with FSHD with a later disease onset.

**Table 2** Systemic features in patients with early-onset and classic-onset FSHD

Systemic features	Early-onset FSHD (n = 28)	Age-matched classic-onset FSHD (n = 28)	Duration-matched classic-onset FSHD (n = 27)
FSHD-related hearing loss, n <sup>a</sup>	5	0	1
Hearing aids, n	4	0	0
FSHD-related vision loss (Coats syndrome), n	1	0	0
Epilepsy without other known cause, n	2	0	0
Severe spinal deformities, n	14	0	5
Noninvasive ventilation, n	6	0	2
Forced vital capacity, mean ± SD, % of expected	56 ± 22	79 ± 14	75 ± 17
Educational level, ISCED 2011	4.7 ± 1.8	4.5 ± 1.6	4.2 ± 1.9
Work status, % patients with paid job or retired after paid job	64	73	58

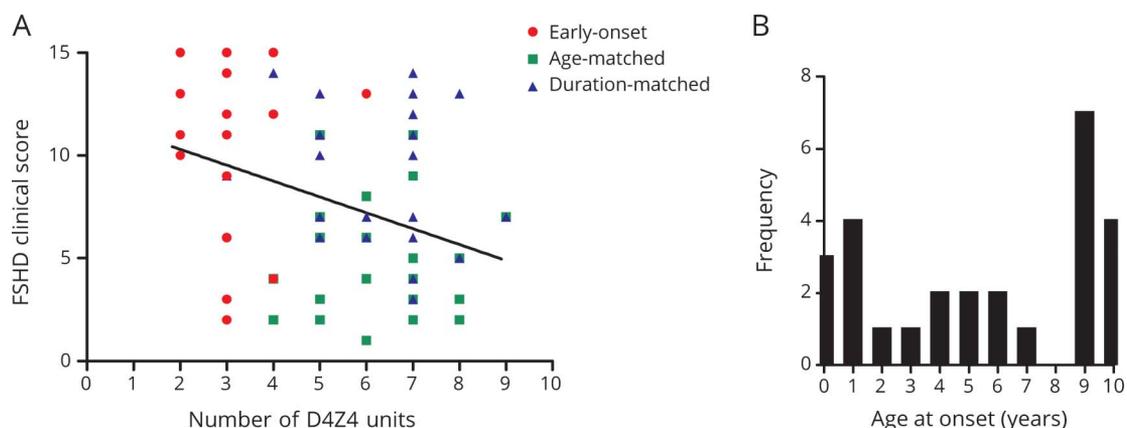
Abbreviations: FSHD = facioscapulohumeral dystrophy; ISCED = International Standard Classification of Education.  
<sup>a</sup> Defined as high-frequency hearing loss before the age of 65 years without other known cause for hearing loss.

Therefore, age at onset can potentially serve as a prognostic marker for disease severity. Recognizing this subgroup of patients with FSHD could improve counseling, clinical management, and future therapeutic trials.

Patients with an early disease onset experienced severe muscle weakness and wheelchair dependency at a younger age compared to patients with FSHD with a classic onset. Therefore, the more severe disease in early-onset FSHD is not explained by current age or disease duration only. In addition, a shorter D4Z4 repeat array size (1–3 units) alone was not associated with a higher frequency of systemic features, meaning that disease severity is also not explained by repeat array size only. One possible explanation for the different phenotype could be the general underlying genetic profile in which the D4Z4 repeat

array size and other modifying factors interact. Because DNA methylation captures only 1 aspect of the D4Z4 chromatin structure, in the future, it will be interesting to test variants in modifiers of other features of the D4Z4 chromatin structure such as the recently described NuRD and CAF-1 complexes.<sup>17</sup> Another explanation could be the particular vulnerability to DUX4 of the developing muscles and nervous system during childhood and puberty. An argument for the developmental instead of degenerative pathophysiology of FSHD could be the finding that within the early-onset group, but not in the classic-onset groups, an earlier onset was associated with a more severe phenotype.

This study showed a higher frequency of systemic features in patients with early-onset FSHD, thereby confirming

**Figure 3** Correlation between the (A) D4Z4 repeat array size and (B) FSHD clinical score and distribution of age at onset in the early-onset FSHD group

Correlation with a Pearson  $r$  of  $-0.34$  ( $p = 0.003$ ). FSHD = facioscapulohumeral dystrophy.

**Table 3** Differences between earlier onset and later age at onset

	Early onset, onset <8 years	Early onset, onset at 8–10 years
<b>Demographics</b>		
Male participants, n (%)	17 (53)	11 (36)
Age at examination, mean ± SD, y	40 ± 11	48 ± 19
<b>Clinical history</b>		
Clinical severity score mean (range 0–10)	9.06 (6–10)	5.73 (1–10)
FSHD clinical score mean (range 0–15)	12.9 (9–15)	7.9 (2–14)
Wheelchair dependency, n%	11 (65)	4 (36)
Age at wheelchair dependency, mean (range), y	23 (7–43)	54 (43–60)
<b>Genetic characteristics</b>		
D4Z4 repeats, mean ± SD (range), n	3.33 (2–6)	3.99 (3–7)
De novo mutations, n (%)	11 (65)	2 (18)
<b>Systemic features, n (%)</b>		
FSHD-related hearing loss <sup>a</sup>	5 (29)	1 (9)
Noninvasive ventilation	4 (24)	2 (18)

Abbreviation: FSHD = facioscapulohumeral dystrophy.

