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COVID-19–Related Outcomes in Primary Mitochondrial Diseases: An International Study

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ABSTRACT

Objectives To identify factors associated with severe COVID-19, defined by hospitalization status, in patients with primary mitochondrial diseases (PMDs), thereby enabling future risk stratification and informed management decisions.

Methods We undertook a cross-sectional, international, registry-based study. Data was extracted from the "International Neuromuscular COVID-19 Database" and collected between 1st May 2020 and 31st May 2021. The database included subjects with: 1) PMD diagnosis (any age), clinically/histopathologically suspected and/or genetically confirmed; and (2) COVID-19 diagnosis classified as "confirmed", "probable", or "suspected" based on World Health Organization definitions. The primary outcome was hospitalization due to COVID-19. We collected demographic information, smoking status, coexisting comorbidities, outcome following COVID-19 infection, and PMD genotype-phenotype. Baseline status was assessed using the modified Rankin scale (mRS) and the Newcastle Mitochondrial Disease Adult Scale (NMDAS).

Results Seventy-nine subjects with PMDs from 10 countries were included (mean age 41.5±18 years): 25 (32%) were hospitalized; 48 (61%) recovered fully; 28 (35%) improved with sequelae; and three (4%) died. Statistically significant differences in hospitalization status were observed in: baseline status, including NMDAS score (p=0.003) and mRS (p=0.001); presence of respiratory dysfunction (p<0.001), neurologic involvement (p=0.003); and more than four comorbidities

(p=0.002). In multivariable analysis, respiratory dysfunction was independently associated with COVID-19 hospitalization (OR, 7.66; 95%CI, 2 to 28; p=0.002).

Discussion Respiratory dysfunction is an independent risk factor for severe COVID-19 in PMDs, while high disease burden and coexisting comorbidities contribute towards COVID-19 related hospitalization. These findings will enable risk stratification and informed management decisions for this vulnerable population.

INTRODUCTION

Despite their variable clinical manifestations and severity, people with primary mitochondrial diseases (PMDs) were considered at high-risk for serious Coronavirus disease 2019 (COVID-19), given the potential for multisystemic involvement and metabolic decompensation during intercurrent illness.[1] Consequently, people with PMDs were grouped internationally within the COVID-19 clinically highest risk category (designated "clinically extremely vulnerable" by NHS England, United Kingdom [UK], and "higher risk of severe COVID-19 illness", by the Centers for Disease Control and Prevention, USA)[2] and advised to implement the shielding approach, limiting contact with the general population when SARS-CoV-2 infection rates were high.[3]

In this cross-sectional, international, registry-based study, we aimed to identify factors linked with severe COVID-19 in PMDs, thereby enabling future risk stratification and informed management decisions.

METHODS

The NHS England Highly Specialized Services for Rare Mitochondrial Disorders in London and Newcastle, UK, designed a PMD-specific module within the "International Neuromuscular COVID-19 Database";[4] this was hosted by University College London (see eMethods in the Supplement), to record details concerning PMD genotype-phenotype and COVID-19 during the pandemic. Inclusion criteria were: 1) a PMD diagnosis (any age) in the opinion of the recruiting healthcare provider, clinically/histopathologically suspected and/or genetically confirmed; and (2) a COVID-19 diagnosis stratified as "confirmed", "probable", or "suspected" based on World Health Organization (WHO) definitions.[5] Baseline status was assessed using the modified Rankin scale (mRS) and the Newcastle Mitochondrial Disease Adult Scale (NMDAS) (see eMethods in the Supplement). Key comorbidities included respiratory dysfunction, mitochondrial diabetes (a distinct monogenic form of diabetes mellitus that is specific to PMDs and has been associated to a variety of mitochondrial and nuclear

