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Hearing Loss, Retinal Abnormality, and Seizures in People With Facioscapulohumeral Muscular Dystrophy

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Abstract

Introduction/Aims: Few studies describing comorbidities in individuals with facioscapulohumeral muscular dystrophy (FSHD) are available. We used data from the Muscular Dystrophy Surveillance, Tracking and Research Network (MD STARnet) to identify and describe the prevalence of three comorbidities—hearing loss, retinal abnormalities, and seizures—in individuals with FSHD.

Methods: We analyzed retrospective population-based data from 548 individuals diagnosed with FSHD who had at least one health visit during 2008–2019. The primary variables of interest were the presence of one or more of the three comorbidities and the age at diagnosis of the comorbidity. We calculated percentages of each comorbidity by population characteristics.

Results: Among the study cohort, 17.2% ($n = 94$) had at least one comorbidity, with 1.5% ($n = 8$) having multiple comorbidities. Hearing loss (13%; $n = 71$) was the most frequently reported comorbidity, followed by retinal abnormalities (3.6%; $n = 20$) and seizures (2.0%; $n = 11$).

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Author Contributions

Shannon N. Kilburn: formal analysis, visualization, writing – original draft, writing – review and editing, methodology, conceptualization. **Shiny Thomas:** writing – original draft, writing – review and editing, conceptualization. **Anne L. Havlik:** writing – review and editing, validation, formal analysis. **Katherine D. Mathews:** writing – review and editing. **Natalie Street:** writing – review and editing. **Aida Soim:** writing – review and editing.

Conflicts of Interest

Author Katherine D. Mathews is a site PI for PTC Therapeutics, Sarepta Therapeutics, Pfizer, Reata, Italfarmaco, Fibrogen, Capricor, Edgewise, Lexeo, Larimar, ML Bio, AskBio, Biogen, Biohaven, Scholar Rock, AMO, and CSL Behring; provides research support for NIH U54 NS053672, CDC U01 DD001248, and Friedreich's Ataxia Research Alliance; and is on the consulting and advisory boards for Sarepta, Dyne, Edgewise, and Ikaika. The other authors declare no conflicts of interest.

Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Median age at diagnosis for hearing loss, retinal abnormalities, and seizures was 46.5 [interquartile range (IQR):11.8–65.3 years], 58.7 (IQR: 41.5–66.5 years), and 16.5 years (IQR: 3.0–34.7 years), respectively.

Discussion: This study demonstrated that a substantial minority of the study cohort had hearing loss, while fewer had retinal abnormalities and seizures. Age at diagnosis varied widely; hearing loss and retinal disease tended to occur in adults, while for seizures, half were ≤ 10 years old. Our results on the prevalence of comorbid conditions among individuals living with FSHD help provide a better understanding of disease burden and support recommendations for ophthalmological and hearing screenings.

Keywords

comorbidity; facioscapulohumeral muscular dystrophy; hearing loss; retinal abnormality; seizure

1 | Introduction

Various comorbid conditions have been found to be associated with facioscapulohumeral muscular dystrophy (FSHD), including hearing loss, retinal abnormalities, and seizures [1–3]. These conditions are seen primarily in those with more severe, early-onset FSHD [4]. The cause of hearing loss in FSHD is unknown; however, involvement of the stapedius muscles or cochlear dysfunction has been suggested [5]. Symptomatic retinal abnormalities such as Coats disease are rare in FSHD but can lead to blindness if not treated in a timely manner [4]. Current guidelines advise evaluation by an ophthalmologist for children with severe FSHD and for anyone with visual symptoms [6]. Tawil and Van Der Maarel have suggested the involvement of multiple genes or a gene with pleiotropic effects as an explanation for the presence of extramuscular conditions such as hearing loss and retinal vascular abnormality [7]. Previous studies have shown that seizures are more common in childhood-onset FSHD [8, 9].

While several clinical studies have described these comorbidities in individuals with FSHD, there is a lack of population-based studies in the United States (US) on the prevalence of these comorbidities. We report the prevalence of the above-listed comorbidities in individuals with FSHD from the Centers for Disease Control and Prevention (CDC)'s Muscular Dystrophy Surveillance Tracking and Research Network (MD STAR net).

2 | Methods

2.1 | Study Population

MD STAR net is a multisite population-based surveillance system to identify individuals with muscular dystrophies in the United States. Currently, data are collected from seven sites: 23 counties in north central Florida (FL), 33 counties in the Piedmont region of North Carolina (NC), 21 counties in western New York (NY), and statewide in Virginia (VA), Iowa (IA), South Carolina (SC), and Utah (UT). Details of the MD STAR net methodology have been previously described [10, 11].

Trained abstractors used established methods to identify affected individuals and collect information using medical records from multiple sources and administrative data within their respective sites [11]. Diagnostic data were reviewed by a committee of neuromuscular clinical specialists, and an FSHD case status of definite, probable, possible, or asymptomatic was assigned. All sites had Institutional Review Board (IRB) approval or exemption. Additionally, some sites (IA, NC, NY, and SC) also had public health authority to conduct surveillance for muscular dystrophy [11].

