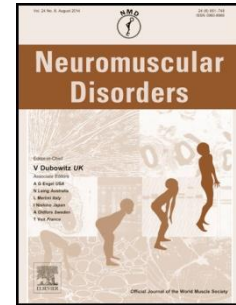


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Early onset facioscapulohumeral dystrophy – a systematic review using individual patient data

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Highlights

- Comprehensive overview of all published individual patient data on early onset FSHD.
- At a mean age of 19 years, 40% is wheelchair dependent.
- Half of the patients have systemic complications, most frequently hearing loss (40%).

- Early onset FSHD has a more severe phenotype compared to classical FSHD.
- Early onset FSHD has a remarkable heterogeneity comparable to classical FSHD.

Abstract

Infantile or early onset is estimated to occur in around 10% of all facioscapulohumeral dystrophy (FSHD) patients. Although small series of early onset FSHD patients have been reported, comprehensive data on the clinical phenotype is missing. We performed a systematic literature search on the clinical features of early onset FSHD comprising a total of 43 articles with individual data on 227 patients. Additional data from four cohorts was provided by the authors. Mean age at reporting was 18.8 years, and 40% of patients were wheelchair-dependent at that age. Half of the patients had systemic features, including hearing loss (40%), retinal abnormalities (37%) and developmental delay (8%). We found an inverse correlation between repeat size and disease severity, similar to adult-onset FSHD. De novo FSHD1 mutations were more prevalent than in adult-onset FSHD. Compared to adult FSHD, our findings indicate that early onset FSHD is overall characterised by a more severe muscle phenotype and a higher prevalence of systemic features. However, similar as in adults, a significant clinical heterogeneity was observed. Based on this, we consider early onset FSHD to be on the severe end of the FSHD disease spectrum. We found natural history studies and treatment studies to be very scarce in early onset FSHD, therefore longitudinal studies are needed to improve prognostication, clinical management and trial-readiness.

Keywords

Facioscapulohumeral dystrophy, early onset, infantile FSHD.

List of abbreviations

CSS: Clinical Severity Score by Ricci ('Ricci score' [11])

DNA: Deoxyribonucleic acid

DUX4: double homeobox 4.

FSHD: facioscapulohumeral dystrophy

DNMT3B: DNA methyltransferase 3B

RNA: ribonucleic acid

SMCHD1: Structural Maintenance Of Chromosomes Flexible Hinge Domain Containing 1

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1. Introduction

Facioscapulohumeral dystrophy (FSHD) is one of the most frequent hereditary muscular diseases with an estimated prevalence of 5-13 in 100.000[1, 2]. In 3-21% of patients the symptoms start at an early age [3, 4]. Currently, two genetically distinct types of FSHD, called FSHD1 and FSHD2, are known. In both types, inefficient epigenetic repression of the retrogene DUX4 plays a key role in the pathogenesis [5, 6]. FSHD1 accounts for 95% of all patients and almost all early onset cases [7], it is associated with contraction of the D4Z4-repeat at chromosome 4q35 in combination with a disease-permissive 4qA allele [8, 9]. In the general population, the number of D4Z4 repeat units varies between 11 to more than 100, while patients with FSHD1 have only 1-10 repeat units. There is a roughly inverse correlation between repeat size and disease severity; most patients with short repeats have a severe disease phenotype [10, 11].

Historically, *infantile FSHD* was considered a distinct disease based on clinical onset before the age of two years (Brooke criteria, 1977 [12]). This concept evolved to *early onset FSHD* and was regarded a subgroup of FSHD, defined by signs or symptoms of facial weakness before the age of 5 and signs or symptoms of scapular weakness before the age of 10 (Brouwer criteria, 1994 [13]). Whereas the typical, classic form of FSHD is characterized by slowly progressive, often asymmetrical muscle weakness of facial- and shoulder muscles starting in the second decade of life [3, 14], the subgroup of early onset FSHD patients is characterized by severe muscle weakness, faster disease progression and systemic features. These systemic features include epilepsy, mental retardation, hearing loss, retinal vasculopathy, spinal deformities, respiratory problems and cardiac arrhythmias [3, 13, 15-19]. It should be noted that clinical variability in terms of age at onset and disease severity is typical of FSHD. Age at onset ranges from birth to 70 years of age and disease severity may

vary from asymptomatic carriers to patients with severe muscle weakness causing functional dependence.