DNA mutations)[6, 7], hypertension or other cardiovascular diseases, obesity (Body Mass Index ≥ 30), and neurological involvement. Respiratory dysfunction was defined by the presence of at least one of: 1) obstructive lung disease (chronic obstructive pulmonary disease or asthma); 2) restrictive lung disease; 3) obstructive sleep apnea; 4) use of non-invasive ventilation; 5) tracheostomy. Neurological involvement was determined by the presence of at least one of: 1) dysphagia; 2) epilepsy; 3) learning disabilities; 4) polyneuropathy; 5) skeletal muscle weakness; 6) stroke/stroke like episodes. All comorbidities included under the "neurological involvement" section were reported as disease-specific neurological features in the mitochondrial disease module of the database. Only anonymized, non-identifiable data were collected; thus, participant consent was not required according with the UK Health Research Authority. Statistical analyses were performed using SPSS v19.0 (SPSS Inc.). P-value <0.05 was considered significant. The primary outcome of the study was hospitalization status for COVID-19. See the eMethods in the Supplement for further details concerning database design and data storage, protocol approvals, and participants.

Data Availability: Dr Pizzamiglio had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

From 1st of May 2020 to 31st of May 2021, 79 patients (mean age 41.5 years; female 46, 58%, white ethnicity 64, 83%) across 10 countries (UK 44, 56%, see Table 1) were registered. Hospitalization status was recorded for all entries; thus, no cases were excluded. Almost one third of patients were hospitalized (25, 32%) and three died (4%, all hospitalized). Forty-eight (61%) subjects recovered fully from the infection, while 28 (35%) recovered with sequelae. COVID-19 diagnosis was WHO "confirmed" in 65 subjects (82%) and "probable", supported by CT scan or chest x-ray, in six (8%). Eight (10%) patients had a "suspected" diagnosis.[5] COVID-19 symptoms were present in 75 (95%) patients. As previously reported in PMDs,[8] the most common symptoms comprised: fever (52, 66%); fatigue (51, 65%); persistent cough (39, 49%); headache (33, 42%); myalgia (39%);

anosmia/hyposmia (24, 30%); and dysgeusia (23, 29%). Only three current or former smokers were identified in the cohort. Consequently, further statistical analysis in this subgroup was not possible. Neurological involvement was the most common comorbidity and was present in 58 subjects (73%), followed by mitochondrial diabetes (21, 27%), hypertension or other cardiovascular diseases (20, 25%), respiratory dysfunction (19, 24%), and obesity (8, 10%). Many patients had multiple single system and/or multisystem comorbidities. Of those with neurological problems, 36 had skeletal muscle weakness; 21 dysphagia; 16 epilepsy; 12 learning disabilities; eight polyneuropathy; and eight stroke like episodes (see eTable 1 in the Supplement). In patients with respiratory dysfunction, there were 14 subjects with restrictive lung disease, six with obstructive lung disease, six using non-invasive ventilation, three with obstructive sleep apnea, and two with a tracheostomy (see eTable 2 in the Supplement).

Univariate analysis (Table 2) showed that hospitalized patients had higher PMD burden (NMDAS score >20, 69%) or moderately severe/severe mRS (52%), compared with people that were not hospitalized (18%, p=0.003, and 17%, p=0.001, respectively). The presence of ≥4 comorbidities was associated with hospitalization (64% versus 28%, p=0.002), in line with previous data from general adult population.[9] Analysis of individual comorbidities showed the presence of respiratory dysfunction (56% versus 9%, p<0.001) and neurological involvement (84% versus 48%, p=0.003) were associated with COVID-19 related hospitalization, and were both present in the three deceased subjects. No significant difference in hospitalization status was detected by age, sex, ethnicity, or PMD diagnosis.

Multivariable analysis, adjusted for age group, respiratory dysfunction, neurological involvement, and the mRS, discerned respiratory dysfunction was independently associated with COVID-19 hospitalization (OR, 7.66; 95%CI, 2 to 28; p=0.002). The results of the sensitivity multivariate is the same when only confirmed cases (n=65) are included (OR 12.2; CI 2.77-53.77, p=0.001).