<sup>a</sup> High-frequency hearing loss before the age of 65 years without other known cause for hearing loss.

results of earlier studies.<sup>1,18,19</sup> These findings emphasize the need for regular screening of hearing loss, retinal abnormalities, and pulmonary complications in early-onset patients.<sup>20</sup> We did not find patients with intellectual disability in our group and therefore cannot confirm the intellectual disability as part of FSHD observed in other

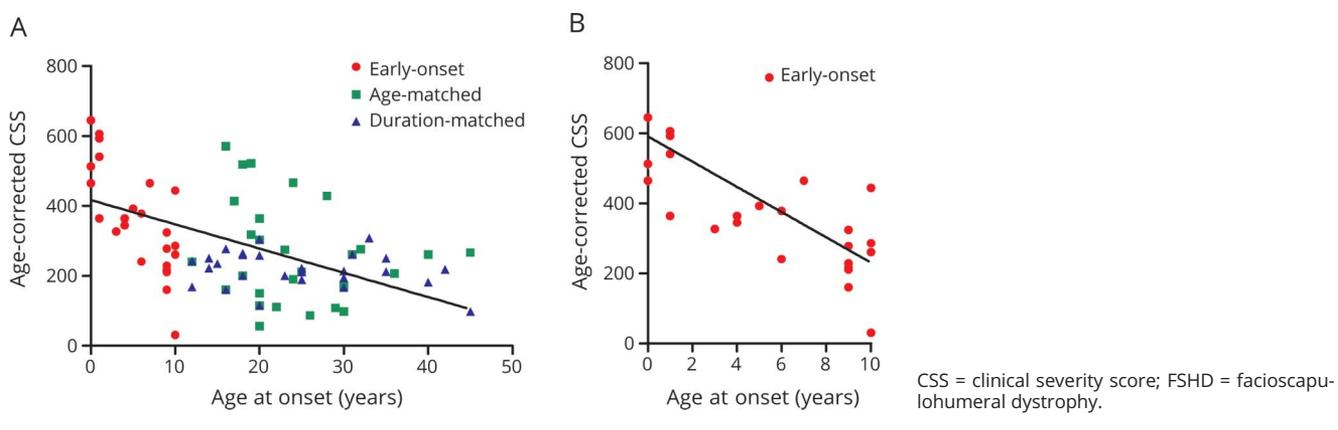
studies. Patients with intellectual disability reported in several case reports frequently showed other features such as dysmorphic features<sup>21</sup> and epilepsy,<sup>7,21</sup> which could suggest other comorbidity. In 20% of the early-onset patients, asymptomatic cardiac arrhythmias were found without clinically relevant symptoms, which is in concordance with the available literature.<sup>22–24</sup>

Two additional factors that could facilitate prognostication in FSHD were identified in this study. First, the age at onset was directly correlated with the FSHD evaluation score in our early-onset subgroup, while this was not the case for the classic-onset groups. It is possible, therefore, to hypothesize that in childhood every disease-free year is important, while in classic onset, the exact age at onset is contributing far less to disease severity. Second, our results suggest a faster disease progression and possibly a developmental pathophysiology in patients with early-onset FSHD, although this needs confirmation in longitudinal studies.

The strengths of this study are the extensive clinical and genetic assessments and the 2 control groups. One limitation is the patient-reported age at disease onset with the risk of recall bias. One could suspect an increased number of familial cases in the early-onset group because symptoms are recognized earlier than in sporadic or index cases. However, the frequency of sporadic cases was much higher in the early-onset group (46% vs 11%), suggesting that familial cases were not overrepresented. Second, the absence of patients with intellectual disability and mildly affected sporadic patients may represent inclusion bias. Lastly, the current study is hypothesis generating, and implementation as a prognostic marker would require a prospective longitudinal follow-up for confirmation.

This study suggests that early onset is a marker for a more severe disease in FSHD, which facilitates counseling and future trial tailoring.

**Figure 4** Correlation between the age at onset and the FSHD clinical score for (A) all patients (B) early-onset group



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## Disclosure

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<b>Karliën Mul</b>	Radboud University Medical Center, Nijmegen, the Netherlands	Author	Design of the study; Major role in the acquisition of data; Interpretation of the data; Revising the manuscript for intellectual content
<b>Caroline R. van Kernebeek</b>	Radboud University Medical Center, Nijmegen, the Netherlands	Author	Major role in the acquisition of data
<b>Richard J.L.F. Lemmers</b>	Leiden University Medical Center, Leiden, The Netherlands	Author	Major role in the acquisition of data
<b>Silvère M. van der Maarel</b>	Leiden University Medical Center, Leiden, The Netherlands		Interpretation of the data; Revising the manuscript for intellectual content

## Appendix 1 (continued)

Name	Location	Role	Contribution
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<b>George W. Padberg</b>	Radboud University Medical Center, Nijmegen, the Netherlands	Author	Analysis and interpretation of the data
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<b>Baziel G.M. van Engelen</b>	Radboud University Medical Center, Nijmegen, the Netherlands	Author	Design of the study; Analysis; Interpretation of the data; Drafting the manuscript for intellectual content

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