Case Report

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COVID-19 triggered encephalopathic crisis in a patient with glutaric aciduria type 1

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Abstract

Objectives: The impact of coronavirus disease-19 (COVID-19) on metabolic outcome in patients with inborn errors of metabolism has rarely been discussed. Herein, we report a case with an acute encephalopathic crisis at the course of COVID-19 disease as the first sign of glutaric aciduria type 1 (GA-1).

Case presentation: A 9-month-old patient was admitted with encephalopathy and acute loss of acquired motor skills during the course of COVID-19 disease. She had lethargy, hypotonia, and choreoathetoid movements. In terms of COVID-19 encephalopathy, the reverse transcription-polymerase chain reaction assay test for COVID-19 was negative in cerebral spinal fluid. Brain imaging showed frontotemporal atrophy, bilateral subcortical and periventricular white matter, basal ganglia, and thalamic involvement. Elevated glutarylcarnitine in plasma and urinary excretion of glutaric and 3-OH-glutaric acids was noted. A homozygote mutation in the glutaryl-CoA dehydrogenase gene led to the diagnosis of GA-1.

Conclusions: With this report, neurological damage associated with COVID-19 has been reported in GA-1 patients for the first time in literature.

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Keywords: COVID-19; glutaric aciduria type 1; metabolic decompensation.

Background

Glutaric aciduria type 1 (GA-1), is an autosomal recessively inherited neurometabolic disorder that is caused by defective enzyme activity of glutaryl-CoA dehydrogenase (GCDH) which catalyzes both dehydrogenation of glutaryl-CoA and decarboxylation of glutaconyl-CoA to crotonyl-CoA in the lysine degradation pathway. Mutations of the GCDH gene that encodes GCDH result in the accumulation of glutaric acid, 3-hydroxyglutaric acid, and glutaryl-CoA in body fluids [1]. The cerebral damaging mechanisms in GA-1 mainly depend on cerebral energy impairment [2]. The clinical spectrum of the disease varies widely and different phenotypes have been described. The most common phenotype of GA-1 presents with an acute encephalopathic crisis generally occur before 24 months of age which was triggered by any catabolic state and results in acute loss of acquired motor skills. Progressive macrocephaly, truncal hypotonia, dystonic movement disorder, and seizures can be listed as the classical manifestations of GA-1 [3]. Insidious onset type GA-1 includes patients who do not experience encephalopathic crises but develop classical neurological findings of GA-1. Most recently, a late-onset form of GA-1 has been described in patients who do not present the classical neurological findings of the disease and generally present with nonspecific signs as headache, vertigo, ataxia, and disturbed fine motor skills [4]. Brain magnetic resonance imaging (MRI) of the patients mainly reveals frontotemporal atrophy, ventricular dilatation, white matter alterations, striatal injury, and subdural hemorrhages [3, 5]. Diagnosis is made by measurement of elevated concentrations of glutarylcarnitine (C5DC), glutaric acid, and 3-hydroxyglutaric acid in the light of supportive clinical and radiological signs. A low-lysine diet, carnitine supplementation, and riboflavin are the main principles of the maintenance treatment [4]. Metabolic outcome mainly depends on the management of

intercurrent catabolic processes and prognosis is poor in late-diagnosed patients in whom striatal injury occurred before the initiation of the standard therapy regimes [4, 5].

Infectious diseases can result in increased catabolism and possibly trigger an acute encephalopathic crisis in GA-1. The coronavirus disease-19 (COVID-19) that is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was announced as a pandemic worldwide by the World Health Organization (WHO) in March 2020. According to WHO COVID-19 database, 153,187,889 confirmed cases including 3,209,109 deaths were reported until 4 May 2021 [6]. However, only limited data are available that evaluate the effect of COVID-19 on the metabolic outcome and investigate whether it causes an acute metabolic decompensation in patients with inborn errors of metabolism (IEM) [7–9].

Here, we present a 9-month-old female patient who experienced her first encephalopathic crisis presenting with encephalopathy and acute loss of acquired motor skills that led to the diagnosis of GA-1 during the course of COVID-19 disease.

Case presentation

A previously healthy 9-month-old female patient was admitted to the pediatric intensive care unit (PICU) with complaints of altered level of consciousness and acute loss of acquired motor skills within 2 days of febrile disease. She was the second child of consanguineous parents and her prenatal, natal, and postnatal history was uneventful. She achieved developmental milestones appropriate for her age and she had no history of seizures. She first presented upper respiratory tract infection signs as dry cough and fever two days ago. Since the reverse transcription-polymerase chain reaction (RT-PCR) assay test was positive in her mother, she was also examined and also diagnosed with COVID-19 via a positive RT-PCR test. As her patients recognized an increased tendency to sleep and an acute loss of acquired motor skills, the patient was hospitalized to PICU with a possible diagnosis of COVID-19 encephalopathy.

In her admission, she was lethargic and the modified Glasgow coma scale was 12. Her neurological examination revealed a relative macrocephaly (79.1 percentile, sds: 0.81) and generalized hypotonia. She had a complete loss of voluntary movements including head control. Mild choreoathetoid movements, especially marked on extremities were observed during examination. Hematological and biochemical investigations including complete blood count, renal functions, liver functions, and transaminases, electrolyte levels, plasma ammonia, and lactate levels were normal. The control nasopharyngeal RT-PCR assay test for COVID-19 was positive. In terms of the differential diagnosis of COVID-19 encephalopathy, a lumbar puncture was performed. Biochemical and microbiologic analysis of cerebrospinal fluid (CSF) was normal and RT-PCR assay test for COVID-19 was negative in CSF.