Our current understanding of disease severity, systemic features and prognosis in early onset FSHD is based on small case-series. Consequently, many questions about the clinical phenotype and natural history of early onset FSHD remain unanswered, thus limiting evidence based clinical management. Here, we systematically review the literature using individual patient data to gain insight into the clinical spectrum of early onset FSHD. The ultimate goals are to improve recognition and understanding of early onset FSHD and to advance clinical management.

2. Methods

2.1 Search strategy

We searched Embase (index period 1970-2016) and PubMed (index period 1970-2016) for articles reporting early onset FSHD cases (Appendix 1). We applied a sensitive search strategy using search terms as described in table 1. Additional studies of potential interest were searched via cross-referencing.

2.2 Eligibility screening

We included articles presenting empirical data on early onset FSHD patients. We excluded conference abstracts, posters, publications not reporting original data (*e.g.* reviews, book chapters) and studies not reported in English. Articles of potential interest were screened on the basis of title and abstract after which full-text evaluation was performed on the remaining articles (R.G.).

After article selection, two authors (R.G. and T.S.) independently assessed the eligibility of individual patients and disagreements were resolved by consensus. We included patients who fulfilled the criteria by Brooke (signs of FSHD within the first two years of life [12]) or the criteria by Brouwer (signs or symptoms of facial weakness before the age of five and signs or symptoms of shoulder weakness before the age of ten [13]). Cases were excluded if a concomitant, neuromuscular disease was present.

2.3 Data-extraction

For every reported patient, we collected the following parameters: demographics (sex, race, age at onset, age at examination), clinical characteristics (clinical severity, age at wheelchair dependency, muscle involvement pattern), systemic features (developmental abnormalities, perinatal complications, mental capacity, hearing loss, retinal abnormalities, epilepsy, spinal deformities, respiratory problems and cardiac problems), and genetic characteristics (hereditary pattern and repeat length). For assessment of the clinical severity the Clinical Severity Score by Ricci ('Ricci score' [11]) was used. We obtained the score from the article or estimated it based on the clinical description. The age corrected CSS, correcting for age at examination published by van Overveld [20] was also calculated. The authors from the two largest cohorts and two other cohorts [4, 13, 21, 22] supplied additional individual patient data.

2.4 Statistics

Descriptive statistics were performed for continuous and categorical data as appropriate. We performed exploratory statistical analyses to assess relations between variables of demography, disease severity, systemic features and genetic parameters. We used linear regression if the dependent variable was continuous and logistical regression for

dichotomous variables. Correction for multiple testing was not applied and our analyses should be considered as hypothesis generating [23]. To this end, we only considered relations with $p < 0.05$ of potential interest. All statistical analyses were performed using IBM SPSS (version 22.0, IBM Corp, Armonk, NY).

3. Results

3.1 Search and selection results

The combined searches yielded 953 records, of which 303 were duplicates, leaving a total of 650 unique articles (figure 1). This resulted in 43 articles including 1683 patients of which 227 are early-onset FSHD patients.

3.2 Clinical description of early onset FSHD

Mean age at assessment was 18.8 years (range 2-72 years, SD 11.9 years). Symptoms started at a mean age of 2.8 years (range 0-5 years, SD 2.8 years). 56/227 of patients (25%) showed symptoms in the first year of life, mainly facial weakness resulting in feeding difficulties and less frequently inadequate eye closure. Perinatal complications (prematurity, low birth weight, and dysmorphic features) were reported in five cases (5/99, 5%) and none was related to muscle weakness of the child.

At assessment, the mean Ricci-score was 7 out of 10 (SD 2.6) and the mean age-corrected clinical severity score 1040 (SD 800). In general, the pattern of muscle involvement was

similar to the classical FSHD phenotype with facial, scapulohumeral, axial and peroneal muscle weakness. Forty percent of patients were wheelchair dependent; the average age of wheelchair dependency was 17 years (SD 7.8) (figure 2). Mean duration from age at onset to wheelchair dependency was 14.6 years (SD 7.8, range 4-37 years). Skeletal deformities were present in 70% of patients and included lumbar hyperlordosis (51%), kyphoscoliosis (9%) pectus excavatum (2%) and multiple deformities (8%).

