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LETTER TO THE EDITORS

SARS-CoV-2 in patients with Friedreich ataxia

Megan M. Shen[1,2] · Layne N. Rodden[1] · Kellie McIntyre[1] · Adriana Arias[1] · Victoria Profeta[1] · Kimberly Schadt[1] · David R. Lynch[1,2]

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Dear Sirs,

The global spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has drawn attention to the relationship between chronic underlying conditions and complications of coronavirus disease 2019 (COVID-19). Scarce data exists on the course of COVID-19 in the cerebellar ataxias, which thus far suggests a similar course of disease [1]; however, the assumption often remains that patients with advanced disease and disability are more vulnerable due to compromised respiratory capacity or function [2]. For Friedreich ataxia (FRDA) in particular, one of the most common hereditary ataxias, COVID-19 causes potential concern due to the systemic features of FRDA including cardiomyopathy, diabetes, scoliosis, and sleep apnea. Within the general population, heart disease and diabetes have emerged as major risk factors for COVID-19 severity and mortality [3]. Multiple studies have reported that diabetes is 2–3 times more prevalent in COVID-19 patients requiring ICU admission and mechanical ventilation, along with increased mortality rates [4]. However, whether the unique disease features of FRDA mediate similar effects as in the general population is unknown. Here, we review the course and outcomes of COVID-19 in a single site sub-cohort of a large natural history study to examine characteristics of FRDA that may guide future risk stratification in this population.

The analysis used subjects from the Children's Hospital of Philadelphia enrolled in the Friedreich Ataxia—Clinical Outcome Measures Study (FA-COMS), a longitudinal prospective cohort study of FRDA. Participants evaluated between February 1, 2020 and June 30, 2022, either in-person at the Children's Hospital of Philadelphia or via telehealth, were included. Questionnaires given to patients at their annual FA-COMS visit and chart review was performed to identify PCR or antigen test-confirmed SARS-CoV-2 cases by documented or self-reported lab results. In addition to data on illness course and vaccination outcomes, the most recent hemoglobin A1c was collected from records. Patients were stratified according to standard HbA1c diagnostic criteria into diabetic, prediabetic, and non-diabetic groups. Breakthrough infection status was defined as having received at least 1 vaccination dose at least 2 weeks prior to infection.

Genetic testing information and age of FRDA-onset were assessed at the baseline FA-COMS visit. Annual follow-ups have been outlined previously [5]; pertinent components for this study included modified Friedreich Ataxia Rating Scale (mFARS) score at the most recent in-person visit, comorbidities including diabetes mellitus (DM) and cardiomyopathy, and medications. Non-ambulatory status was defined by the maximum score of 5 on item E7 (gait) on the FARS exam. Gait is one component of the mFARS, which is a clinically validated rating scale for neurologic disease progression of FA including assessment of bulbar function, upper and lower limb coordination, and upright stability.

Statistical analyses were performed using STATA version 17 (College Station, TX). Continuous data were compared by t test while categorical data were compared by χ^2 or Fisher's exact test, and logistical regression was used for multivariate analysis, with statistical significance considered at $p < 0.05$. Variables significantly associated with hospitalization by χ^2 or Fisher's exact test (age, mFARS, and comorbid diabetes) were chosen for inclusion in multivariate analysis for COVID-19 severity, along with breakthrough infection indicating vaccination status, given that it was the only modifiable variable studied.

Institutional review board approval was obtained at the Children's Hospital of Philadelphia, and informed consent was obtained from all FA-COMS participants (or their parent/guardian if under age 18).

✉ David R. Lynch
lynchd@pennmedicine.upenn.edu

[1] Division of Neurology, The Children's Hospital of Philadelphia, 502 Abramson, Philadelphia, PA 19104, USA

[2] Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

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We identified 104 cases of confirmed COVID-19 (30.1%) in a cohort of 345 patients. The total cohort was 52.2% female, with a median age of 24 (IQR: 18–34) and median age of onset at 10 (IQR 7–14). For patients homozygous for two expanded GAA repeats, the median length was 699 (IQR 549–833) on the shorter allele.

Of the 104 COVID-19 cases, 96 (92.3%) were either asymptomatic or had a mild-moderate course of infection (symptomatic but did not require hospitalization). Eight patients (7.7%) were hospitalized (average stay 7.1 days, range 1–18), of whom six received supplemental oxygen and had CXR findings of pneumonia. Four of those hospitalized were also treated with remdesivir and dexamethasone, after which two recovered, and two required intubation and subsequently died (1.9%). Both COVID-19 cases and hospitalizations spanned a range of age groups, with infection incidence generally decreasing with increasing age (Table 1).

