Original Article

Inborn errors of metabolism and coronavirus disease 2019: Evaluation of the metabolic outcome

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Abstract

Background: Infectious diseases can result in a catabolic state and possibly trigger an acute metabolic decompensation in inborn errors of metabolism (IEM), which could be life threatening. Studies regarding the course of severe acute respiratory syndrome coronavirus 2 infections in patients with IEM are generally limited to case reports. Here, we aimed to evaluate the clinical findings of coronavirus disease 2019 (COVID-19) and describe the impact of severe acute respiratory syndrome coronavirus 2 infections on metabolic outcomes in IEM patients.

Methods: Patients who were diagnosed with different types of IEM and developed microbiologically confirmed COVID-19 infection were included. Clinical findings and laboratory results were recorded retrospectively in terms of both IEM and COVID-19.

Results: Eleven patients with diagnosis of intoxication type metabolic disorders, five patients with energy metabolism disorders, and six patients with complex molecular disorders were enrolled. The most frequent clinical finding was fever (52.1%) followed by fatigue/myalgia (47.8%). None of the patients was younger than 1 year. None of the patients presented severe or critical disease. In terms of metabolic decompensation, two patients diagnosed with propionic acidemia, one patient with methylmalonic acidemia and one patient with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency presented clinical and biochemical findings of an acute metabolic attack.

Conclusions: Based on our results, IEM are not found to be an additional risk factor for severe COVID-19 infection. However, patients with intoxication type and energy metabolism disorders should be considered as a vulnerable population for COVID-19 and have a major risk of developing acute metabolic decompensation that can lead to life-threatening complications.

Key words COVID-19, metabolic decompensation, metabolic disorders, prognosis, SARS-CoV-2.

Inborn errors of metabolism (IEM) are rare, chronic disorders that generally present with progressive multisystem findings. A multidisciplinary and close approach is required for diagnosis, follow up, and management in IEM to prevent comorbidity and mortality. Inborn errors of metabolism can be classified into three subgroups according to the underlying pathophysiological process: (i) intoxication type metabolic disorders include IEMs caused by the accumulation of small molecules proximal to the metabolic block in the related intermediary metabolism pathway (inborn errors of amino acid metabolism, urea cycle disorders, sugar intolerances, etc.); (ii) energy metabolism disorders are caused by the defective production or utilization of energy and consist of both cytoplasmic and mitochondrial metabolism disorders; (iii) complex molecular disorders mainly include disorders of cellular organelles, which disturb the synthesis, remodeling, recycling, trafficking, and catabolism of complex molecules. Infectious diseases in IEM can result in an increase in catabolism and possibly trigger an acute metabolic decompensation that could be life threatening.1

Coronavirus disease-19 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 SARS-CoV-2, was declared a global health emergency and then announced as a worldwide pandemic by the World Health Organization (WHO) in March 2020. According to the WHO COVID-19 database, 142,557,268 confirmed cases including 2,008,400,180 confirmed cases including 4,265,903 deaths were reported in the period 4 August 2021.2 As all age groups are susceptible to COVID-19, studies concerning COVID-19 in pediatric patients aged from neonate to late adolescents have
been described in detail in the literature from the first announcement of the disease. The clinical severity of COVID-19 can vary widely in pediatric patients, from asymptomatic disease to multisystemic involvement, especially in patients with underlying comorbidity and immunosuppression. Frequent clinical findings can be listed as fever, cough, sore throat, malaise, myalgia, dyspnea, headache, nasal discharge, and gastrointestinal symptoms in children.\textsuperscript{3–5} Most recently, multisystem inflammatory syndrome in children (MIS-C) was described as characterized by laboratory and clinical evidence of inflammation with multisystemic organ involvement within 4 weeks of COVID-19.\textsuperscript{6,7}