Approximately 50% of early onset FSHD patients had systemic features (hearing loss, vision loss, epilepsy, intellectual disability, pulmonary abnormalities, and cardiac abnormalities) (table 3). Of these, approximately two thirds had a single systemic feature, the other third had multiple systemic features. Clinical hearing loss, predominantly high frequency loss without need of hearing aids was the most frequent feature (40%), and 7% of patients had subclinical hearing loss at auditory testing. Clinical vision loss was described in 13 out of 227 patients (6%) and signs of retinopathy were detected in 41 of 112 tested patients (37%). Spirometry results were available for 112 patients, and decreased percentage predicted forced vital capacity was detected in approximately one third. Eighteen out of the total 227 patients were on assisted ventilation at the time of assessment. Cardiac abnormalities were found in 9% of the 93 conducted electrocardiograms in 93 patients, consisting of incomplete right bundle branch blocks (4 patients), right ventricular hypertrophy (2 patients), right atrial hypertrophy (1 patient), and 1st degree atrioventricular block (1 patient). Epilepsy was present in 18 patients (8%); 5 patients had localization-related (focal) epilepsy, 2 patients had generalised epilepsy and 11 patients had unclassified epileptic seizures.

Genetic confirmation of the diagnosis FSHD was present in 171 of 227 reported cases. For 93 patients, DNA from parents was available. In 68 out of these 93 families, a 'de novo'

mutation was found (73%). The mean repeat length was 14,2 Kb (SD 4.8, range 9-31). Eleven out of 93 patients were mosaic (12%).

3.3 Associations with disease severity

A complete overview of all calculated associations between disease variables is shown in appendix 2. We here focus on the clinically most relevant associations. A shorter D4Z4 repeat length was associated with a higher age-corrected clinical severity score (standardized beta -0.202, $p=0.019$), more wheelchair dependency (OR 0.178, $p=0.035$), more hearing loss (OR 0.254, $p=0.002$), and more epilepsy (OR 0.205, $p=0.014$). An earlier age at onset is correlated with more frequently hearing loss (OR 0.827, $p=0.001$) and hearing loss is correlated with vision loss (OR 6.370, $p=0.007$) and intellectual disability (OR 2.272, $p=0.028$). Intellectual disability is associated with epilepsy (OR 80.0, $p=0.000$). Wheelchair dependency is associated with skeletal deformities (OR 1.855, $p=0.034$) and with assisted ventilation (OR 4.839, $p=0.000$).

4. Discussion

Based on data from 227 early onset FSHD cases, we conclude that early onset FSHD is on the severe end of the FSHD spectrum. The genetic defect, the distribution pattern of muscular weakness and the type of systemic features are similar to the classical FSHD phenotype. Early onset FSHD distinguishes itself from the adult-onset patients by a more severe muscle weakness, more rapid progression and more frequently occurring systemic features. Some systemic features (cognitive disability, epilepsy) are only associated with early onset FSHD.

Early onset FSHD patients demonstrate high CSS scores (mean 7.35, SD 2.6; median 7, IQR 5.5-10) and age corrected CSS (mean 1008, SD 645; median 842, IQR 571-1273). Of note, standard deviations and interquartile ranges are indicative of substantial clinical variation that is characteristic of FSHD. Also, these severity scores have not been validated in early onset FSHD populations. However, the percentage of early onset patients being wheelchair-dependent (40%) versus that in the general FSHD population (6.4% [24]) underscores the severe muscle weakness in the former group. This is reflected by the high prevalence of spinal deformities, especially lumbar hyperlordosis, indicative of early axial weakness. Respiratory abnormalities are associated with spinal deformities in this and other studies. Therefore, the higher prevalence of assisted ventilation in our early onset population (8%) versus the general FSHD populations (0-7%) is not surprising [25-27]. The latter findings underline the need for regular pulmonary monitoring by spirometry in early onset FSHD patients[28]. In addition, we confirm the progressive nature of FSHD in the early onset population (appendix 2; wheelchair dependency and respiratory failure increase with age).

Furthermore, systemic features occur frequently in early onset FSHD. The most frequent systemic feature in this population was hearing loss (40%). It was characterized by sensorineural loss of preferentially higher frequencies of limited severity, and hearing aids are usually not necessary. The frequency of hearing loss in the general FSHD population is unclear due to widely varying frequencies (ranging from no association to 64% in selected populations, mean 15%[18, 28-31]. The high frequency of hearing loss underscores the need for screening hearing function by audiometry, especially during speech development.