When comparing hospitalized versus non-hospitalized cases (Table 2) and patients with versus without COVID-19 (Table 3), comorbid DM was strongly associated with severity requiring hospitalization (RR 14.1, 95% CI 3.89–51.1) and supplemental oxygen (RR 26.4, 95% CI 8.2–85.0) but not an increased risk of infection. Three COVID-19 cases were observed among 20 prediabetic patients. Notably, 5 of 8 hospitalized patients had DM, 3 classified as early-onset DM and 2 as later-onset. This proportion increased to 5 of 6 when considering only those who required supplemental oxygen.

On average, hospitalized patients were older (35.2 vs 23.7, $p=0.010$) and had more clinically advanced neurological disease as assessed by mFARS scores (66.6 vs 47.4, $p=0.008$) compared to those not hospitalized. However, those who had a COVID-19 infection were overall, more likely to be young and ambulatory (Table 3). GAA repeat length, age of FRDA-onset, and cardiomyopathy were not associated with COVID-19 infection or hospitalization.

Multivariable analysis adjusted for age, mFARS, comorbid DM, and vaccination status showed that DM was independently associated with COVID-19 hospitalization (OR 13.0; 95% CI 2–107; $p=0.017$) and supplemental oxygen requirement (OR 118; 95% CI 2–5599; $p=0.015$).

Table 1 COVID-19 stratified by age group

	0–13 ($n=29$)	14–17 ($n=50$)	18–24 ($n=94$)	25–49 ($n=149$)	50–79 ($n=23$)	Total ($n=345$)
Cases	13 (45%)	18 (36%)	31 (33%)	38 (26%)	4 (17%)	104 (30%)
Hospitalization	–	1 (2%)	3 (3.2%)	2 (1.3%)	2 (8.7%)	8 (2.3%)
Supplemental oxygen	–	1 (2%)	1 (1.1%)	2 (1.3%)	2 (8.7%)	6 (1.7%)
Ventilatory support	–	–	–	1 (0.7%)	1 (4.3%)	2 (0.6%)
Mortality	–	–	–	1 (0.7%)	1 (4.3%)	2 (0.6%)
Comorbid diabetes	–	2 (4%)	1 (1.1%)	6 (4.0%)	2 (8.7%)	11 (3.2%)

Table 2 Clinical characteristics of FA-COMS participants with COVID-19

	Hospitalized ($n=8$)	Non-hospitalized ($n=96$)	p value
Age in years, mean (SD)	35.2 (18.7)	23.7 (11.3)	**0.010**
Female, n	7 (87.5%)	47 (49.0%)	0.061
Shorter GAA repeat length, mean[a] (SD)	775 (181)	689 (202)	0.250
Point mutation, n	–	11	
Age of FRDA-onset in years, mean (SD)	10.8 (5.5)	10.6 (5.9)	0.958
mFARS, mean (SD)	66.6 (18.1)	47.4 (19.1)	**0.008**
Ambulatory, n	2 (25%)	61 (63.5%)	0.055
Cardiomyopathy, n	7 (87.5%)	58 (60.4%)	0.253
On medications	3	24	
Diabetes, n	5 (67.5%)	6 (6.3%)	**<0.001**
Type 1	3	3	
Type 2	2	3	
Insulin-dependent	3	3	
SARS-CoV-2 infection after at least 1 vaccine dose	2 (25%)	48 (50%)	0.273

Bold values indicate the statistically significant

[a]Number of GAA triplets, excluding point mutations ($n=11$)

Table 3 Clinical characteristics of patients with or without COVID-19

	COVID-19 infected ($n=104$)	No COVID-19 infection ($n=241$)	p value	All patients ($n=345$)
Age in years, mean (SD)	24.6 (12.3)	28.3 (12.8)	**0.014**	27.2 (12.7)
Female, *n*	54 (51.9%)	126 (52.3%)	0.951	180 (52.2%)
Shorter GAA repeat length, mean[a] (SD)	696 (201)	661 (227)	0.207	672 (220)
Point mutation, *n*	11	22		33
Age of FRDA-onset in years, mean (SD)	10.6 (5.9)	11.9 (7.7)	0.130	11.5 (7.3)
mFARS, mean (SD)[b]	48.9 (19.6)	51.2 (18.5)	0.302	50.5 (18.9)
Ambulatory, *n*	63 (60.6%)	114 (47.3%)	**0.024**	177 (51.3%)
Cardiomyopathy, n	65 (62.5%)	166 (68.9%)	0.248	231 (67.0%)
Diabetes, *n*	11 (10.6%)	20 (8.3%)	0.497	31 (9.0%)
Type 1, *n*	6	11		17
Type 2, *n*	5	9		14
Insulin-dependent	6	16		22
Prediabetic, *n*	3	17		20

Bold values indicate the statistically significant

[a]Number of GAA triplets, missing for $n=7$ and excluding point mutations ($n=33$)

[b]Missing for $n=6$

Of 340 patients analyzed, 227 (66.8%) received at least 1 SARS-CoV-2 vaccine dose with no major adverse events reported, including cardiac inflammation. 50 patients had COVID-19 post-vaccination, with 2 cases resulting in hospitalization and 1 of those in death (though death occurred less than 2 weeks following a second vaccine dose); breakthrough infection status was not associated with illness severity ($p=0.273$).

