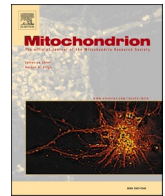Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

SARS-CoV-2 infection in patients with primary mitochondrial diseases: Features and outcomes in Italy

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ABSTRACT

Patients with mitochondrial diseases, who usually manifest a multisystem disease, are considered potentially at-risk for a severe coronavirus disease 2019 (COVID-19). The objective of this study is to analyze the clinical features, prognosis and outcomes of COVID-19 in patients with primary mitochondrial diseases in a cohort of patients followed in Italy.

We searched for patients with primary mitochondrial diseases and COVID-19 followed by the Italian Collaborative Network of Mitochondrial Diseases. In a total of 1843 patients followed by the National Network, we have identified from March 1st to January 30th, 2021, 27 SARS-CoV-2 infection. Most of the patients were pauci or asymptomatic (85%) and treated at home. The most common signs of COVID-19 were fever (78,9%), fatigue (47,4%), myalgia (42,1%), cough and headache (36,8%), and dyspnea (31,6%). Those who required COVID-19 therapy were treated with low-molecular-weight heparin, glucocorticoids, and antibiotics (mainly azithromycin) without serious side effects related to the therapy. Five patients (18,5%) clinically deteriorated during the infection, and one of them died for pneumonia.

Primary mitochondrial diseases infected individuals seemed to be similarly affected by SARS-CoV-2 compared with the general Italian population in terms of clinical presentation and outcome.

1. Introduction

Primary mitochondrial disorders are a challenging group of genetic diseases characterized by defective oxidative phosphorylation (Gorman et al., 2016). It is one of the most common groups of metabolic inherited disease and they can be caused by mutation in either nuclear or mitochondrial DNA (mtDNA) genes that directly or indirectly interfere with the respiratory chain function.

Patients with mitochondrial diseases, who usually manifest a multisystem disease, are considered potentially at-risk for a severe coronavirus disease 2019 (COVID-19) considering their clinical manifestations (encephalopathy, myopathy, diabetes, lactic acidosis, multi-organs dysfunction). However, so far, no cases of SARS-CoV-2 infection in mitochondrial diseases have been reported, and no data are available on the susceptibility and severity of Sars-cov2 in mitochondrial disorders. The objective of this study is to analyze the clinical

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features, prognosis and outcomes of COVID-19 in patients with primary mitochondrial diseases in a cohort of patients followed in Italy.

2. Patients and methods

In Italy, a "Nation-wide Italian Collaborative Network of Mitochondrial Diseases" was established in 2009. All Italian pediatric and adulthood centers with expertise in mitochondrial disorders are enrolled. In this Network, to date we globally follow more than 1800 mitochondrial diseases' patients, with both childhood (<18 years old, 42.7%) and adulthood onset, and almost 95% (n = 1650) still alive at July 2020. This Nation-wide Network has a National registry in accordance with the privacy standards and it is approved by the ethics committees of the centers involved in the Network. These centers obtained written informed consent from all participating patients or their legal guardians, in accordance with the ethical standards of the 1964 Declaration of Helsinki.

From March 1st, 2020, we started monitoring in Italy if COVID-19 was affecting also our cohort of patients according to the European Centre for Disease Prevention and Control guidelines (None, 2020) on the basis of epidemiological criteria (having a close contact with a confirmed COVID-19 case in the 14 days prior to onset of symptoms), clinical criteria (fever, cough, dyspnea, sudden onset of anosmia, ageusia or dysgeusia, headache, chills, muscle pain, fatigue, gastrointestinal signs), diagnostic criteria (radiological evidence showing lesions compatible with COVID-19) and microbiological criteria (detection of SARS-CoV-2 nucleic acid in a clinical specimen). Only PCR confirmed cases were included in this study. We excluded patients presenting with suggestive symptoms without any objective test confirming COVID-19 (possible cases), and patients in whom the results of the diagnostic tests were not available/reachable. Asymptomatic cases were identified because of contacts with symptomatic cases.

Clinically, patients with SARS-CoV-2 infection were classified as asymptomatic cases (people presenting with no clinical signs and symptoms from medical interviews and physical examinations), mild symptomatic (no need for hospitalization/supplemental oxygen), and severe symptomatic cases (need for hospitalization). Laboratory results were collected as close to the time of COVID-19 diagnosis or initial hospital admission as possible. Mitochondrial diseases-related clinical features were collected following definition included in previous studies (Gorman et al., 2016, Mancuso et al., 2017, Barca et al., 2020).