We found a lower prevalence of subclinical retinopathy (37%) than reported in literature (50-75%) [31, 32], This is probably due to suboptimal screening methods (no fluorescence

angiography). Another explanation might be the later onset of retinal abnormalities. We did find a higher rate of clinical vision loss compared to the general FSHD population (6% vs. 0.8%-1.7%[31, 33]). Of note, this percentage is significantly higher than previously reported.

Electrocardiographic anomalies were present in 9% of early onset FSHD patients, a prevalence roughly corresponding to literature on the general FSHD population (albeit being very heterogenic (range 0-60% [28, 34-36], for an overview see Tawil et al. [28]) and consisted of arrhythmia and other minor abnormalities. The clinical consequences of arrhythmia seem to be minor since none of the patients required pacemaker intervention. Interestingly, we found electrocardiographic changes mainly in patients of Asian origin. This geographic difference has not been previously reported and deserves attention in future studies, especially because we also found significantly different prevalence of mental impairment and epilepsy between patients from Caucasian and Asian descent.

We found a high percentage of 'de novo' mutations in the early onset FSHD patients: 73% versus 30% in the general FSHD population[37]. Presumably, severe muscular weakness limits procreation in early onset FSHD patients. Of note, we did not find significant differences between early onset patients with 'de novo' mutations versus those with a positive family history. An association between repeat length and the age-corrected disease severity score previously reported in the general FSHD population [38], could be confirmed in the early onset FSHD patients.

4.1 Limitations and future directions

Besides its strength of a multinational systematic review of individual patient data on a large number of patients, this study has a number of limitations. Case reports and case series bear the potential of publication and selection bias, which might lead to overestimation of the

severity of disease and prevalence of systemic features. Inclusion criteria in some of the included studies, such as selection of patients with short repeat lengths or those with hearing difficulties, increases such bias. Moreover, utilising the criteria for early onset/infantile FSHD by Brooke and Brouwer, which address motor symptoms, leads to the possible exclusion of patients with atypical (i.e. non-motor) onset of FSHD; we are aware of cases with a retinal vasculopathy presentation[39, 40]. Due to the cross-sectional nature of the current review and the studies included herein, we remain unaware on the longitudinal course of early onset FSHD. The average age at assessment was approximately 18 years. Considering the progressive nature of the disease and the fact that these patients are on the severe end of the FSHD spectrum, progressive handicap and complications could be expected. The nature of our data and the limitations discussed above underline the need for well designed, larger longitudinal cohort studies in early onset FSHD. Such studies are underway and have the potential of improving the prognostication and classification of early onset FSHD patients [41, 42]. For now, classification on the basis of age of onset has practical utility both in clinical practice and clinical trials; the authors therefore recommend using the criteria by Brouwer to define early-onset FSHD.

5. Conflicts of interest

ms. Goselink, mr. Okkersen, ms. Voermans, mr. Brouwer, mr. Padberg, ms. Nikolic, ms. Tupler, ms. Dorobek, ms. Mah, mr. van Engelen, ms. Erasmus and mr. Schreuder have nothing to disclose.

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Figure 1. Flow-chart of study and case selection.

Figure 2. Age at loss of ambulation from subgroup of wheelchair dependent patients (n=78). Mean age is 17 years (standard deviation 7.8 years).

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Table 1. Search terms used in Pubmed and Embase.

FSHD	AND	case OR patient OR series
OR		OR
facioscapulohumeral dystrophy		child OR infant OR infantile OR early-onset OR severe
OR		OR
landouzy		epilepsy OR mental retardation OR hearing loss
		OR
		Coats OR retinal OR teleangiectasis

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Table 2. Summary of included articles. #: Southern blot p13E. \$: Double digested EcoRI/BlnI.