2.2 | Study Cohort and Variables

The eligible cohort included individuals diagnosed with FSHD through December 31, 2019, who resided within an MD STAR_{net} site at any time from January 1, 2008 to December 31, 2019 (surveillance period), and who had at least one healthcare visit during the surveillance period. Only individuals assigned a case status of definite or probable were included in the final study cohort. A definite case had documented FSHD clinical symptoms and diagnosis by DNA analysis. A probable case had documented FSHD clinical symptoms and family history consistent with dominant inheritance.

We analyzed the frequency and age at diagnosis for three comorbidities—hearing loss, retinal abnormalities, and seizures. Documented comorbidities were abstracted from medical records. Retinal abnormalities included retinopathy, Coats disease, retinal vasculopathy, retinal detachment, and retinal tortuosity. Age at diagnosis was defined as the age at the first documented symptom for each comorbidity. Other characteristics evaluated included age at last clinic visit, MD STAR_{net} site, and sociodemographic characteristics including sex, race, last known employment status, and health insurance information. For evaluation of employment status, individuals reported as unemployed were restricted to those aged 18 to < 65 years. The age of the individual at the time of employment status was calculated using available date of birth and employment status date.

2.3 | Statistical Analysis

Counts and percentages for categorical variables and medians and interquartile ranges (IQR) for continuous variables were calculated. All statistical analyses were conducted using Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Cary, NC).

3 | Results

Of 726 individuals with FSHD, 548 individuals (344 definite and 204 probable) were included in the study; 17.2% ($n = 94$) had at least one comorbidity of interest, with 1.5% ($n = 8$) having more than one. Of the three comorbid disorders evaluated, hearing loss was the most frequent (13.0%; $n = 71$). Retinal abnormalities (3.6%; $n = 20$) and seizures (2.0%; $n = 11$) were reported less frequently. A higher proportion of individuals with definite case status (18.0%) had at least one comorbidity compared to those with probable case status (15.7%). The frequency pattern for the three comorbidities for each case status was similar to that for the full study cohort, with hearing loss being most frequent (14% for definite and 11.3% for probable cases).

The characteristics of the study cohort are presented in Table 1. A slight majority of individuals were male, and most were Non-Hispanic White. Individuals were most frequently employed and had public health insurance.

Table S1 reports the characteristics of individuals with FSHD with hearing loss and individuals with FSHD without a documented comorbidity. Individuals with seizures and/or retinal abnormalities are not included in this table due to small numbers. The distribution of race/ethnicity and sex in this group was similar to that of the full study cohort in Table 1. Individuals with hearing loss most frequently reported being retired and having public insurance. Individuals without a comorbidity most frequently reported being employed and privately insured.

Overall, median age at comorbidity diagnosis was highest for retinal abnormalities and lowest for seizures (Figure 1). Additionally, ages of comorbidity diagnosis for the three comorbidities combined and for hearing loss specifically were more frequently > 40 years, followed by age group 0–20 years. For probable case status, median (IQR) ages at diagnosis for hearing loss [47.1 (35.0–68.8)], retinal abnormalities [68.9 (64.2–73.8)], and seizures [34.7 (24.3–86.2)] were higher than those for definite case status [43.2 (5.8–65.3); 54.7 (25.0–63.1); and 8.4 (1.0–34.5), respectively].

4 | Discussion

A substantial minority of our FSHD study cohort had hearing loss, while fewer had seizures and retinal abnormalities, consistent with some previous studies that included both childhood and typical-onset patients with FSHD [8, 9, 12]. Individuals with childhood-onset FSHD are more likely to experience hearing or visual impairment than those with typical-onset FSHD [12–14]. Studies have reported median ages of ≤ 10 years old for diagnoses of hearing loss and retinal abnormality in FSHD [15, 16], while median ages at these diagnoses occurred in adulthood in our study. However, several studies [8, 12, 16] examined only childhood-onset FSHD, while ours was not restricted by age at FSHD diagnosis.

Frequency of hearing loss among individuals with FSHD in previous studies ranged widely (8% to 56%) [4, 8, 9, 16]. Evidence suggests that the diagnosis of hearing loss is not more prevalent in individuals with FSHD with typical onset (> 10 years) when compared to the general population [13, 17]. The hearing loss frequency in our FSHD cohort (13.5%) is comparable to that reported in the US population of individuals age ≥ 12 who have bilateral hearing loss (12.7%) and bilateral or unilateral hearing loss (20.3%) [18]. Although overall frequencies are similar, mean or median ages at diagnosis differ; the median age at hearing loss in our study was 46.5 years, and the US general population mean was 74 years [19]. This difference in age could be explained by our data showing 25% of individuals with hearing loss onset age < 20 years and 49% > 40 years (Table S1).

