Real-World Clinical Burden of Friedreich Ataxia in the United States

RWD46

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Background

- Friedreich ataxia (FA) is a terminal, rare, autosomal recessive genetic disorder associated with debilitating comorbidities.
- It is the most common inherited ataxia with an estimated prevalence of 1:50,000.[1]
- Most patients experience loss of ambulation and require the use of wheelchair within two decades of symptom onset.[3] Common non-neurological comorbidities include cardiomyopathy, scoliosis, and diabetes mellitus.[2]
- The lifespan of patients with FA is shortened, with a mean age of 37 years at death,[4, 5] and cardiac involvement is a major determinant of mortality risk.[6]
- To date, limited real-world data on clinical outcomes associated with FA have been presented.

Objective

- To assess the clinical burden of FA in the United States (US).

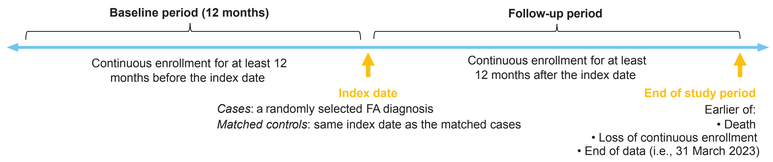
Conclusions

- This US retrospective study using recent real-world data illustrates that patients with untreated FA experience a substantial clinical burden when compared with age- and sex-matched controls without FA. This study also demonstrates that patients with FA are associated with significantly higher risk of death.
- The findings underscore high clinical burden and unmet need in FA for effective treatments to improve overall patient outcomes in this disease state.

Methods

- The Komodo Research Data (KRD) (Jan 2016 - March 2023) was used to identify patients with FA and matched controls.
  - KRD ingests closed claims data from >150 payers representing over 185 million closed patient lives with different insurances, including Commercial, Medicaid as well as Medicare.
- Patients who had at least two independent non-diagnostic early-onset cerebellar ataxia codes (ICD-10: G11.1 or G11.11), and one non-diagnostic FA specific code (ICD-10: G11.11) were included as *cases*.
- Persons without early-onset cerebellar ataxia (controls) were selected by matching to cases at a 5:1 ratio on age, sex, insurance type, US region, and continuous enrollment.
- The definitions of index date, baseline period, and follow-up period for each cohort were presented in **Figure 1**.

Figure 1. Index Date, Baseline Period, and Follow-up Period for Each Cohort



Abbreviation: FA, Friedreich ataxia.

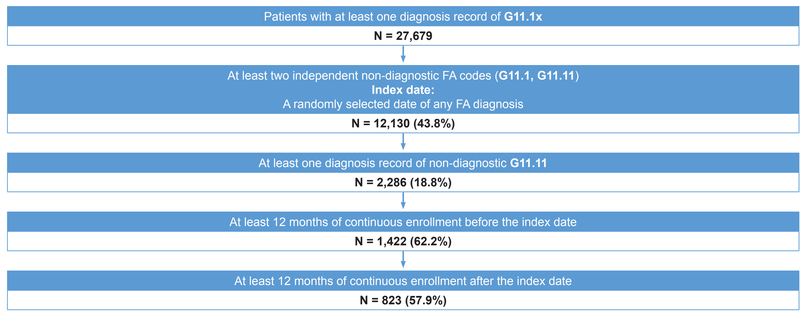
Study Outcomes And Statistical Analysis

- Baseline characteristics were summarized descriptively for cases and controls: means, standard deviations (SD), and/or median with interquartile range (IQR) for continuous variables; frequency counts and percentages for categorical variables. Standardized differences between cases and matched controls were estimated for each variable.
- For a selected list of FA-related clinical outcomes based on literature, the proportions of persons who had an event post-index were summarized and compared between cases and matched controls; cases/matched controls odds ratios (ORs) were estimated using generalized equation estimation (GEE) models. Binomial distribution and logit-link function were used to account for the correlation within matched patient pairs. Offset terms were included in the models to account for different lengths of follow-up.
- The cumulative incidence for loss of ambulation, diabetes, and death was also described using Kaplan-Meier analysis and compared between cases and matched controls for those without the respective event at baseline using log-rank test, respectively.

Results

- A total of 823 FA cases were selected from the database (**Figure 2**).