First Author[ref]	Year	Country	Study type	#iFSHD	#cases	Selection criteria	Genetic confirmation
Hanson[24]	1971	USA	Case-series	3	3	iFSHD	
Carroll[25]	1979	USA	Case-series	11	11	iFSHD	
Taylor[26]	1982	USA	Case-series	2	2	iFSHD + retinopathy	
Wulff[27]	1982	USA	Case-report	1	1	iFSHD	
McGarry[28]	1983	USA	Case-report	2	2	iFSHD	
Meyerson[29]	1984	USA	Case-report	2	3	iFSHD + hearing loss	
Gieron[30]	1985	USA	Case-report	3	4	iFSHD	
Gurwin[31]	1985	GBR	Case-report	3	4	iFSHD	
Korf[32]	1985	USA	Case-series	6	6	iFSHD + hearing loss	
Bailey[33]	1986	USA	Case-report	1	8	iFSHD	
Voit[34]	1986	DEU	Case-series	7	10	iFSHD + hearing loss	
Yasukochi[35]	1988	JPN	Case-series	2	2	iFSHD + retinopathy	
Shapiro[36]	1991	USA	Case-series	9	9	iFSHD	
Kamata[37]	1993	JPN	Case-report	1	1	iFSHD	
Brouwer [13]*	1994	NLD	Case-series	6	6	iFSHD	#
Jardine[38]	1994	GBR/DEU	Case-series	19	27	iFSHD	#
Brouwer[21]*	1995	NLD	Case-series	4	4	iFSHD	
Je Hyeon[39]	1995	JPN	Case-report	1	1	iFSHD	#
Nakagawa[40]	1996	JPN	Case-report	1	2	iFSHD	#
Nakagawa[41]	1997	JPN	Population cohort	7	42	FSDH	#
Okinaga[42]	1997	JPN	Case-series	2	3	iFSHD	#
Funakoshi[15]	1998	JPN	Population cohort	20	127	FSDH	\$
Miura[43]	1998	JPN	Case-series	2	2	iFSHD	#
Lapena[44]	2001	AUS	Case-series	1	1	Vocal cord paralysis	\$
Dorobek[45]	2004	POL	Case-report	1	2	iFSHD	\$
Wohlgemuth[46]	2004	NLD	Case-series	4	10	FSDH + assisted ventilation	\$
Felice[47]	2005	USA	Case-report	2	3	iFSHD	\$
Bindoff[48]	2006	NOR	Case-series	2	2	iFSHD	\$
Klinge[16]	2006	GBR	Case-series	7	7	iFSHD	\$
Saito[49]	2007	JPN	Case-report	1	1	iFSHD	
Shields[50]	2007	USA	Case-report	1	1	iFSHD	\$
Kolski[51]	2008	CAN	Case-report	1	1	iFSHD	\$
Kriswalsky[52]	2008	USA	Case-report	1	1	iFSHD	\$
Trevisan[17]	2008	ITA	Case-series	5	7	iFSHD + 10-13Kb	\$
Lee[53]	2009	JPN	Case-report	1	1	iFSHD	\$
Grosso[54]	2011	ITA	Case-report	3	7	iFSHD	\$
Sakellariou[55]	2012	GRE	Population cohort	3	127	FSDH	\$
Wang[56]	2012	TWN	Population cohort	7	24	FSDH	\$
Chen[19]	2013	TWN	Case-series	9	9	iFSHD + 10-13Kb	\$
Statland[57]	2013	USA	Case-series	3	10	FSDH +	\$

						retinopathy	
Kana[58]	2013	JPN	Case-report	1	1	iFSHD	\$
Dorobek[4]*	2015	POL	Population cohort	22	103	FSHD	\$
Nikolic[22]*	2016	ITA	Population cohort	36	850	FSHD + 1-3 D4Z4 RU	\$

*: additional data provided by the authors.

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Table 3. Patient characteristics of published early onset FSHD cases (n=227)

Demographics	
Age at reporting (yrs)	18.8 ± 11.9
Male sex – no.	103 (45%)
African background – no./total no.*	2/227 (1%)
Asian background – no./total no.*	56/227 (25%)
Caucasian background – no./total no.*	169/227 (74%)
Clinical history	
Perinatal complications – no./total no.	5/99 (5%)
Age at onset – mean (yrs) [^]	2.8 ± 2.8
Clinical severity score (CSS) – mean ± SD	7.4 ± 2.6
Age corrected CSS – mean ± SD	1042 ± 800
Wheelchair dependency – no./total no.	87/217 (40%)
Age at wheelchair dependency (yrs)	17.2 ± 7.8
Systemic symptoms	
Hearing loss - no./total	91/227 (40%)
Subclinical hearing loss - no./total no.	15/210 (7%)
Retinopathy – no./total no.	41/112 (37%)
Vision loss - no./total no.	13/227 (6%)
Epilepsy - no./total no.	18/227 (8%)
Developmental delay- no./total no.§	35/227 (15%)
ECG abnormalities - no./total no.	8/93 (9%)
Spinal deformities - no./total no.	105/152 (70%)
Decreased forced vital capacity (%FVC) - no./total no.	37/121 (31%)
Assisted ventilation - no./total no.	18/227 (8%)
Genetic characteristics	
Repeat length – mean (range, SD)	14.2 Kb (9-31 Kb, 4.8)
De novo mutations – no./total no. (%)	68/93 (73%)
Mosaic inheritance– no./total no. (%)	11/93 (12%)

*based on study location. [^] as reported by the parents/caregivers.