For all patients, the mitochondrial phenotypes, the clinical course of both mitochondrial disease and COVID-19 were collected, as well as the COVID-19 treatments, when applied.

3. Results

At January 30th, 2021, within the National Network we have identified 27 patients (1,6% of the supposed alive Italian cohort), 12 males (Supplementary Table), who developed the COVID-19, with a mean age at the COVID-19 onset of 34,6 years, age range 0–78-yrs, median age 31 years. Table 1 and the Supplementary Table 1 contains the main features of SARS-CoV-2 infection in the 27 patients with primary mitochondrial disease.

Most of the patients were pauci- or asymptomatic (85,7%) and treated at home. While eight patients were completely asymptomatic, nineteen presented at least one symptom suggestive of COVID-19. The most frequent symptoms (see Fig. 1) were fever (78,9%), fatigue (47,4%), myalgia (42,1%), cough and headache (36,8%), hyposmia (31,6%), dyspnea (31,6%), pneumonia and hyposmia (26,3%) and hypogeusia (26,3%). Of the four patients who required hospitalization for the COVID-19, we were able to collect the results from laboratory and radiological studies in two (presented in the Table).

Those who required COVID-19 therapy were treated with low-molecular-weight heparin, glucocorticoids, and antibiotics (mainly azithromycin) without serious side effects related to these drugs.

Table 1

Main features of SARS-CoV-2 infection in the Italian mitochondrial patients (n = 27). PMM: primary mitochondrial myopathy. MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF: myoclonic epilepsy with ragged red fibers; NARP: neuropathy, ataxia, and retinitis pigmentosa; ADOA: autosomal dominant optic atrophy; LHON: Leber's hereditary optic neuropathy; MIDD: maternally inherited diabetes and deafness.

		Number (%)
AGE years mean (range), median	34,6 (0–78), 31	
AGE onset PMD years (mean, range)	13,5 (0–48)	
SEX GENDER	Male	12 (44,5)
	Female	15 (55,5)
Mitochondrial mutation	nuclear gene	9 (33,3)
	mitochondrial gene	13 (48,1)
	mtDNA single deletion	2 (7,4)
	ongoing	3 (11,1)
Mitochondrial Phenotype (%)	PMM	4 (14,8)
	MELAS	4 (14,8)
	MERRF	2 (7,4)
	Multisystem disease	6 (22,2)
	LHON/ADOA	4 (14,8)
	NARP	3 (11,1)
	Leigh	3 (11,1)
	MIDD	1 (3,7)
COVID-19	Asymptomatic	8 (29,6)
	Oligosymptomatic	15 (55,5)
	Hospitalization	4 (14,8)
Laboratory parameters	Not performed/not known	21 (77,7)
	Raised CRP levels	5 (18,5)
	Raised ferritin levels	2 (7,4)
	Raised LDH levels	0
	White cells count < 4000/mm^3	1 (3,7)
	Raised CK	1 (3,7)
COVID-19 treatment	Any (%)	15 (55,5)
	Glucocorticoids	10 (37)
	Hydroxychloroquine	1 (3,7)
	Azithromycin	5 (18,5)
	low-molecular-weight heparin	7 (25,9)
	paracetamol	8 (29,6)
	oxygen	2 (7,4)
Mitochondrial symptoms\signs deteriorated during the infection	muscle weakness	4 (14,8)
	exercise intolerance	4 (14,8)
	fatigue	3 (11,1)
	myalgia	4 (14,8)
	Seizures, visual acuity, cognitive impairment, heart function	1 (3,7)
Evolution of the mitochondrial disease	Stable	21 (77,7)
	Deteriorated	6 (22,3)
Outcome	Death	1 (3,7)
	Recovered	25 (92,6)

During the infection, the mitochondrial symptoms that worsened more were mainly related to the skeletal muscle impairment (myalgia, fatigue, exercise intolerance, muscle weakness) and similar to muscular signs commonly reported during COVID-19 (Ellul et al., 2020). In the majority of cases (77,7%) the mitochondrial disease did not deteriorate. Five patients clinically deteriorated during the infection, one MELAS case is still in intensive care, and one (a PMM POLG case of 51-yrs of age) died for pneumonia.