Figure 2. Sample Selection of Patients with FA, Prior to Matching



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- After matching, 652 FA cases and 3,260 matched controls were included.
- The follow-up duration in months (mean ± SD [median]) was 30.5 ± 15.4 (26.2) for FA cases and 31.7 ± 15.6 (28.3) for matched controls.
- Patient baseline characteristics after matching were summarized and compared in **Table 1**.
  - The mean age was 33.2 ± 17.9 years and 51.4% were female in both cohorts. Among persons with race/ethnicity data, a total of 73.9% and 50.4% of cases and controls, respectively, were white.
  - At baseline, FA cases had significantly higher comorbidity burden, with a mean ± SD weighted Elixhauser comorbidity index (ECI) score of 6.6 ± 8.0 compared to 0.6 ± 4.4 among the matched controls. A total of 45.1% of cases were non-ambulatory at baseline, compared to just 0.6% of controls. Non-ambulatory was defined as at least one diagnosis of paraplegia, quadriplegia, confined to bed, or wheelchair use.
  - Compared to controls, FA cases had higher rates of almost all examined comorbidities, including cardiomyopathy (33.4% vs. 0.9%), scoliosis (31.7% vs. 0.9%), and vision impairment (24.2% vs. 13.7%). FA cases also had higher rates of depression, (24.1% vs. 10.5%), anxiety (19.8% vs. 13.0%), and diabetes (14.3% vs. 7.4%).
  - FA cases experienced higher rates of cardiac arrythmia (26.8% vs. 5.2%), neuropathic pain (23.0% vs. 6.3%), falls (20.1% vs. 2.8%), dysphagia (16.1% vs. 1.3%), head injury (9.0% vs. 3.6%), and fracture (7.7% vs. 3.4%) than matched controls at baseline.

Table 1. Baseline Characteristics of Matched Patients with FA and Controls

Characteristics	Matched Patients with FA (N = 652)	Matched Controls (N = 3,260)	
Demographics			
Age at index date, years, mean ± SD [median, IQR]	33.2 ± 17.9 [28, 19 - 44]	33.2 ± 17.9 [28, 19 - 44]	
Duration of follow-up, days, mean ± SD [median, IQR]	929.1 ± 467.1 [798, 543 - 1,221]	965.3 ± 474.6 [860, 565 - 1,284]	
Sex, n (%)			
Female	335 (51.4)	1,675 (51.4)	
Male	317 (48.6)	1,585 (48.6)	
Race/ethnicity, n (%)			
White	368 (73.9)	1,239 (50.4)	*
Hispanic or Latino	56 (11.2)	496 (20.2)	*
Black or African America	27 (5.4)	501 (20.4)	*
Other	33 (6.6)	108 (4.4)	
Asian or Pacific Islander	14 (2.8)	116 (4.7)	*
Unknown	154 (23.6)	800 (24.5)	
Region, n (%)			
Midwest	147 (22.5)	796 (24.4)	
Northeast	131 (20.1)	655 (20.1)	
South	270 (41.4)	1,311 (40.2)	
West	104 (16.0)	498 (15.3)	
Insurance type, n (%)			
Medicaid	355 (54.4)	1,765 (54.1)	
Medicare	56 (8.6)	280 (8.6)	
Commercial	241 (37.0)	1,215 (37.3)	
Unknown	0 (0.0)	0 (0.0)	
Clinical characteristics			
Ambulatory status, n (%)			
Non-ambulatory	294 (45.1)	20 (0.6)	*
Walking with assistance	130 (19.9)	80 (2.5)	*
Fully ambulatory	228 (35.0)	3,160 (96.9)	*
Elixhauser comorbidity index, mean ± SD [median, IQR]	6.6 ± 8.0 [5, 0 - 11]	0.6 ± 4.4 [0, 0 - 0]	*
Comorbidities associated with FA, n (%)			
Cardiomyopathy	218 (33.4)	28 (0.9)	*
Scoliosis	207 (31.7)	33 (1.0)	*
Vision impairment	158 (24.2)	448 (13.7)	*
Depression	157 (24.1)	342 (10.5)	*
Anxiety	129 (19.8)	425 (13.0)	*
Diabetes	93 (14.3)	242 (7.4)	*
Sensorineural hearing loss	23 (3.5)	18 (0.6)	*
Inflammatory bowel disease	11 (1.7)	12 (0.4)	*
Symptoms associated with FA, n (%)			
Cardiac arrythmia	175 (26.8)	169 (5.2)	*
Neuropathic pain	150 (23.0)	207 (6.3)	*
Falls	131 (20.1)	92 (2.8)	*
Dysphagia	105 (16.1)	44 (1.3)	*
Dyspnea	101 (15.5)	181 (5.6)	*
Muscle cramps	85 (13.0)	82 (2.5)	*
Head injury	59 (9.0)	116 (3.6)	*
Cognitive impairment	68 (10.4)	86 (2.6)	*
Dysarthria	67 (10.3)	3 (0.1)	*
Fracture	50 (7.7)	111 (3.4)	*
Bladder dysfunction	49 (7.5)	21 (0.6)	*
Pneumonia	33 (5.1)	53 (1.6)	*
Sexual dysfunction	11 (1.7)	39 (1.2)	
Dysphasia	3 (0.5)	0 (0.0)	