Appendix A: search strategy

1. PubMed 28-04-2016:

((facioscapulohumeral) OR (fshd)) AND (childhood OR pediatric OR early OR coat OR hearing OR retinal OR case).

2. Embase 28-04-2016:

1.	((facioscapulohumeral) OR (fshd)) AND (mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier)
2.	(child* or infant* or pedi* or early onset or severe).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3.	(coat* or retina* or teleangi*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4.	(hearing or epilepsy or retardation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5.	(patient or case or cohort or series).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6.	2 or 3 or 4 or 5
7.	1 and 6
8.	limit 7 to (English language and yr="1970 -Current")

Table 4. Embase search.

Appendix B.

Table 5. Associations between variables using linear regression (scalar dependent variables) and logistic regression (dichotomous dependent variables), top row denotes dependent variables. Standardized β (linear regression) and $\exp(B)$ (logistic regression) are presented, as well as p -values. Significant findings ($p < 0.05$) are depicted in bold font.

Dependent → Independent ↓	Sex (♂/♀)	Race (Caucasian/ Asian)	Perinatal compl. (no/yes)	Age at onset (years)	CSS (score)	Age corr. CSS (score)	Whe el- chair (no/y es)	Age loss ambul. (years)	Hearing loss (no/yes)	Vision loss (no/ye s)	Epile psy (no/y es)	Develop. Delay (no/yes)	ECG abnorm. (no/yes)	Spinal deform. (no/yes)	Assisted vent. (no/yes)	Repeat size (kb)	Inheri ted (no/y es)	Mental Retard. (no/yes)
Age (years)	0,991 $p=0,420$	0,980 $p=0,174$	0,985 $p=0,654$	0,353 $p<0,001$	0,366 $p<0,001$	-0,612 $p<0,001$	1,084 $p<0,001$	0,503 $p<0,001$	0,980 $p=0,096$	0,985 $p=0,581$	0,984 $p=0,498$	0,940 $p=0,049$	1,017 $p=0,531$	1,015 $p=0,234$	1,041 $p=0,004$	0,118 $p=0,165$	1,000 $p=0,984$	0,978 $p=0,219$
Sex (♂/♀)	-	0,817 $p=0,519$	2,604 $p=0,248$	-0,203 $p=0,002$	0,097 $p=0,157$	0,105 $p=0,129$	1,970 $p=0,018$	-0,123 $p=0,290$	1,179 $p=0,548$	1,527 $p=0,478$	1,060 $p=0,906$	3,208 $p=0,046$	0,113 $p=0,043$	1,144 $p=0,631$	0,819 $p=0,592$	-0,043 $p=0,613$	0,945 $p=0,838$	0,765 $p=0,466$
