Safety of COVID-19 vaccines in children with inborn errors of metabolism in terms of developing metabolic decompensation

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Aim: There are no recommended guidelines or clinical studies on safety of COVID-19 vaccines in patients with inborn errors of metabolism (IEMs). Here, we aimed to examine the relationship between COVID-19 vaccination and metabolic outcome in paediatric IEM patients.

Methods: Patients with IEM between the ages of 12 and 18 were enrolled. Term metabolic decompensation was defined as acute disruption in metabolic homeostasis due to vaccination. Clinical and biochemical markers were compared between pre- and post-vaccination periods.

Results: Data from a total of 36 vaccination episodes in 18 patients were included. Thirteen patients had intoxication-type metabolic disorders including organic acidemia (OA), urea cycle disorders (UCDs), maple syrup urine disease (MSUD) and phenylketonuria (PKU); 4 patients had energy metabolism disorders including fatty acid metabolism disorders and LIPIN deficiency; and 1 patient had glycogen storage disorder (GSD) type 5. Seventeen patients received BNT162b2, and 1 received CoronaVac because of an underlying long QT syndrome. Fatty acid metabolism disorders, LIPIN deficiency and GSD type 5 were included in the same group named ‘metabolic myopathies’. In two PKU patients, plasma phenylalanine level increased significantly within 24 h following the second dose of vaccination. None of the OA, UCD, MSUD and metabolic myopathy patients experienced acute metabolic attack and had emergency department admission due to metabolic decompensation within 1 month after vaccination.

Conclusions: COVID-19 vaccines did not cause acute metabolic decompensation in a cohort of 18 children with IEM.

Key words: COVID-19 vaccines; inborn errors of metabolism; metabolic decompensation; paediatric.

What is already known on this topic
1 COVID-19 vaccines have been shown safe, immunogenic and protective between the ages of 12 and 17.
2 Vaccination against COVID-19 in children with inborn errors of metabolism (IEMs) has a pivotal importance, similar to healthy children, not only to prevent COVID-19 infection and transmission but also to provide metabolic control.
3 Vaccination in patients with IEM has some different considerations in terms of safety and efficacy.
4 Vaccination also may trigger a catabolic state by increasing the energy expenditure especially in intoxication type and energy metabolism disorders resulting in an acute metabolic decompensation that will be even life-threatening.

What this paper adds
1 There are no recommended guidelines or clinical studies on the safety of COVID-19 vaccines in IEM patients.
2 Our study is the first study that evaluates COVID-19 vaccine-related metabolic decompensation in paediatric IEM patients.
3 According to our results, COVID-19 vaccination appears to have a safe and acceptable profile in IEM patients in terms of acute metabolic decompensation; however, the authors underline the limitations of the study like small sample size and unequal distribution of IEM subgroups.
4 It is also recommended that IEM patients be monitored closely after vaccine administration to prevent vaccine-related metabolic exacerbation.

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As of 22 March 2022, the Coronavirus Disease-19 (COVID-19) pandemic has caused 6 077 252 deaths among 469 212 705 confirmed cases worldwide according to World Health Organization data. Although children generally have milder COVID-19 than adults, a severe disease may also develop that requires hospitalisation and intensive care unit support. According to the limited data in literature, it can be suggested that inborn errors of metabolism (IEMs) do not increase the clinical severity of COVID-19. However, SARS-CoV-2 infection can trigger a severe or even life-threatening acute metabolic decompensation in IEMs especially in intoxication type and energy metabolism disorders. Considering all these reasons, it is of great importance to vaccinate against COVID-19 in children with IEM, like healthy children, not only to prevent COVID-19 infection and transmission but also to provide metabolic control.

After the urgent need caused by the severity of the pandemic, different types of vaccines against COVID-19 have been developed and most of them have been shown to be effective and safe in adults. It has also been shown safe, immunogenic, and protective between the ages of 12 and 17, although the data in these studies have limitations such as the small sample size and the lack of long-term data. However, a few numbers of studies have been conducted on the safety of vaccines and whether the COVID-19 vaccination will cause an acute exacerbation of the chronic disease in children with special needs.

IEMs are chronic genetic disorders caused by disruption of a metabolic pathway. Vaccination may trigger a catabolic state by increasing the energy expenditure especially in intoxication type and energy metabolism disorders resulting in an acute metabolic decompensation. There is limited knowledge on the need for a specific management plan or hospitalisation for vaccination in these patients. To date, there are no recommended guidelines or any clinical studies regarding the safety of COVID-19 vaccines in IEM patients. Here, we aimed to evaluate whether the COVID-19 vaccine could cause clinical/laboratory acute metabolic exacerbation in paediatric IEM patients.