4. Discussion

The impact of the SARS-CoV-2 infection on mitochondrial diseases has not been reported so far.

In this study, we captured the real-life spectrum of SARS-CoV-2 infection in Italy, including hospitalized cases, patients diagnosed and
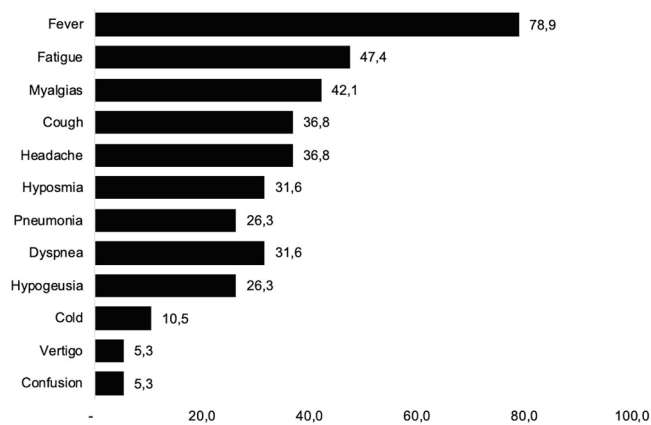
Fig. 1. Percentage of COVID-19-related symptoms in the 27 symptomatic mitochondrial patients.

followed-up in a primary care setting and asymptomatic or pauci-symptomatic cases isolated at home. We have estimated a frequency of confirmed SARS-CoV-2 infection in the Italian cohort of mitochondrial diseases of 1,6%; however, this figure needs to be interpreted cautiously considering the risk for bias because (i) not all mitochondrial cases in Italy could have been captured since not all of them are recognized and included in the "Nation-wide Italian Collaborative Network of Mitochondrial Diseases" cohort (ii) most patients were diagnosed and followed-up in a primary care setting, (iii) most of the data we have obtained are based on tele-visits or phone interviews, (iv) patients with preexisting diseases may have more difficulties to go for testing and, finally, (v) the exact number of alive patients followed by the Italian Network is updated at July 2020. Despite these limitations, it seems that the estimated infection rate in patients with primary mitochondrial diseases is lower than the infection rate estimated by the WHO in the Italian general population during the same study period (4,28%, https://covid19.who.int/region/euro/country/it, last access February 2nd, 2021).

We could speculate that this lower prevalence of SARS-CoV-2 infection in Italian mitochondrial patients could reflect the isolation at home of these fragile patients during the pandemic, with lower risk of social interaction or more difficulties to move for testing.

The phenotype of SARS-CoV-2 infection in our patients with mitochondrial diseases is similar to that described in the largest reported cohorts of infected patients (Borobia et al., 2020, Lapostolle et al., 2020). This suggests that mitochondrial individuals with COVID-19 do not manifest a more aggressive clinical course of the infection, and that they could be treated with the same standard of care that is being applied for the general population. Regarding the clinical outcome, we found that the main baseline features associated with a more complicated infection were similar to that identified in non-mitochondrial studies. Moreover, the mitochondrial disease clinical course did not deteriorate in most of our patients (77.7%), and mainly muscular signs worsened during the infection. However, it is difficult to discriminate if muscular signs may represent a real worsening of the mitochondrial disease or are just the clinical manifestation of the COVID-19 (Ellul et al., 2020, Borobia et al., 2020, Lapostolle et al., 2020). Moreover, it is well known that there is a distinct difference in those greater than 60 years of age who have co-morbidity who have a more aggressive disease and hospitalization, including Italy (https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard). In our cohort, only four patients affected by COVID-19 were older than 60 years, they were all symptomatic and in one case a clinical deterioration during the infection was

observed. Therefore, we do not have enough power to discuss if age -beside disease and comorbidities- represents an adjunctive risk for disease severity on mitochondrial diseases.

In conclusion, primary mitochondrial diseases infected individuals seemed to be similarly affected by SARS-CoV-2 compared with the general population in terms of clinical presentation and outcome. Larger cohort data from other countries are required to firmly confirm our current preliminary observations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mito.2021.03.011.

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