Literature concerning the impact of COVID-19 on patients with IEM mainly included patients with lysosomal storage disorders (LSD). The main topics generally discussed in the relevant literature were the problems experienced by patients with IEM because of the challenging issues related to healthcare services and their solutions in the follow up during COVID-19 pandemic.\textsuperscript{8–13} However, only limited data are available evaluating the effect of COVID-19 on metabolic outcome and whether it causes an acute metabolic decompensation in patients with IEM. Studies regarding the course of SARS-CoV-2 infections in patients with IEM are generally limited to case reports.\textsuperscript{14,15} In this study, we aimed to evaluate the clinical findings of COVID-19 in patients diagnosed with IEM and define any relationship between SARS-CoV-2 infections and metabolic outcome in IEM patients.

Methods

This descriptive study was conducted between March 2020 and March 2021 with patients who have been regularly followed up in Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Pediatric Nutrition and Metabolism Department. Patients who were diagnosed as IEM and developed COVID-19 infection were included if:

- a definite diagnosis of IEM was made by molecular and/or biochemical analysis;
- patients were under regular follow up;
- a clinical and laboratory evaluation was made in the last 3 months for intoxication type metabolic disorders and energy metabolism disorders before the diagnosis of COVID-19;
- a clinical and laboratory evaluation was made in the last 6 months for complex molecular disorders before the diagnosis of COVID-19;
- diagnosis of COVID-19 infection was confirmed by positive reverse transcriptase–polymerase chain reaction (RT-PCR) or serum-specific antibodies against SARS-CoV-2.

Patients in whom diagnosis of a definite IEM could not be made, who were not under regular follow up, with missing data and in whom microbiological confirmation of COVID-19 was not made, were excluded from the study.

In this study, the clinical and biochemical features of the patients were reviewed in detail and the following items were recorded: age, sex, diagnosis of IEM, medical treatment for IEM, confirmation method of COVID-19, exposure history, signs and symptoms of COVID-19, laboratory and radiologic findings relevant to COVID-19, history of hospitalization and/or pediatric intensive care unit (PICU) admission and pharmacotherapy, clinical and biochemical findings of metabolic decompensation relevant to IEM during COVID-19.

The severity of COVID-19 infection was classified according to Dong et al.’s criteria as follows: (i) asymptomatic infection, described as patients without any clinical or radiological findings; (ii) mild disease, described as patients with symptoms of acute upper respiratory tract infections who had no radiological findings compatible with pneumonia; (iii) moderate disease, described as patients with clinical and radiological findings of pneumonia but no obvious hypoxemia; (iv) severe disease, described as patients with progressive respiratory disease indicating the clinical and laboratory signs of hypoxemia, and (v) critical disease, described as patients with acute respiratory distress syndrome (ARDS) or respiratory failure leading to a multisystemic organ dysfunction, including encephalopathy, myocardial injury, coagulation abnormalities, and acute kidney injury.\textsuperscript{3}

All procedures followed were in accordance with the ethical standards of the local Ethical Committee of Cerrahpasa Medical Faculty and with the Helsinki Declaration of 1975, as revised in 2013. All parents of the patients included in the present study gave informed consent.

Results

Twenty-two patients diagnosed with different subtypes of IEM were enrolled in this study. As one patient developed a second COVID-19 infection 4 months after the first infection, data from a total of 23 COVID-19 episodes were included. Fourteen patients (63.6%) were female and eight patients (36.3%) were male. The median age of the patients was 14 years, ranging between 32 months and 32.5 years. Five patients (22.7%) were between 1 and 6 years old, eight patients (36.3%) were 6–15 years old, and nine patients (40.9%) were more than 15 years old. None of the patients was younger than 1 year old. According to the severity classification of COVID-19 infection, none of the patients presented signs of severe or critical disease. Data concerning the clinical severity of the disease according to the age distribution are shown in Figure 1.

Confirmation of the COVID-19 infection was done by positive reverse transcriptase–polymerase chain reaction (RT-PCR) results in all patients. Thirteen patients (59%) were family clustered; one patient (4.5%) had a history of close contact with a COVID-19 positive friend whereas index patients could not be identified for eight patients (36.3%).

