

COVID-19–Related Outcomes in Primary Mitochondrial Diseases

An International Study

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Neurology® 2022;98:576–582. doi:10.1212/WNL.000000000000200240

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Abstract

Background and Objectives

To identify factors associated with severe coronavirus disease 2019 (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 were extracted from the International Neuromuscular COVID-19 Database and collected between May 1, 2020, and May 31, 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 because of COVID-19. We collected demographic information, smoking status, coexisting comorbidities, outcomes after 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 3 (4%) died. Statistically significant differences in hospitalization status were observed in baseline status, including the 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 4 comorbidities ($p = 0.002$). In multivariable analysis, respiratory dysfunction was independently associated with COVID-19 hospitalization (odds ratio, 7.66; 95% CI, 2–28; $p = 0.002$).

Discussion

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

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

MitoCOVID-19 Study Group coinvestigators are listed in the appendix at the end of the article.

The Article Processing Charge was funded by the Medical Research Council (UK).

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Table 1 Demographic, Clinical, and Molecular Characteristics of Patients With Primary Mitochondrial Disease Diagnosed With COVID-19 (n = 79)

Demographic, clinical, and molecular characteristics	Number (%)	Demographic, clinical, and molecular 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	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 (y)		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)	Neurologic involvement ^d	58 (73)
3243A > G, <i>MT-TL1</i>	23	Smoking status (n = 74)	
8344A > G, <i>MT-TK</i>	4	Ever ^e	3 (4)
3460 G > A, <i>MT-ND1</i>	3	Never	71 (96)
8993T > G, <i>MT-ATP6</i>	3	COVID-19 symptoms	
9134A > G, <i>MT-ATP6</i>	1	Yes	75 (95)
1555A > G, <i>MT-RNR1</i>	2	No	4 (5)
11778 G > A, <i>MT-ND4</i>	2	Hospitalization	
15092 G > A, <i>MT-CYB</i>	1	Yes, no oxygen therapy required	6 (8)
Single large-scale mtDNA deletion	7	Yes, oxygen therapy required	15 (19)

Continued

Table 1 Demographic, Clinical, and Molecular Characteristics of Patients With Primary Mitochondrial Disease Diagnosed With COVID-19 (n = 79) (continued)

Demographic, clinical, and molecular characteristics	Number (%)	Demographic, clinical, and molecular characteristics	Number (%)
Multiple mtDNA deletions	3	Yes, mechanical ventilation required	4 (5)
nuclear DNA mutation	19 (24)	No	54 (68)
<i>POLG</i>	5	Outcome of COVID-19 infection	
<i>PDHA1</i>	2	Fully recovered	48 (61)
<i>RRM2B</i>	2	Resolved, with sequelae ^f	28 (35)
<i>ANT1, C19orf12, DARS2, COXFA4, OPA3, PC, SERAC1, SURF1, TWNK, TK2</i>	1	Deceased	3 (4)
		Mean days from COVID-19 onset to resolution (±SD)	26 ± 23.7
		Mean days from COVID-19 onset to death (±SD)	11.7 ± 10.8

Abbreviations: BMI = body mass index; COVID-19 = coronavirus disease 2019; mRS = modified Rankin scale; mtDNA = mitochondrial DNA; NMDAS = Newcastle Mitochondrial Disease Adult Scale; PMD = primary mitochondrial disease.

^a South Asian (n = 7), Latin American (n = 3), East Asian (n = 2), Black (n = 1).

^b Clinical phenotype and pathologic/biochemical findings consistent with a diagnosis of PMD according to the 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 noninvasive 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 preexisting neurologic symptoms (n = 11), worsening of fatigue in isolation (n = 4), development of new symptoms (n = 13).

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 worldwide 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, links.lww.com/WNL/B828) 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 health-care 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 with a variety of mitochondrial and nuclear DNA sequence variations),^{6,7} hypertension or other cardiovascular diseases, obesity (body mass index ≥ 30), and neurologic involvement. Respiratory dysfunction was defined by the presence of at least one of the following: (1) obstructive lung disease (chronic obstructive pulmonary disease or asthma), (2) restrictive lung disease, (3) obstructive sleep apnea, (4) use of noninvasive ventilation, and (5) tracheostomy. Neurologic involvement was determined by the presence of at least one of the following: (1) dysphagia, (2) epilepsy, (3) learning disabilities, (4) polyneuropathy, (5) skeletal muscle weakness, and (6) stroke/stroke-like episodes. All comorbidities included under the “neurologic involvement” section were reported as disease-specific neurologic features in the mitochondrial disease module of the database. Only anonymized, nonidentifiable data were collected; thus, participant consent was not required according to 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 this 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.

Table 2 Demographic, Clinical, and Molecular Characteristics of Patients With Primary Mitochondrial Disease Diagnosed With Coronavirus Disease 2019 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 (y)			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)	
PMD diagnosis			0.11
m.3243A > G, <i>MT-TL1</i>	19 (35)	4 (16)	
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
Neurologic involvement ^e	26 (48)	21 (84)	0.003
Number of comorbidities			0.002
0–3	39 (72)	9 (36)	
4 or more	15 (28)	16 (64)	

Abbreviations: BMI = body mass index; mRS = modified Rankin scale; NMDAS = Newcastle Mitochondrial Disease Adult Scale; PMD = primary mitochondrial disease.