Brain MRI showed opercular frontotemporal atrophy, bilateral subcortical, and periventricular white matter, bilateral basal ganglia involvement, and thalamic hyperintensities in T2-weighted axial image (Figure 1). Bilateral crus cerebri was also involved in the mesencephalon. Based on clinical findings of acute neuromotor deterioration, macrocephaly, mild dystonic findings dominated by hypotonia, and abnormal MRI findings; GA-1 was included in the differential diagnosis. In plasma acylcarnitine analysis performed by tandem mass spectrometry free carnitine (C0) was 5.35 μmol/L (N: 8.6–90) and C5DC was elevated as 1.17 μmol/L (N: 0–0.27). Urinary excretion of glutaric and 3-OH-glutaric acids (416 mmol/mol creatinine, N: 0–15; 214 mmol/mol creatinine, N: 0–4.5, respectively) were elevated. A homozygote c.126C>A mutation in GCDH gene led the diagnosis of glutaric aciduria type 1.

Discussion

Here, we reported a patient with GA-1 admitted to PICU due to an encephalopathic crisis caused by COVID-19. She had

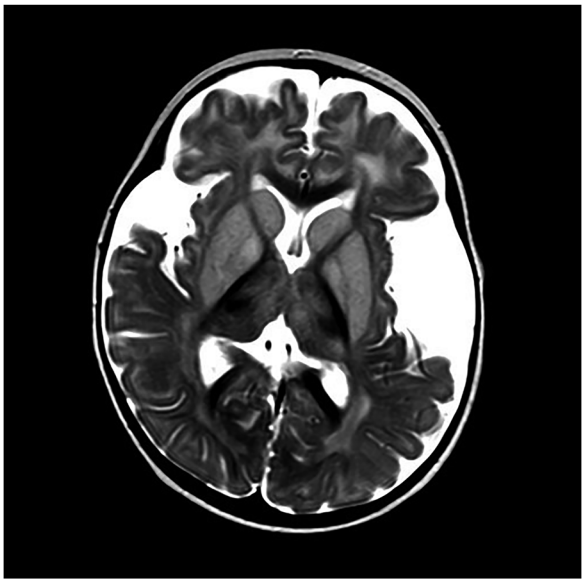

Figure 1: Cranial MRI of the patient: T2-weighted image revealed opercular frontotemporal atrophy, bilateral subcortical and periventricular white matter, bilateral basal ganglia involvement, and thalamic hyperintensities.

normal motor development until SARS-CoV-2 infection. The encephalopathic crisis triggered by COVID-19 led to an acute loss of acquired motor skills and altered level of consciousness. It is the first report mentioning the impact of COVID-19 on the initiation of neurological damage in GA-1 in the medical literature.

Studies concerning COVID-19 in pediatric aged patients reported that children were generally prone to have a milder course of the disease, most of the patients were asymptomatic or presented mild/moderate disease. However, the clinical severity of COVID-19 can vary from asymptomatic disease to multisystemic involvement, especially in patients with underlying comorbidity and immunosuppression [10]. To date, IEM has been limitedly discussed as a comorbidity for COVID-19 and the relationship between SARS-CoV-2 infections and metabolic decompensation still remains unclear.

COVID-19 disease was reported to cause mild hyperammonemia that did not require any additional ammonia lowering treatment and did not lead to metabolic acidosis or hyperlactatemia in a one-year-old patient with the diagnosis of propionic acidemia [7]. In another report, COVID-19 disease triggered a severe metabolic decompensation in a 23-year-old patient with the diagnosis of long-chain 3-hydroxyacyl-coa-dehydrogenase deficiency. Profound lactic acidosis, elevated transaminases and creatinine kinase levels, severe rhabdomyolysis, and acute renal failure contributed to the metabolic decompensation under SARS-CoV-2 infection and she died due to respiratory failure and cardiomyopathy [8]. Most recently, increased risk of metabolic decompensation in IEM patients who developed COVID-19 disease was reported in two patients diagnosed with propionic acidemia and GA-1, respectively. The first patient was an eight-month-old female patient with propionic acidemia and she presented a profound metabolic acidosis, ketonuria, slight hyperammonemia at the course of severe COVID-19 disease. The second patient was an eight-month-old female patient with GA-1. She had no recorded neuromotor disability before SARS-CoV-2 infection. COVID-19 disease did not cause any encephalopathic crisis or biochemical abnormality in terms of metabolic decompensation in this patient [9].

Learning points

- Inborn errors of metabolism should be considered as a risk group for developing life-threatening metabolic decompensation during COVID-19 disease.
- Having knowledge about brain MRI findings of inborn errors of metabolism plays an important role to avoid diagnostic delays and misdiagnosis.
- Emergency treatment principles of GA-1 have a pivotal role to prevent an acute encephalopathic attack triggered by an acute infection.

What's new

- With this report, neurological damage associated with COVID-19 has been reported in GA-1 patients for the first time in the literature.

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