Patients were divided into three subgroups according to the type of IEM in terms of main classification modality: 11 patients (50%) were diagnosed with intoxication type
metabolic disorders, five patients (22.7%) were diagnosed with energy metabolism disorders and six patients (27.2%) were diagnosed with complex molecular disorders. Data concerning the distribution of the underlying IEM subgroups is shown in Figure 2.

As one patient diagnosed with Pompe disease developed two separate COVID-19 infections 4 months apart, data concerning the clinical findings included 23 COVID-19 episodes. The most frequent clinical finding was fever that was reported in 12 episodes (52.1%) followed by fatigue/myalgia (n = 11, 47.8%) and vomiting (n = 7, 30.4%). Other findings were listed according to their frequency as follows: cough (n = 6, 26%), loss of smell and/or taste (n = 4, 17.3%), headache (n = 4, 17.3%), dyspnea/ chest pain (n = 3, 13%), sore throat (n = 3, 13%), and diarrhea (n = 2, 8.6%). Two patients were asymptomatic and diagnosed by family screening for COVID-19.

In terms of metabolic decompensation relevant to IEM during COVID-19, four patients (18.1%) presented clinical and biochemical findings of an acute metabolic attack. Two of these patients were diagnosed with propionic academia. The course of COVID-19 infection was compatible with mild disease in two patients; however, the infectious status caused metabolic decompensation with moderate metabolic acidosis, hyperlactatemia, hyperuricemia, and ketosis in both patients. In another patient who was diagnosed with methylmalonic acidemia, profound metabolic acidosis, hyperlactatemia and disturbance in renal functions were reported during the course of a mild COVID-19 infection. Hypoglycemia, hyperlactatemia, and metabolic acidosis were noted in another patient diagnosed as 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG-CoA lyase deficiency) during the course of a moderate COVID-19 infection. She was hospitalized for 10 days because of prolonged vomiting and insufficient feeding. In these four patients, immediate therapeutic interventions were performed in terms of emergency management of metabolic decompensation. In organic acidemia, patients including propionic academia and methylmalonic academia, oral treatment was replaced by intravenous carnitine at a dose of 100 mg/kg/day. Hypercaloric parenteral nutrition providing lipid and glucose in addition to continuous intravenous insulin infusion was initiated to promote anabolism. Metabolic acidosis was treated by intravenous bicarbonate replacement and natural protein intake was stopped for 24 h. Emergency management of the patient diagnosed with HMG-CoA lyase deficiency mainly included intravenous carnitine treatment, high glucose rated intravenous nutrition therapy and intravenous bicarbonate replacement. Data concerning the molecular analysis, age onset of the IEM and laboratory markers of metabolic decompensation at the time of COVID-19 disease of these four patients are shown in Table 1.

![Fig. 1 Data regarding the clinical severity of the COVID-19 disease according to the age distribution.](image-url)
A COVID-19 targeted antiviral treatment consisting of favipiravir was used in seven episodes (30.4%). Among these seven episodes, antibacterial treatment was added to favipiravir due to secondary bacterial infection in one patient. Antibacterial treatment in which favipiravir was not added was used in the treatment course of six episodes (26%). Among 23 COVID-19 episodes of 22 patients with IEM, nine patients (40.9%) required hospitalization. None of the patients required PICU admission. Table 2 shows the detailed demographic and clinical data of the patients according to the underlying IEM subgroup.

Discussion
To date, a large amount of data regarding the clinical course of the disease in pediatric and adult COVID-19 patients have been published. The relationship between different underlying comorbidities such as asthma, cardiovascular disorders, malignities, and the outcome of COVID-19 infection has also been studied. However, studies evaluating the effect of COVID-19 on metabolic outcome and frequency of acute metabolic decompensation during COVID-19 infection in IEM patients are generally limited to case reports. This study mentioned the course of COVID-19 infection and possible acute metabolic exacerbations in different IEM diseases, mostly in the pediatric age group.