The major finding of this study is that comorbid diabetes is a significant feature associated with poorer COVID-19 outcomes in FRDA patients, who otherwise demonstrate largely similar infection courses as those of the general population. Higher neurological disease burden also predicts greater severity of COVID-19, although this effect is likely at least partially mediated by the association of disease progression with older age, which is a well-established risk factor for COVID-19 complications [3]. On multivariate analysis including these factors, as well as breakthrough infection indicating vaccination status, only DM was an independent predictor of COVID-19 severity.

The prevalence of DM among COVID-19 cases that resulted in hospitalization (5/8) and deaths (2/2) was striking compared to that in the total cohort (31/345 or 9.0%, consistent with previous estimates [6, 7]). Of note, the true incidence of DM in severe cases is more accurately represented by the proportion requiring supplemental oxygen (5/6). The two hospitalized patients who were not hypoxic were both admitted for a single night of observation, largely due to provider discomfort with their underlying neurological diagnosis and elevated troponin levels (most FRDA patients have a high baseline). Both of these patients did not have DM.

Interestingly, hospitalizations as well as deaths with comorbid DM were evenly split between individuals with early-onset versus later-onset DM. While these conditions have been classified as "type 1" and "type 2", respectively, for clinical management purposes, FRDA-related diabetes includes features of both beta-cell deficiency and insulin resistance, presumably due to frataxin deficiency in pancreatic and peripheral tissues, respectively [8]. Furthermore, two FRDA/COVID patients hospitalized with comorbid DM were < 25 years of age. These findings suggest that studies of DM-associated risk in the general population, some of which have shown that type 1 diabetes (especially in youth < 25) is not independently associated with COVID-19 severity [9–11], may not generalize to FRDA-related DM. Another possibility is that DM is a marker for other variables contributing to risk since DM is independently associated with greater FRDA symptom burden and disability, most apparent at younger ages [6]. However, we cannot directly compare to DM-related risk in a non-FRDA cohort due to the constraints of our study population; selectivity to a specialized tertiary referral center restricts distribution of patients geographically and demographically, among other factors that would hinder identification of a suitable matched control group.

In this study, FRDA-related cardiomyopathy was not associated with susceptibility to COVID-19 infection or severity. Among FRDA patients, structural and/or non-specific EKG abnormalities are nearly universal but not always clinically significant, particularly in early disease stages [12]. A limitation of this study was characterizing only the presence but not severity of disease features. Late FRDA complications including restrictive lung disease from

scoliosis and severe cardiomyopathy compromising systolic function may indeed increase risk of acute decompensation in COVID-19. Respiratory dysfunction in patients with primary mitochondrial diseases (PMD) independently predicts COVID-19 severity [13], with overall high disease burden also contributing across various chronic neurological disorders [14]. In addition, cardiac disease has been associated with FRDA-related DM, though the causative mechanism is unclear [7].

Another limitation is that in this young cohort, in which asymptomatic or mild infections are more common, our methods may have missed some cases, leading to an overestimation of hospitalization and mortality rates. Younger age was likely a protective factor that masked other risk sources.

On a broader scale, the pandemic's effects on this cohort are likely more prominent not from infection itself but rather disruptions to physical activity and therapy services. Anecdotally, a substantial proportion of patients have perceived significant declines in global health resulting from these disruptions, consistent with previous reports [1]. Future investigation with an expanded cohort and updated vaccination data as novel SARS-CoV-2 variants emerge will continue to inform adaptations in care.

All FA-COMS data are released to FA-ICD at the C-Path Institute upon publication.

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Author contributions DRL, MMS, KM, VP, AA and KS performed the exams and supervised the data collections in the natural history study. MMS, KS and DRL designed the project, supervised the data management at the central site, and performed the statistical calculations (along with LNR). MMS wrote the initial draft, and all the authors provided critical revisions.

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Data availability Data will not be made publicly available at the present time.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval IRB approval was obtained by the Institutional Review Board at the Children's Hospital of Philadelphia.

Employment All the authors are employees of the University of Pennsylvania or CHOP.

Consent to participate Written informed consent was obtained from all the subjects before initiation of study procedures.

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