Our result for retinal abnormalities prevalence is similar to a study reporting Coats disease, a severe retinovascular disease, in 3.6% of 28 individuals with childhood-onset FSHD [9]. Another study reported symptomatic Coats disease in 0.8% of 396 individuals with FSHD [15]. However, retinal abnormalities in our study were not limited to Coats disease. The

estimated prevalence of retinopathy reported in the US general population (3.4%) is similar to our study cohort's retinal abnormalities frequency [20].

Several studies have reported high frequencies (7.1%–44%) of epilepsy in FSHD [3, 8, 9, 14]; however, due to a lack of sufficient data on seizure types in our study cohort, we were unable to ascertain the number of individuals with epilepsy, and therefore cannot directly compare our findings to these studies.

Limitations of our study include the lack of comprehensive data available about some comorbid conditions documented for some individuals (e.g., seizure types, extent of hearing loss). Also, the date/age at comorbid disease diagnosis in our dataset may not always be an accurate timepoint of onset or first diagnosis. Additionally, not all individuals in our study cohort had likely undergone hearing tests.

These results demonstrate that hearing loss and retinal abnormalities were just as prevalent in our FSHD study cohort as they are in the US general population, while seizures were more frequent. Our results on the prevalence of comorbid conditions among individuals living with FSHD help provide a better understanding of disease burden and support recommendations for early ophthalmological and audiometry screening for individuals with severe FSHD [6]. Further population-based studies are needed to investigate whether these comorbidities are more frequent in individuals with childhood-onset FSHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

Due to privacy concerns, data from the MD STARnet are not publicly available. Researchers interested in MD STARnet data can contact md-starnet@cdc.gov. Data used for this analysis are housed and maintained by the New York State Department of Health.

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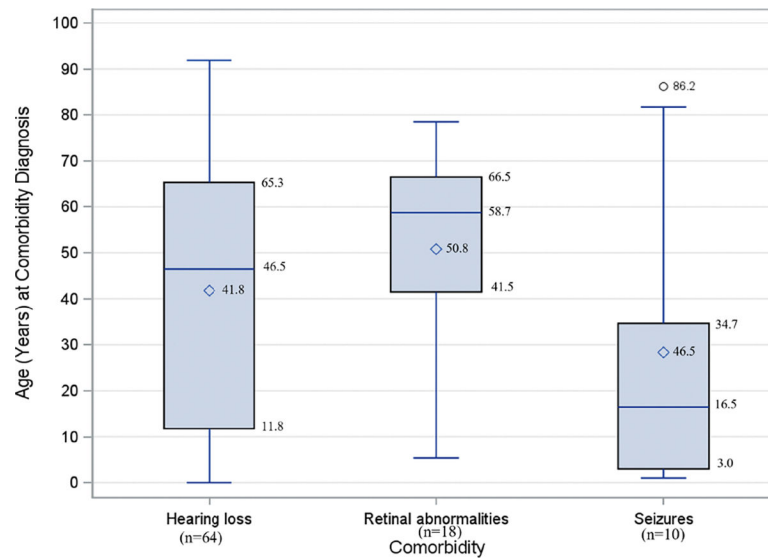


FIGURE 1 |

Median, mean, range and interquartile range of age when comorbidities were first documented in the study cohort. A total of 94 individuals with FSHD had one comorbidity, and eight more individuals had more than one comorbidity ($n = 102$). The figure represents reports where age at comorbidity diagnosis was available (n). The comorbidity categories are not mutually exclusive. The blue diamond in the box represents the mean age and the circle labeled 86.2 years represents an outlier age.

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TABLE 1 |
Sociodemographic characteristics among individuals with FSHD in MD STAR net .

Characteristics	Total <i>n</i>
Total	548
Sex	
Female	254 (46.4%)
Male	294 (53.6%)
Race	
Non-Hispanic white	445 (81.2%)
Other/unknown	103 (18.8%)
Age at last clinic visit in years, median (IQR)	53.4 (35.6–66.1)
Age at comorbidity diagnosis in years, median (IQR)	47.3 (11.8–65.3)
Age group at comorbidity diagnosis in years (<i>n</i> = 102) ^a	
0–20	26 (25.5%)
> 20–40	15 (14.7%)
> 40	51 (50.0%)
Unknown	10 (9.8%)
MD STAR net site	
Florida	25 (4.6%)
Iowa	101 (18.4%)
North Carolina	97 (17.7%)
New York	107 (19.5%)
South Carolina	46 (8.4%)
Utah	143 (26.1%)
Virginia	29 (5.3%)
Employment	
Disabled/unable to work	114 (20.8%)
Employed	176 (32.1%)
Retired	106 (19.3%)
Student or underage	50 (9.1%)
Unemployed ^b	33 (6.0%)

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Characteristics	Total <i>n</i>
Other/unknown	69 (12.6%)
Insurance	
Private	229 (41.8%)
Public	213 (38.9%)
Private and public	67 (12.2%)
Other/unknown	39 (7.1%)

^aThe *n* includes eight individuals who had more than one comorbidity.

^bUnemployed category was restricted to those who were 18 to ≤ 64 years old at the time of report.