Fever and cough were reported as the most frequent symptoms relevant to COVID-19 in children followed by fatigue/malaise, sore throat, muscle pain, headache, dyspnea, and gastrointestinal symptoms in different studies.5,16,17 Pediatric aged patients were generally found to be prone to have a milder course of disease; most of the patients were asymptomatic or presented mild/moderate disease. In one of the largest pediatric series, only 5.9% among 728 confirmed and 1,407 probable COVID-19 infected patients were found to be severely and/or critically ill.3 However, clinical severity varies and different ratios have been reported. In a study from Turkey, the percentage of severe and/or critically ill patients was reported to be 27.1% among 37 confirmed pediatric COVID-19 patients and 10 patients (27%) required PICU admission.17 The mortality rate was 4.2% among 48 children who required PICU admission during COVID-19 infection in the USA and Canada.18 Results of a large review including 417 studies and 875 patients, MIS-C was mentioned as a potentially life-threatening complication of SARS-CoV-2 in pediatric patients.19 In our study, patients’ symptoms relevant to the COVID-19 infection were similar to the literature. During the COVID-19 episode,
none of the patients developed MIS-C. Clinical severity of the disease varied from asymptomatic to moderate disease. Based on these results, it was suggested that inborn errors of metabolisms are not an additional risk factor for severe COVID-19 infection and IEM is not a poor prognostic marker in terms of the severity index of COVID-19.

Among all types of IEM, individuals with intoxication-type metabolic disorders and energy metabolism disorders are especially at risk for metabolic decompensation during an intercurrent infectious disorder. In intoxication-type metabolic disorders, infectious diseases can trigger catabolism, which results in endogenous breakdown of proteins and causes

| Table 1 | Laboratory data regarding the inborn errors of metabolism (IEM) patients concerning metabolic decompensation at the time of COVID-19 disease |
|---------|---------------------------------------------------------------------------------------------------------------|
| Patient | Diagnosis of IEM | Age onset of the IEM | Molecular analysis | Biochemical data regarding metabolic decompensation at the time of SARS-CoV-2 infection |
|---------|------------------|----------------------|-------------------|--------------------------------------------------------------------------------------|
| Patient 1 | Propionic acidemia | Neonatal onset | PCCB gene p.1216fs*15 (c.645delG) homozygote | pH (N:7.35–7.45) 7.22 |
| Patient 2 | Propionic acidemia | Neonatal onset | PCCA gene p. Cys290Tyr (c.869G>A) homozygote | HCO3 (mmol/L) (N:21–28) 17.3 |
| Patient 3 | Methylmalonic acidemia | Neonatal onset | MUT gene p.L328F (c.982C>T) homozygote | Lactate (mmol/L) (N:0.5–1.6) 6.4 |
| Patient 4 | 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency | Neonatal onset | HMGCL gene IVS8+1G>C homozygote | Ammonia (µmol/L) (N:11–60) 37 |