Race (Caucasian/ Asian)	-	-	0,000 $p=0,997$	-0,020 $p=0,762$	0,207 $p=0,002$	-0,079 $p=0,254$	0,650 $p=0,190$	0,001 $p=0,993$	0,961 $p=0,900$	0,000 $p=0,998$	3,404 $p=0,014$	0,354 $p=0,176$	10,020 $p=0,006$	0,195 $p<0,001$	2,020 $p=0,072$	-0,166 $p=0,047$	0,872 $p=0,669$	2,726 $p=0,009$
Perinatal complications (no/yes)	-	-	-	-0,165 $p=0,017$	0,071 $p=0,317$	-0,001 $p=0,989$	1,500 $p=0,575$	-0,098 $p=0,418$	1,410 $p=0,634$	4,909 $p=0,084$	0,000 $p=0,999$	6,333 $p=0,036$	3,939 $p=0,228$	9,943 $p=0,035$	0,750 $p=0,791$	0,334 $p<0,001$	0,923 $p=0,914$	0,810 $p=0,846$
Age at onset (years)	-	-	-	-	0,023 $p=0,738$	-0,360 $p<0,001$	0,983 $p=0,727$	0,532 $p<0,001$	0,827 $p=0,001$	0,849 $p=0,184$	0,777 $p=0,055$	0,728 $p=0,029$	1,061 $p=0,624$	0,982 $p=0,723$	0,916 $p=0,237$	0,008 $p=0,927$	1,025 $p=0,614$	0,885 $p=0,118$
CSS (score)	-	-	-	-	-	0,183 $p=0,008$	6,115 $p<0,001$	-0,109 $p=0,342$	1,113 $p=0,052$	0,926 $p=0,510$	0,955 $p=0,622$	1,108 $p=0,312$	1,140 $p=0,395$	1,287 $p<0,001$	1,447 $p<0,001$	-0,160 $p=0,058$	0,930 $p=0,178$	1,030 $p=0,676$
Age corrected CSS (score)	-	-	-	-	-	-	1,000 $p=0,991$	-0,497 $p<0,001$	1,000 $p=0,356$	1,000 $p=0,575$	1,000 $p=0,657$	1,001 $p=0,001$	0,999 $p=0,392$	1,000 $p=0,838$	1,000 $p=0,238$	-0,202 $p=0,019$	1,000 $p=0,669$	1,000 $p=0,272$
Wheelchair (no/yes)	-	-	-	-	-	-	-	-	1,608 $p=0,094$	0,654 $p=0,498$	0,947 $p=0,913$	1,215 $p=0,694$	2,581 $p=0,202$	1,855 $p=0,034$	4,839 $p<0,001$	-0,178 $p=0,035$	0,597 $p=0,077$	1,146 $p=0,716$
Age at loss ambulation (years)	-	-	-	-	-	-	-	-	0,975 $p=0,407$	1,046 $p=0,411$	1,019 $p=0,726$	0,947 $p=0,376$	0,962 $p=0,592$	0,986 $p=0,647$	0,932 $p=0,074$	0,191 $p=0,193$	0,996 $p=0,899$	0,992 $p=0,855$
Hearing loss (no/yes)	-	-	-	-	-	-	-	-	-	6,370 $p=0,007$	1,975 $p=0,169$	1,549 $p=0,374$	0,893 $p=0,879$	1,322 $p=0,324$	0,746 $p=0,447$	-0,254 $p=0,002$	0,467 $p=0,009$	2,272 $p=0,028$
Vision loss (no/yes)	-	-	-	-	-	-	-	-	-	-	4,067 $p=0,059$	3,273 $p=0,104$	0,000 $p=0,999$	1,377 $p=0,602$	0,000 $p=0,999$	0,004 $p=0,972$	1,464 $p=0,515$	1,768 $p=0,418$
Epilepsy (no/yes)	-	-	-	-	-	-	-	-	-	-	-	2,587 $p=0,166$	0,1697 $p=0,630$	0,539 $p=0,263$	0,667 $p=0,600$	-0,205 $p=0,014$	0,598 $p=0,346$	80,000 $p<0,001$