DISCUSSION

To date, this study represents the largest cohort of people with PMDs and COVID-19 ever reported. We have identified a group of patients with PMD who are extremely vulnerable to SARS-CoV-2 as a result of respiratory dysfunction. Their respiratory dysfunction is an independent risk factor for developing severe COVID-19, and coexisting comorbidities and high disease burden contribute towards the risk of COVID-19 related hospitalization; a factor now recognized in other chronic neurological disorders.[10] We could not confirm the incremental impact of age for COVID-19 severity and so advice for people with PMDs should be adhered to for any age.[11,12] Ongoing sequelae following resolution of COVID-19 were detected in 35% of our cohort. These included deterioration of pre-existing neurological symptoms (n=11), worsening of isolated fatigue (n=4), and development of new symptoms (n=13). Limitations of the study include the cross-sectional design and voluntary nature of the registry; thus, a selection bias towards severe, rather than asymptomatic and mild, COVID-19 could exist. Furthermore, the limited sample size does not allow outcomes to be correlated with specific genotypes or comorbidities.

In conclusion, the data presented here was collected during the initial stages of the COVID-19 pandemic and was not available to influence clinical decision-making during the initial wave. However, we consider that in future waves of COVID-19, or similar pandemics, this information will be crucial to clinicians worldwide managing patients with PMDs, and other conditions where there is mitochondrial dysfunction and significant respiratory muscle weakness.

APPENDIX 2: Coinvestigators

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Supplement ---- http://links.lww.com/WNL/B828

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TABLES

Table 1: Demographic and clinical characteristics of patients with primary mitochondrial disease diagnosed with COVID-19 (n=79)

Demographic and clinical characteristics	**Number (%)**	**Demographic and clinical characteristics**	**Number (%)**
Country of recruitment		**PMD, genetically unconfirmed**[b]	11 (14)
United Kingdom	44 (56)	**Baseline status**	
Italy	17 (22)	***NMDAS score* (n=38)**	
Hungary	6 (8)	No symptoms (score: 0)	4 (11)
Brazil	3 (4)	Mild symptoms (score: 1 to 5)	5 (13)
Spain	3 (4)	Moderate symptoms (score: 6 to 20)	14 (37)
Portugal	2 (2)	Severe symptoms (score: >20)	15 (39)
Finland	1 (1)	***mRS***	
India	1 (1)	0. No symptoms	8 (10)
Netherlands	1 (1)	1. No significant disability	35 (44)
United States of America	1 (1)	2. Slight disability	9 (12)
Sex at birth		3. Moderate disability	5 (6)
Female	46 (58)	4. Moderately severe disability	19 (24)
Male	33 (42)	5. Severe disability	3 (4)
Age group (years)		**mRS after COVID-19 infection**	
<18	4 (5)	0. No symptoms	6 (8)
18-39	32 (41)	1. No significant disability	28 (35)
40-49	18 (23)	2. Slight disability	13 (17)
50-59	9 (11)	3. Moderate disability	5 (6)
60-69	12 (15)	4. Moderately severe disability	19 (24)
70-79	3 (4)	5. Severe disability	5 (6)
≥80	1 (1)	6. Death	3 (4)
Mean (± SD)	41.5 (±18)	**Most common comorbidities**	
Ethnicity (n=77)		Respiratory dysfunction[c]	19 (24)
White	64 (83)	Mitochondrial diabetes	21 (27)
Other[a]	13 (17)	Hypertension or other cardiovascular diseases	20 (25)
PMD, genetically confirmed		Obesity (BMI ≥ 30)	8 (10)
mtDNA mutation	49 (62)	Neurological involvement[d]	58 (73)
3243A>G, *MT-TL1*	23	**Smoking status (n=74)**	
8344A>G, *MT-TK*	4	Ever[e]	3 (4)
3460G>A, *MT-ND1*	3	Never	71 (96)
8993T>G, *MT-ATP6*	3	**COVID-19 symptoms**	
9134A>G, *MT-ATP6*	1	Yes	75 (95)
1555A>G, *MT-RNR1*	2	No	4 (5)
11778G>A, *MT-ND4*	2	**Hospitalization**	
15092G>A, *MT-CYB*	1	Yes, no oxygen therapy required	6 (8)
Single large scale mtDNA deletion	7	Yes, oxygen therapy required	15 (19)
Multiple mtDNA deletions	3	Yes, mechanical ventilation required	4 (5)
nuclear DNA mutation	19 (24)	No	54 (68)
POLG	5	**Outcome of COVID-19 infection**	
PDHA1	2	Fully recovered	48 (61)
RRM2B	2	Resolved, with sequelae[f]	28 (35)
ANT1, C19orf12, DARS2, COXFA4, OPA3, PC, SERAC1, SURF1, TWNK, TK2	1	Deceased	3 (4)
		Mean days from COVID-19 onset to	26 ± 23.7

