Case Report

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Transient benign hyperphosphatasemia due to COVID-19: the first case report

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Abstract

Objectives: Coronavirus disease (COVID-19) rapidly spread worldwide in a few months and was declared as a worldwide pandemic by WHO in March 2020. Transient benign hyperphosphatasemia (THI) is a benign condition associated with marked elevation of alkaline phosphatase (ALP) without any other kidney, bone, and liver pathologies.

Case presentation: Herein, we report a previously healthy 16-month-old female patient who developed a secondary transient benign hyperphosphatasemia associated with SARS-CoV-2. Patient whole family's SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) results were positive. Since THI is a diagnosis of exclusion, other reasons that may cause ALP elevation should be ruled out. ALP activity decreased and turned to normal ranges within the following month. THI has been reported to be in association with various conditions. Its relationship with many viruses has been reported previously.

Conclusions: If ALP elevation is detected in patients with COVID 19 due to the increasing number of infections, THI should be considered if there is no other accompanying pathology.

Keywords: COVID-19; transient hyperphosphatasemia.

Background

Coronavirus disease (COVID-19) was firstly reported in Wuhan, the capital of Hubei, China, at the end of 2019. The disease rapidly spread worldwide in a few months and was declared a worldwide pandemic by WHO in March 2020. The ongoing outbreak of COVID-19 has become an emergency of international concern since millions of people were infected, and thousands died every day worldwide. Globally, as of August 26, 2020, there have been 23,752,965 confirmed cases of COVID-19, including 815,038 deaths, reported to WHO. In Turkey, from March 11 to August 26, 2020, there were 261,194 confirmed cases of COVID-19 and 6,163 deaths [1]. The disease, caused by COVID-19, has a broad spectrum ranging from mild upper respiratory tract infection to lower respiratory tract infection and death. There are several case reports associated with SARS-CoV-2, but transient benign hyperphosphatasemia (THI) has not been presented.

THI is a benign condition associated with marked elevation of alkaline phosphatase (ALP) without any other kidney, bone, and liver pathologies, and normal levels are reached within weeks and months. It is commonly seen during infancy and childhood, especially under age 5, with the upper respiratory system and gastrointestinal infections [2]. Awareness of this complete benign disorder can prevent patients from undergoing unnecessary examinations and procedures.

Case presentation

A previously healthy 16-month-old female was admitted to our hospital with fever and positive family history for COVID-19. The patient's brother was infected with SARS-CoV-2, and he had close contact with SARS-CoV-2 positive cases at the factory he was working. Our patient's symptoms started 5 days after her brother's diagnosis. Her whole family's SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) results were positive as the patient, and the whole family was hospitalized in the pandemic department.

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Our patient had an acute onset of malaise, nausea, cough, and a fever at the time of admission. Her body temperature was 38.5 °C, pulse was 86 bpm, respiratory rate was 28 breaths per minute, and oxygen saturation was 98% in room air. Except for the oropharyngeal hyperemia, her physical examination was ordinary. Her growth parameters were normal for her age. She received 400 IU vitamin D daily due to a nationwide vitamin D prophylaxis program for 1 year. Initial laboratory results were as follows: white blood cell count was 10.300 μ L, lymphocyte count was 6.800 μ L, hemoglobin was 12 g/dL, platelet count was 301,000 μ L, and C-reactive protein was 1.2 mg/L. During her follow-up, laboratory examination also revealed high ALP activity [1860 IU/L (normal range: 145–420 IU/L)]. Despite the absence of any clinical finding suggestive of bone and hepatic disease, we have examined her for all possible causes. The patient's serum creatinine level was normal (0.22 mg/dL). Other parameters were as follows: aspartate aminotransferase was 34 U/L, alanine aminotransferase was 14 U/L, gamma-glutamyl transferase was 13 U/L, total bilirubin and direct bilirubin were in normal ranges, calcium was 9.8 mg/dL, magnesium was 2.2 mg/dL, phosphorus was 5.5 mg/dL, 25-hydroxyvitamin D was 32 μ g/L, and intact parathormone level was 28.1 pg/mL. THI was thought to be a possible diagnosis during the follow-up, and both parents' ALP levels were checked for familial ALP elevation, and the results were in normal ranges.