Developmental delay (no/yes)	-	-	-	-	-	-	-	-	-	-	-	-	0,000 p=0,998	1,390 p=0,527	0,667 p=0,600	-0,130 p=0,119	0,653 p=0,440	3,103 p=0,035
ECG Abnormalities (no/yes)	-	-	-	-	-	-	-	-	-	-	-	-	2,333 p=0,255	47,750 p<0,001	-0,072 p=0,393	1,646 p=0,489	0,000 p=0,999	
Spinal Deformities (no/yes)	-	-	-	-	-	-	-	-	-	-	-	-	3,200 p=0,005	0,097 p=0,272	0,734 p=0,283	0,785 p=0,539		
Assisted ventilation (no/yes)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0,132 p=0,116	1,444 p=0,323	0,292 p=0,102	
Repeat size (kb)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1,068 p=0,078	0,753 p=0,001	
Inherited (no/yes)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0,446 p=0,060	

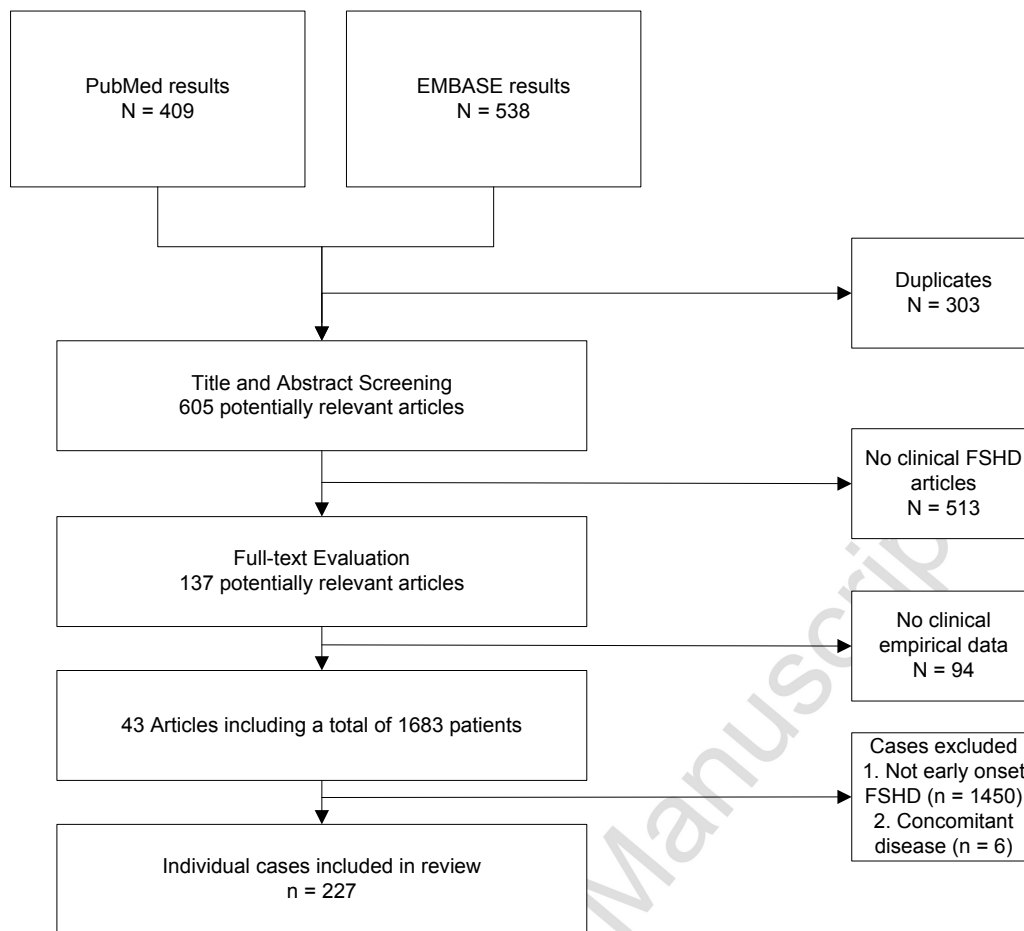


Figure 1

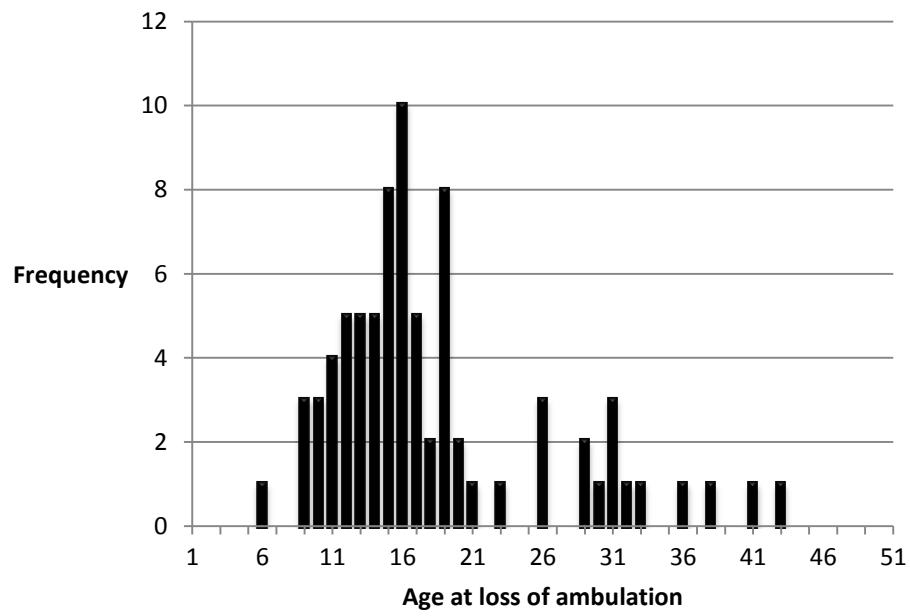


Figure 2.

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