Methods

After Turkey’s Ministry of Health announced the initiation of the COVID-19 vaccination with CoronaVac developed by Sinovac and BNT162b2 developed by Pfizer/BioNTech in children aged 12–18, our patients with the diagnosis of IEM were contacted and informed about the vaccination. Among these patients, hospitalisation and 24-h follow-up were recommended for IEM subgroups with a high expected risk of decompensation in case of catabolism, while the other patients were vaccinated as an outpatient. This retrospective study was conducted between 01.09.2021 and 01.01.2022, following this COVID-19 vaccination process, at Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Paediatric Nutrition and Metabolism. Patients who met the following inclusion criteria were enrolled to the study: (i) male and female patients, ≥12 to <18 years of age, (ii) having a biochemically and/or molecularly confirmed diagnosis of IEM, and (iii) having a regular follow-up. Patients who had not a biochemically and/or molecularly confirmed diagnosis of IEM and had missing data were excluded from the study.

In this study, clinical and biochemical characteristics of patients were examined in detail, and data concerning age, sex, diagnosis and medical/nutritional treatments were also recorded in terms of IEM. Regarding COVID-19 vaccination; type of vaccine administered, time of vaccination, and whether the patient was hospitalised were also recorded. The term metabolic decompensation was defined as the acute disruption in metabolic homeostasis due to vaccination. Clinical and biochemical markers suggesting metabolic homeostasis were compared between pre- and post-vaccination periods. As the vaccination day was counted as ‘day 0’, clinical and biochemical data of patients within 7- and/or 21-day post-vaccination periods for each vaccination episode were also collected in detail. Biochemical markers indicating metabolic decompensation and timeline of the sampling according to IEM subgroups were shown in Table 1 and Table 2, respectively.

According to the Vaccine Adverse Event Reporting System (VAERS), myocarditis and myopericarditis were reported as serious adverse events especially after the second dose of BNT162b2 vaccination. On the other hand, IEM patients are at higher risk of developing cardiac disorders. Dilated and/or hypertrophic cardiomyopathy, conduction abnormalities are the main cardiac complications of energy metabolism disorders and organic acidemias (OAs). For all these reasons, electrocardiography and cardiac markers including CK-MB, pro-brain natriuretic peptide (pro-BNP) and troponin were performed to report the cardiac adverse effects that were considered to develop post-COVID-19 vaccination in hospitalised patients in this study. All the patients were also questioned in terms of post-COVID-19 vaccination symptoms referring to cardiac adverse effects (chest pain, dyspnoea, palpitation and syncope).

All procedures followed were in accordance with the ethical standards of the local Ethical Committee of Istanbul Ataturk University Medical Faculty (E-22686390-050.01.04-11 882) and with the Helsinki Declaration of 1975, as revised in 2013. All parents of the patients included in the present study gave informed consent.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). The mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used as descriptive statistics. Categorical variables were expressed as numbers and percentages. The normal distribution of data was evaluated with a Kolmogorov–Smirnov test. Analysis of the normally distributed variables was made by paired sample t-test for pairwise comparisons and repeated measures ANOVA for multiple comparisons. A value of P < 0.05 was considered statistically significant.

Results

Data from a total of 36 COVID-19 vaccination episodes, each performed at 1-month intervals, in 18 patients followed-up with the diagnosis of different IEM subtypes were included in this study. Eleven patients (61.1%) were female, and 7 patients (38.9%) were male. The mean age of the patients was 14.56 ± 1.91 years. Demographic characteristics of the patients are shown in Table 3.

According to the underlying pathophysiological mechanism of the IEM, patients were divided into three subgroups: 13 (72.2%) were diagnosed with intoxication-type metabolic disorders...
Table 1  Clinical and biochemical parameters indicating acute metabolic decompensation according to IEM subgroups

| IEM subgroup                  | Clinical findings                                      | Laboratory parameters                                                                 |
|-------------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------------|
| Metabolic myopathies          | Myalgia, Muscle weakness, Rhabdomyolysis              | Glucose, Ammonia, Lactate, Uric acid, AST, ALT, CK, LDH, Urea, Creatinine, Blood gas analysis, Plasma acylcarnitine analysis |
| Urea cycle disorders          | Altered level of consciousness, Ataxia, Metabolic stroke, Acute behavioural disturbances, Seizure | Ammonia, Plasma quantitative amino acid analysis                                       |
| Maple syrup urine disease     | Altered level of consciousness, Ataxia, Metabolic stroke, Acute behavioural disturbances, Seizure | Urinary dinitrophenylhydrazine test, Plasma quantitative amino acid analysis           |
| Organic acidemias             | Altered level of consciousness, Ataxia, Metabolic stroke, Acute behavioural disturbances, Seizure | Glucose, Ammonia, Lactate, Uric acid, Blood gas analysis, Plasma ketone concentration   |
| Phenylketonuria               | NA†                                                    | Plasma phenylalanine concentration in dried blood spot analysis                       |

† As phenylketonuria does not present with acute metabolic encephalopathy, only laboratory parameters are available in diagnosing acute metabolic decompensation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; IEM, inborn errors of metabolism; LDH, lactate dehydrogenase.