* Denotes absolute standardized difference ≥ 0.1. Baseline characteristics with absolute standardized difference ≥ 0.1 were considered as imbalanced between cases and matched controls.
Abbreviations: FA, Friedreich ataxia; IQR, interquartile range; SD, standard deviation.

- FA cases were associated with significantly higher odds of experiencing clinical manifestations (**Table 2**) during the study period.
  - Patients with FA had more loss of ambulation (62.6% vs. 1.3%; OR:158.0), cardiomyopathy (41.9% vs. 1.4%; OR: 59.2), visual impairment (41.1% vs. 24.5%; OR: 2.3), scoliosis (41.4% vs. 1.6%; OR: 49.0), diabetes (21.3% vs. 10.3%; OR: 2.5), falls (31.4% vs. 6.4%; OR: 7.4), head injury (17.8% vs. 8.9%; OR: 2.4), and fracture (17.6% vs. 6.5%; OR: 3.3, all p<0.001).

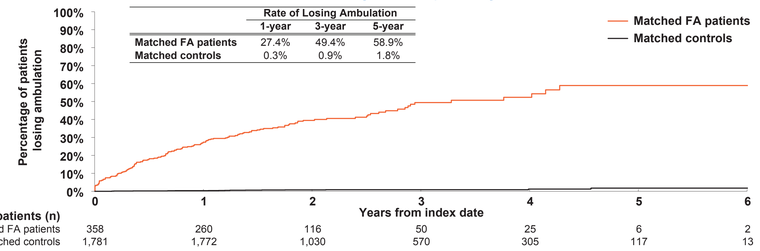
Table 2. Clinical Outcomes of Matched Patients with FA and Controls During Follow-up

Clinical Outcomes	Patients with an event (%) Matched Patients with FA (N = 652)	Matched Controls (N = 3,260)	GEE Model OR (95% CI)	P-value	
Loss of ambulation	408 (62.6)	41 (1.3)	158.03 (112.36, 222.27)	<0.001	*
Cardiac arrythmia	281 (43.1)	358 (11.0)	6.87 (5.58, 8.46)	<0.001	*
Cardiomyopathy	273 (41.9)	45 (1.4)	59.18 (41.64, 84.12)	<0.001	*
Visual impairment	268 (41.1)	798 (24.5)	2.33 (1.94, 2.79)	<0.001	*
Scoliosis	270 (41.4)	53 (1.6)	49.00 (35.35, 67.93)	<0.001	*
Falls	205 (31.4)	210 (6.4)	7.36 (5.89, 9.19)	<0.001	*
Dyspnea	179 (27.5)	426 (13.1)	2.71 (2.22, 3.31)	<0.001	*
Diabetes	139 (21.3)	335 (10.3)	2.52 (2.01, 3.16)	<0.001	*
Head injury	116 (17.8)	289 (8.9)	2.36 (1.87, 2.99)	<0.001	*
Fracture	115 (17.6)	213 (6.5)	3.27 (2.58, 4.15)	<0.001	*
Dysarthria	101 (15.5)	3 (0.1)	214.84 (68.44, 674.35)	<0.001	*
Bladder dysfunction	86 (13.2)	59 (1.8)	8.80 (6.17, 12.55)	<0.001	*
Pneumonia	73 (11.2)	118 (3.6)	3.55 (2.63, 4.80)	<0.001	*
Sensorineural hearing loss	62 (9.5)	65 (2.0)	5.46 (3.81, 7.81)	<0.001	*
Dysphasia	10 (1.5)	3 (0.1)	17.65 (4.82, 64.61)	<0.001	*
Cardiac transplantation	3 (0.5)	2 (0.1)	7.83 (1.30, 47.05)	0.025	*

Abbreviations: FA, Friedreich ataxia; GEE, generalized estimating equation; OR, odds ratio.

- FA cases were also associated with significantly higher cumulative incidence of loss of ambulation, diabetes, and death than matched controls:
  - Among FA cases and matched controls with ambulation at baseline, the proportions that lost ambulation by 1, 3, and 5-years post-index were 27.4% vs. 0.3%, 49.4% vs. 0.9%, and 58.9% vs. 1.8%, respectively (log-rank p<0.001) (**Figure 3**). The median time to loss of ambulation during follow-up period was 39.4 months for cases and not reached for matched controls.