^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 noninvasive ventilation (NIV), tracheostomy.

^e Dysphagia, epilepsy, learning disabilities, polyneuropathy, skeletal muscle weakness, stroke/stroke-like episodes.

Results

From May 1, 2020, to May 31, 2021, 79 patients (mean age 41.5 years; female 46, 58%, White ethnicity 64, 83%) across 10 countries (UK 44, 56%, Table 1) were registered. Hospitalization status was recorded for all entries; thus, no cases were excluded. Almost one-third of the patients were hospitalized

(25, 32%) and 3 died (4%, all hospitalized). Forty-eight subjects (61%) recovered fully from the infection, whereas 28 (35%) recovered with sequelae. COVID-19 diagnosis was WHO “confirmed” in 65 subjects (82%) and “probable,” supported by a CT scan or chest x-ray, in 6 (8%). Eight patients (10%) had a “suspected” diagnosis.⁵ COVID-19 symptoms were present in 75 patients (95%). 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 3 current or former smokers were identified in the cohort. Consequently, further statistical analysis in this subgroup was not possible.

Neurologic 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 neurologic problems, 36 had skeletal muscle weakness, 21 dysphagia, 16 epilepsy, 12 learning disabilities, 8 polyneuropathy, and 8 stroke-like episodes (see eTable 1 in the Supplement, links.lww.com/WNL/B828). In patients with respiratory dysfunction, there were 14 subjects with restrictive lung disease, 6 with obstructive lung disease, 6 using noninvasive ventilation, 3 with obstructive sleep apnea, and 2 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 who were not hospitalized (18%, $p = 0.003$, and 17%, $p = 0.001$, respectively). The presence of ≥ 4 comorbidities was associated with hospitalization (64% vs 28%, $p = 0.002$), in line with previous data from general adult population.⁹ Analysis of individual comorbidities showed that the presence of respiratory dysfunction (56% vs 9%, $p < 0.001$) and neurologic involvement (84% vs 48%, $p = 0.003$) were associated with COVID-19–related hospitalization, and were both present in the 3 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, neurologic involvement, and the mRS, discerned respiratory dysfunction was independently associated with COVID-19 hospitalization (odds ratio [OR], 7.66; 95% CI, 2–28; $p = 0.002$). The results of the sensitivity multivariate are 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 because of respiratory dysfunction. Their respiratory dysfunction is an independent risk factor for developing severe COVID-19, and coexisting comorbidities and high disease burden contribute toward the risk of COVID-19–related hospitalization, a factor now recognized in other chronic neurologic 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 after resolution of COVID-19 was detected in 35% of our cohort. These included deterioration of preexisting neurologic symptoms ($n = 11$), worsening of isolated fatigue ($n = 4$), and development of new symptoms ($n = 13$). Limitations of this study include the cross-sectional design and voluntary nature of the registry; thus, a selection bias toward 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 were collected during the initial stages of the COVID-19 pandemic and were 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.

Acknowledgment

We are extremely grateful to the Lily Foundation, International Mito Patients, United Mitochondrial Disease Foundation, and MitoCanada for disseminating information concerning the study to their stakeholders.

Study Funding

The University College London Hospitals/University College London Queen Square Institute of Neurology sequencing facility receives a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centers funding scheme. The clinical and diagnostic "Rare Mitochondrial Disorders Service" in London and Newcastle are funded by the UK National Health Service (NHS) Highly Specialized Commissioners. C.P. is supported by a Clore Duffield Foundation grant. PMM is supported by the National Institute for Health Research (NIHR), University College London Hospitals (UCLH) and Biomedical Research Centre (BRC). R.D.S.P. is supported by a Medical Research Council (UK) Clinician Scientist Fellowship (MR/S002065/1). R.M., M.G.H., and R.D.S.P. are funded by a Medical Research Council (UK) strategic award to establish an International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) (MR/S005021/1). G.S.G. and R.M. are supported by the Wellcome Centre for Mitochondrial Research (203105/Z/16/Z), the UK NIHR Biomedical Research Centre for Ageing and Age-related disease award to the Newcastle upon Tyne Foundation Hospitals NHS Trust, the Mitochondrial Disease Patient Cohort (UK) (G0800674), and The Lily Foundation.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* December 2, 2021. Accepted in final form February 3, 2022.

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Robert D. S. Pitceathly, MD, PhD	Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, UK	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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Appendix 2 (continued)

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Continued

Appendix 2 (continued)

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Appendix 2 (continued)

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Chiara Pizzamiglio, Pedro M. Machado, Rhys H. Thomas, et al.
Neurology 2022;98;576-582 Published Online before print February 21, 2022
DOI 10.1212/WNL.0000000000200240

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