	resolution (± SD)	
	Mean days from COVID-19 onset to death (± SD)	11.7 ± 10.8

Abbreviations: BMI, body mass index; mRS, modified Rankin Scale; mtDNA, mitochondrial DNA; NMDAS, Newcastle mitochondrial disease adult scale; PMD, primary mitochondrial disease; SD, standard deviation. **a:** South Asian (n=7); Latin American (n=3); East Asian (n=2); Black (n=1). **b:** Clinical phenotype and pathological/biochemical findings consistent with a diagnosis of primary mitochondrial disease according to recruiting clinician. **c:** Obstructive lung disease (chronic obstructive pulmonary disease or asthma) (n=6), restrictive lung disease (n=14), obstructive sleep apnea (n=3), use of non-invasive ventilation (NIV) (n=6), tracheostomy (n=2). **d:** Dysphagia (n=21), epilepsy (n=16), learning disabilities (n=12), polyneuropathy (n=8), skeletal muscle weakness (n=36), stroke/stroke like episodes (n=8). **e:** current smoker (n=2), former smoker (n=1). **f:** Deterioration of pre-existing neurological symptoms (n=11); worsening of fatigue in isolation (n=4); development of new symptoms (n=13).

Table 2: Demographic and clinical factors of patients with primary mitochondrial disease diagnosed with COVID-19 by hospitalization status

	Not hospitalized n=54	Hospitalized n=25	P value
Sex at birth			0.48
Female	30 (56)	16 (64)	
Male	24 (44)	9 (36)	
Age group (years)			0.08
<60	46 (85)	17 (68)	
≥60	8 (15)	8 (32)	
Ethnicity			0.53
White	45 (85)	19 (79)	
Other[a]	8 (15)	5 (21)	
Mitochondrial disease diagnosis			
m.3243A>G, *MT-TL1*	19 (35)	4 (16)	0.11
Other[b]	35 (65)	21 (84)	
Baseline status			
NMDAS (n=36)			0.003
No, mild or moderate symptoms (score 0 to 20)	18 (82)	5 (31)	
Severe symptoms (score >20)	4 (18)	11 (69)	
mRS			0.001
0 - 1 - 2 - 3[c]	44 (83)	12 (48)	
4 - 5[c]	9 (17)	13 (52)	
Most common comorbidities			
Respiratory dysfunction[d]	5 (9)	14 (56)	<0.001
Mitochondrial diabetes	15 (28)	6 (24)	0.76
Hypertension or other cardiovascular diseases	13 (24)	7 (28)	0.71
Obesity (BMI ≥ 30)	4 (7)	4 (16)	0.25
Neurological involvement[e]	26 (48)	21 (84)	0.003
Number of comorbidities			
0-3	39 (72)	9 (36)	0.002
4 or more	15 (28)	16 (64)	

Abbreviations: BMI: body mass index; NMDAS: Newcastle mitochondrial disease adult scale; mRS: modified Rankin Scale. **a:** South Asian (n=7); Latin American (n=3); East Asian (n=2); Black (n=1). **b:** mtDNA mutations, m.3243A>G excluded (n=26), nuclear DNA mutations (n=19), mitochondrial disease genetically unconfirmed (n=11). **c:** 0, No symptoms; 1, No significant disability; 2, Slight disability; 3, Moderate disability; 4, Moderately severe disability; 5, Severe disability. **d:** Obstructive lung disease, restrictive lung disease, obstructive sleep apnea, use of non-invasive ventilation (NIV), tracheostomy. **e:** Dysphagia, epilepsy, learning disabilities, polyneuropathy, skeletal muscle weakness, stroke/stroke like episodes.

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