Table 2  Timeline of clinical and biochemical markers used in the assessment of metabolic decompensation according to IEM subgroups

|                  | 0 h | 6th hour | 12th hour | 18th hour | 24th hour | 14th day |
|------------------|-----|----------|-----------|-----------|-----------|----------|
| Phenylketonuria  | X   | X        |           |           |           |          |
| Urea cycle disorders | X   |           | X         |           |           |          |
| Maple syrup urine disease | X   |           |           | X         |           |          |
| Organic acidemias | X   |           |           |           | X         |          |
| Metabolic myopathies | X   | X        |           | X         | X         |          |

Table 3  Demographic characteristics of the patients

| Patient | Age (years) | Gender | Diagnosis            | Vaccination |
|---------|-------------|--------|----------------------|-------------|
| P1      | 12          | Male   | Phenylketonuria      | BNT162b2    |
| P2      | 14          | Female | Phenylketonuria      | BNT162b2    |
| P3      | 14          | Female | Phenylketonuria      | BNT162b2    |
| P4      | 15          | Male   | Phenylketonuria      | BNT162b2    |
| P5      | 13          | Female | Phenylketonuria      | BNT162b2    |
| P6      | 13          | Male   | Maple syrup urine disease | BNT162b2 |
| P7      | 13          | Female | Urea cycle disorder  | BNT162b2    |
| P8      | 13          | Female | Urea cycle disorder  | BNT162b2    |
| P9      | 13          | Female | Urea cycle disorder  | BNT162b2    |
| P10     | 16          | Female | Metabolic myopathy   | BNT162b2    |
| P11     | 17          | Female | Metabolic myopathy   | BNT162b2    |
| P12     | 14          | Male   | Metabolic myopathy   | BNT162b2    |
| P13     | 15          | Male   | Metabolic myopathy   | BNT162b2    |
| P14     | 15          | Male   | Metabolic myopathy   | BNT162b2    |
| P15     | 17          | Female | Organic acidemia     | BNT162b2    |
| P16     | 17          | Female | Organic acidemia     | BNT162b2    |
| P17     | 15          | Male   | Organic acidemia     | BNT162b2    |
| P18     | 13          | Female | Organic acidemia     | CoronaVac    |
In addition, infections diseases can possibly trigger a catabolic state that results in an acute metabolic decomposition. In conclusion, routine childhood vaccination plays a pivotal role in preventing infectious diseases in IEM patients. Although the general recommendation is to proceed with standard scheduled immunisation, some IEM subgroups and metabolic myopathies. Rhabdomyolysis was the cardinal clinical finding that was questioned in metabolic myopathy patients. None of the patients developed rhabdomyolysis and they only complained of a non-persistent mild myalgia. Laboratory findings of energy deficiency including hypoglycaemia, metabolic acidosis, hyperlactatemia, elevated transaminases, hyperuricemia and increase in creatine kinase (CK) levels were not observed.

None of the patients developed an acute OA attack within 24 h of vaccination. In addition, none of the patients had emergency department admission due to metabolic decompensation within 1 month after vaccination. One of these OA patients was a 13-year-old female patient and had propionic academia. As she had been following up with long QT syndrome caused by propionic acidemia, her family did not prefer BNT162b2 vaccine (Patient 18). Similar to the findings of other OA patients who received BNT162b2, she had not experienced any metabolic decompensation and cardiac adverse effects.

**Discussion**

COVID-19 vaccine-related metabolic decompensation in paediatric IEM patients has not been studied in literature yet. Best of our knowledge, our study is the first study that mentions the safe and acceptable profile of COVID-19 vaccination in IEM patients in terms of acute metabolic decompensation. Patients diagnosed with IEM are generally considered to be a vulnerable group for infectious diseases. In addition, infectious diseases can possibly trigger a catabolic state that results in an acute metabolic decompensation. In conclusion, routine childhood vaccination plays a pivotal role in preventing infectious diseases in IEM patients. Although the general recommendation is to proceed with standard scheduled immunisation, some IEM subgroups were thought to be prone to develop an acute decompensation following vaccination. Yang et al. reported acute metabolic crises after administration of vaccines as the presenting sign in five IEM patients. Three were diagnosed with Leigh’s disease, one with methylmalonic aciduria (MMA) and one with GA-1 following the post-vaccination metabolic decompensation.11

| IEM subgroup                  | Number of patients (n) |
|-------------------------------|------------------------|
| Metabolic myopathies          |                         |
| Fatty acid metabolism disorders | n = 3                  |
| Glycogen storage disorder     | n = 1                  |
| LPIN1 deficiency              | n = 1                  |
| Organic acidemias             |                         |
| Glutaric aciduria type 1      | n = 1                  |
| Propionic academia            | n = 2                  |
| Isovaleric acidemia           | n = 1                  |
| Urea cycle disorders          |                         |
| Ornithine                     | n = 2                  |
| transcarbamylase deficiency   |                         |
| Citrullinemia                 | n = 1                  |
| Maple syrup urine disease     | n = 1                  |
| Phenylketonuria               | n = 5                  |