There was no infiltration presence on the initial and follow-up chest X-ray images for COVID-19 infection. On the second day of hospitalization, the patient experienced diarrhea. Cough and fever continued for 3 days, and mild gastrointestinal symptoms persisted for 5 days. Since the patient was receiving symptomatic treatment, antiviral treatment was not initiated. The patient and her family were hospitalized for 7 days. After the discharge, they were followed up by the provincial public health directorate and isolated for 14 days. Isolation was terminated when the symptoms disappeared, and negative RT-PCR results were obtained. Due to the high ALP values, the patient's calcium, phosphorus, magnesium, and parathormone levels were regularly examined and were completely normal

during follow-up. Vitamin D and wrist radiography were checked, and they were both in normal ranges. Abdominal ultrasound for possible hepatic pathology was normal. Serial ALP levels were checked during her follow-up and the relationship between the ALP level and the course of the disease is shown in Table 1. ALP activity decreased and turned to normal ranges (254 IU/L) in a month. However, ALP isoenzyme analysis could not be performed because of pandemic issues. The patient was diagnosed with THI. Informed consent was received from her parents.

Discussion

ALP, a phosphohydrolase enzyme, is mainly synthesized in the placenta, bone, and liver. ALP levels depend on age and increase, especially during growth spurt periods such as infancy and puberty due to high osteoblastic activity [2]. Bone disorders (rickets, fractures, juvenile Paget's disease, and bone malignancies); hepatic disease (hepatitis, cholestasis, malignancies); and kidney disease (chronic renal failure, tubular disease); and certain drugs (anticonvulsants, antibiotics) may lead to ALP elevation [3].

THI is not an infrequently seen condition and generally detected incidentally in laboratory examinations requested for other purposes. THI is defined as follows: <5 years, no clue for hepatic and/or bone diseases on physical examination or laboratory tests, the elevation of both bone and liver isoenzymes and resolves in 4 months [2]. Although THI diagnosis includes the elevation of both liver and bone isoenzymes, other studies have shown conflicting results. Since THI is a diagnosis of exclusion, other reasons that may cause ALP elevation should be ruled out.

The mechanism of high ALP levels in THI remains controversial. Some hypotheses have been proposed to elucidate the underlying factors. The high sialic acid levels have been suggested as one of the main underlying reasons in THI development. The high sialic acid levels lead to a delay in ALP isoenzymes and high ALP levels. The other poorly accepted mechanism is that ALP levels could be found high in vitamin D deficiency recovery. It was

Table1: Serial ALP measurements and the course of symptoms of COVID-19 disease.

Variable	On admission	2nd day of admission	5th day of admission	30 days after discharge
Fever, °C	38.5	38.3	37.1	36.8
Cough	+	+	-	-
Gastrointestinal symptoms	+	+	+	-
ALP (normal range: 145–420 IU/L)	1860	1411	904	254

determined that THI cases gathered, especially in autumn and winter months. This seasonal variation can be explained with the higher viral infection [2].

Respiratory syncytial virus, rotavirus, human bocavirus, Epstein–Barr virus are claimed to be primary pathogen [4–7]. The study conducted by Suzuki et al. [8] in patients with THI reported increased Echo 22, Enterovirus 71, and Coxsackie B5 antibody titers in these patients.

Coronaviruses are a large family of viruses that spread from animals and occasionally lead to respiratory infections in humans. However, despite its high contagiousness, cases and symptoms in children are relatively uncommon. The clinical spectrum of COVID-19 disease is still a debate. Clinical findings in childhood were generally associated with the respiratory system, while some studies showed that gastrointestinal involvement could occur with diarrhea presence like our case [9]. Our patient's growth was normal, and the patient had taken the vitamin D prophylaxis recommended by the ministry of health. Kidney and liver function tests, calcium, phosphorus, PTH were normal in our patient. Our patient had no history of medication use or chronic disease; therefore, these obvious reasons were quickly ruled out. Symptomatic COVID-19 infection was present in the whole family, and SARS-CoV-2 RT-PCR was positive in our patient. Decreasing ALP level with viral infection improvement is thought to be transient hyperphosphatasemia associated with SARS-CoV-2.

THI is associated with a marked but temporary elevation of ALP without any other abnormalities, and there is no specific treatment. Homecare facilities seem to be appropriate for patients with the asymptomatic or mild infection without any underlying condition. Our patient had mild symptoms and did not receive any specific antiviral treatment.

If ALP elevation is detected in patients with COVID 19 due to the increasing number of infections, THI should be considered if there is no other accompanying pathology.

Learning points

- THI is reported for the first time in the SARS-CoV-2 infection.

- Its relationship with many viruses has been reported previously. It is vital to recognize THI and avoid misdiagnosis and unnecessary examinations.

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