| Table 2 | Demographic and clinical data of patients with COVID-19 according to the underlying inborn errors of metabolism (IEM) subgroup |
|---------|--------------------------------------------------------------------------------------------------------------------------|
| Total COVID-19 episodes | Intoxication type metabolic disorder | Energy metabolism disorder | Complex molecular disorders |
| n=23 | n=11 | n=5 | n=7 |
| Age, years (median, min–max) | 13.8 (2.6–33) | 13.2 (2.6–27) | 10.1 (3.9–18.6) | 17.5 (6–33) |
| Male (%) | 8 (34.8) | 4 (36.4) | 1 (20) | 3 (42.9) |
| Family history/close contact (n, %) | 15 (65.2) | 8 (72.7) | 4 (80) | 3 (42.8) |
| Symptoms, n (%) | | | | |
| Fever | 12 (52.2) | 4 (36.4) | 4 (80) | 4 (57.1) |
| Cough | 6 (26.1) | 6 (54.5) | 1 (20) | 3 (42.9) |
| Myalgia/fatigue | 11 (47.8) | 2 (18.2) | 2 (40) | 3 (42.9) |
| Sore throat | 3 (13) | 0 | 2 (40) | 1 (14.3) |
| Headache | 4 (17.4) | 1 (9.1) | 1 (20) | 2 (28.6) |
| Diarrhea | 3 (13) | 0 | 1 (20) | 2 (28.6) |
| Dyspnea/chest pain | 3 (13) | 1 (9.1) | 0 | 2 (28.6) |
| Vomiting | 7 (30.4) | 4 (36.4) | 1 (20) | 2 (28.6) |
| Loss of smell/taste | 4 (17.4) | 3 (27.3) | 0 | 1 (14.3) |
| Conjunctivitis | 0 | 0 | 0 | 0 |
| Hospitalization, n (%) | 8 (34.8) | 4 (36.4) | 2 (40) | 2 (28.6) |
| Metabolic decompensation, n (%) | 4 (17.3) | 3 (27.2) | 1 (20) | 0 |

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increased accumulation of toxic intermediates. In energy metabolism disorders, infectious diseases can trigger catabolism that increases cellular energy demand. Failure to meet this need causes energy depletion and metabolic decompensation. There are only limited reports on the effect of COVID-19 infection on metabolic outcomes in IEM patients in the literature. In one case report, in a 1-year-old patient who was diagnosed with propionic acidemia, a moderate COVID-19 infection was reported to cause only a slight hyperammonemia, which resolved immediately. In terms of metabolic decompensation, no major changes were observed in blood gas analysis and plasma lactate level. In another case report, COVID-19 infection initially presented as an upper respiratory tract infection caused a severe metabolic decompensation in a 23-year-old patient who was diagnosed with long-chain 3-hydroxyacyl-coa-dehydrogenase deficiency (LCHADD). COVID-19 infection resulted with a severe rhabdomyolysis and acute kidney injury. She had a normal echocardiographic examination 6 weeks prior to COVID-19 infection; however following the acute rhabdomyolysis attack, right ventricular dysfunction occurred. Laboratory analysis revealed remarkably elevated transaminases and creatinine kinase levels in addition to profound lactic acidosis. The patient died due to respiratory failure and cardiomyopathy, despite supportive treatment including venoarterial extracorporeal membrane oxygenation (VA-ECMO). In our study, four of 22 patients with 23 COVID-19 episodes experienced metabolic decompensation. In three organic acidemia patients, profound metabolic acidosis and hyperlactatemia was noted. Another patient diagnosed with HMG-CoA deficiency required prolonged hospitalization and biochemical analysis revealed hypoglycemia, hyperlactatemia, and profound metabolic acidosis in terms of metabolic decompensation. Based on our results, we suggest that inborn errors of metabolism – particularly intoxication type and energy metabolism disorders – should be considered as a vulnerable population for COVID-19 and have a major risk of developing acute metabolic decompensation that can lead to life-threatening complications.

In conclusion, inborn errors of metabolisms do not appear to worsen the course of COVID-19 related symptoms. However, COVID-19 infection plays a potential role in developing a severe life-threatening metabolic decompensation in patients with IEM.

Disclosure
The authors declare no conflict of interest.

Author contributions
All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission. T.Z. serves as the guarantor for the article. She accepts full responsibility for the work, had access to the data, and controlled the decision to publish. She has been involved in conception, design, analysis, and interpretation of the data and also drafting the article. D.H., S.A., and G.U.I. have been involved in the conception, design, analysis, and interpretation of the data. M.S.C. and E.K. have been involved in the analysis and interpretation of the data. C.A.Z. has been involved in conception, design, and interpretation of the data and revising the article critically for important intellectual content.

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