IEM, inborn errors of metabolism.

| Table 4 Distribution of the IEM subgroups of the patients |
|----------------------------------------------------------|
| IEM subgroup                  | Number of patients (n) |
|-------------------------------|------------------------|
| Metabolic myopathies          |                         |
| Fatty acid metabolism disorders | n = 3                  |
| Glycogen storage disorder     | n = 1                  |
| LPIN1 deficiency              | n = 1                  |
| Organic acidemias             |                         |
| Glutaric aciduria type 1      | n = 1                  |
| Propionic academia            | n = 2                  |
| Isovaleric acidemia           | n = 1                  |
| Urea cycle disorders          |                         |
| Ornithine                     | n = 2                  |
| transcarbamylase deficiency   |                         |
| Citrullinemia                 | n = 1                  |
| Maple syrup urine disease     | n = 1                  |
| Phenylketonuria               | n = 5                  |

IEM, inborn errors of metabolism.
Similarly, some case reports described clinical and laboratory findings of an acute metabolic attack following different vaccines and then diagnosed as GA-1, MMA (cblA type) and beta-ketothiolase deficiency. However, none of these patients had a diagnosis of IEM prior to vaccination, so it could not be claimed that they were stable in terms of IEM before vaccination. Considering the large sample size of clinical studies assessing the relationship between childhood vaccination and acute metabolic decompensation, IEMs were generally divided into subgroups according to the expected risk of decompensation. The risk of a severe metabolic decompensation was very low, and vaccination was considered to be safe in stable (PKU, carbohydrate metabolism disorders, GSD types 2, 4, 5, 7 and 8) or slowly progressive IEMs (lysosomal storage disorders, peroxisomal disorders, purine and pyrimidine disorders). Sickest group including the IEM subgroups of amino acid disorders, OA, UCD, fatty acid oxidation disorders, mitochondrial disorders, GSD type 0, 1, 3, 6 and 9 was mentioned to have a significant risk of morbidity and/or mortality with catabolism triggered by vaccination.12,25

Regarding the sickest group, adverse effects of vaccination on metabolic homeostasis such as emergency department admission, hospitalisation and clinical/laboratory parameters of decompensation have been reviewed in a few studies. Records of 112 patients pointed out that vaccination did not trigger hyperammonemic episodes within a 7- and 21-day period in children diagnosed with UCD. All childhood vaccinations were also recommended in management guidelines for patients with MMA and PA, as they have not been found to be associated with metabolic decompensation in stable patients.18,23

Regarding COVID-19 vaccination, there is only one case reporting a severe rhabdomyolysis—on the third day of vaccination, his CK level was measured as 250 000 U/L—developed after COVID-19 Vaccine AstraZeneca in a 27 years old male patient diagnosed with Carnitine palmitoyl transferase 2 deficiency, a subgroup of fatty acid oxidation disorder. In our study, patients diagnosed as UCD, OA and fatty acid oxidation disorder which were labelled as the ‘sickest group’ according to previous literature did not develop any clinical and/or laboratory findings consistent with metabolic decompensation. Plasma Phe levels increased remarkably requiring Phe free diet in two of our PKU patients at the 24th hour of vaccination. Although PKU was mentioned as a stable IEM in terms of vaccination, our data highlighted the need for close Phe monitoring after COVID-19 vaccination. Depending on the whole data of our study, it was suggested that COVID-19 vaccines had an acceptable profile in terms of metabolic decompensation in paediatric IEM patients; however, a close follow-up was required.

The small sample size and unequal distribution of the IEM subgroups was the limitation of our study. This was thought to be due to the rare incidence of IEM in the general population and the limitation of the patients included in the study to a certain age range.

**Conclusion**

COVID-19 vaccines appear to have a safe profile in terms of developing acute metabolic decompensation in children diagnosed with IEM. It is also recommended that they should be monitored closely after vaccine administration to prevent vaccine-related metabolic exacerbation. However, the authors underlie the main limitation of the study, small sample size. Further studies with larger sample sizes will elucidate on the safety profile of COVID-19 vaccines in children with IEM.

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Let's go space by Kimi Lee (aged 8) from “A Pop of Colour” art competition, Youth Arts, Children’s Hospital at Westmead