Figure 3. Cumulative Incidence of Loss of Ambulation During Follow-up among Patients with Ambulation at Baseline



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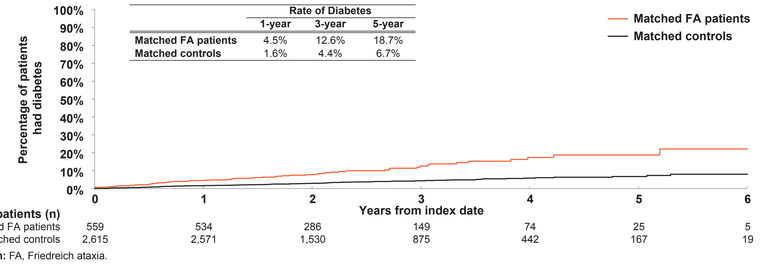
  - Among FA cases and matched controls without diabetes at baseline, the proportions that developed diabetes by 1, 3, and 5-years post-index were 4.5% vs. 1.6%, 12.6% vs. 4.4%, and 18.7% vs. 6.7%, respectively (log-rank p<0.001) (**Figure 4**)

Figure 4. Cumulative Incidence of Diabetes During Follow-up among Patients without Diabetes at Baseline



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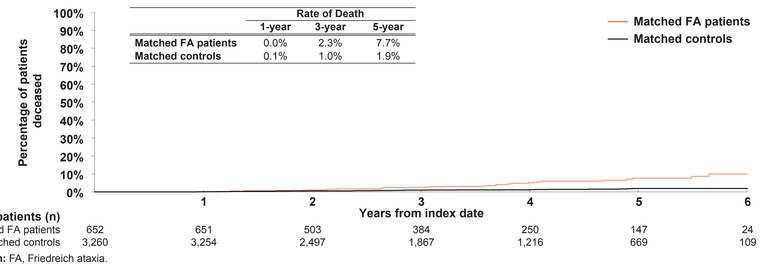
  - The proportions of persons deceased by 1, 3, and 5-years post-index were 0.0% vs. 0.1%, 2.3% vs. 1.0%, and 7.7% vs. 1.9%, respectively (log rank p<0.001). The risk of death in patients with FA was 3.9 times (p<0.001) as that in the matched controls (**Figure 5**).

Figure 5. Cumulative Incidence of Death



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Strengths and Limitation

- The study identified a relatively large and well represented cohort of patients with FA and compared their clinical burdens with age- and gender-matched controls without early onset cerebellar ataxia.
- To the best of our knowledge, this study used the most up-to-date real-world data and the most clinically rigorous criteria to identify patients with FA, which enabled a more accurate estimation of clinical burden associated with FA.
- The study is subject to the following limitations:
  - Medical claims data only capture diagnostic and procedure codes that providers recorded for reimbursement purposes. Misclassification bias attributable to coding errors or data omissions may exist.
  - The current study required all included FA patients to have a FA-specific code G11.11 that was introduced in Oct 2020. This criterion might result in exclusion of certain patients who either did not receive a FA-specific code or were lost to follow up before Oct 2020.
  - While the study used matching method to reduce the effect of confounding, causal inference should be cautiously drawn from the study as there may be uncontrolled confounding factors.

References 1. Santos R, Lefevre S, Sliwa D, Seguin A, Camadro JM, Lesuisse E. Friedreich ataxia: molecular mechanisms, redox considerations, and therapeutic opportunities. *Antioxid Redox Signal.* 2010;13(5):651-90. 2. Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. *Br Med Bull.* 2017;124(1):19-30. 3. Harding AE. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain.* 1981;104(3):589-620. 4. Tsou AY, Paulsen EK, Lagedrost SJ, Perlman SL, Mathews KD, Wilmot GR, et al. Mortality in Friedreich ataxia. *J Neurol Sci.* 2011;307(1-2):46-9. 5. Recent Advances in Friedreich Ataxia Management. *Am J Mang Care.* [Available from: https://www.ajmc.com/view/recent-advances-in-friedreich-ataxia-management#. 6. Pousset F, Legrand L, Monin M-L, Ewenczyk C, Charles P, Komajda M, et al. A 22-Year Follow-up Study of Long-term Cardiac Outcome and Predictors of Survival in Friedreich Ataxia. *JAMA Neurology.* 2015;72(11):1334-41.