

## CASE REPORT

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# Severe hypertransaminasemia during mild SARS-CoV-2 infection: A pediatric case report and literature review

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**ABSTRACT**

**Introduction:** Liver injury during SARS-CoV-2 infection has a multifactorial pathogenesis and it is frequent in pediatric cases.

**Case presentation:** We report a case with severe hypertransaminasemia associated with mild SARS-CoV-2 infection.

**Conclusion:** This highlights the potential need of hepatic function evaluation during acute illness and follow-up even in non-critically ill children with COVID-19.

**KEYWORDS**

SARS-CoV-2, COVID-19, Transaminasemia, Liver, Children

**INTRODUCTION**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a systemic disease, responsible of a variety of clinical manifestations, affecting not only upper and lower respiratory tract but also gastrointestinal system and liver.<sup>1</sup> Small case series have reported hepatic involvement in up to 60% of infected patients, especially in severe and critical cases of coronavirus disease 2019 (COVID-19).<sup>1,2</sup> In children aged 0–3 years, transient mild elevation in serum aminotransferases is common during symptomatic phase, with an overall prevalence of approximately 29%.<sup>3</sup> The mechanism of liver damage is not well defined yet, but several causes have been suggested: drug induced hepatotoxicity (e.g. paracetamol); damage induced by intestinal translocation due to impaired permeability of the barrier; hypoxic ischemic damage from respiratory failure; direct damage by the virus itself through ACE2 receptors or associated with the hyperinflammatory phase—cytokine release of SARS-CoV-2 infection.<sup>2,4,5</sup> The role of pre-existing liver disease may also be relevant in the onset of acute liver injury during SARS-CoV-2 infection and may decompensate liver function leading to acute organ failure.<sup>1–3</sup> Herein we report a case of liver involvement with transient severe hypertransaminasemia

in a female infant with mild SARS-CoV-2 infection.<sup>6</sup>

**CASE REPORT**

A 30-days old female infant presented to our emergency room with fever, rhinorrhea and lack of appetite for about 24 hours. She was born at 40 weeks of gestational age by eutocic delivery and had a neonatal weight of 3750 g. She passed a regular neonatal period and had an optimal growth with formula milk. Metabolic screening at birth was normal.

In the family history, of note, the mother presented myalgia and fatigue and had a positive nasopharyngeal swab for SARS-CoV-2 two days before admission. Contact tracing revealed a possible source of infection in the usual attendance of the family of a local cafe, where febrile employees tested positive for SARS-CoV-2.

In COVID ward, the physical examination was normal except for mild dehydration and hypotonia. Vital signs were in normal range. SARS-CoV-2 infection was confirmed by positive real-time polymerase chain reaction on nasopharyngeal swabs.

She never experienced respiratory distress or needed oxygen support during hospitalization. Chest X-ray

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examination was negative. Lung ultrasound revealed irregular pleural line and irregular vertical artifacts (B-lines) consistent with mild interstitial lung involvement.

Laboratory findings showed alterations in hepatic function measures with acute liver injury in absence of hepatic-based coagulopathy. Transaminase levels increased up to 21-fold and 25-fold the upper reference limit for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) on day 3 of hospitalization, respectively. Gamma glutamyl transferase (GGT) reached a peak of 429 U/mL later on, in the ninth day. Ferritin levels were 4420 ng/mL in the fifth day, and subsequently decreased. Other laboratory examinations including white blood-count and classification, hemoglobin, platelet-count, D-dimer, serum immunoglobulin levels and C-reactive protein (CRP) showed no significant abnormalities (Table 1).

Microbial investigations excluded a superimposed congenital or acquired infection. In particular, HBV, HCV, EBV and *Toxoplasma* serologies, rotavirus, enterovirus and adenovirus in stool and cytomegalovirus deoxyribonucleic acid in urine

sample were respectively negative.

At serial ultrasound examinations (on day 4 and day 8), nor hepatomegaly, ascites, altered echogenicity or Doppler signal alterations were found. Cardiac evaluation was normal.

The patient had a 48-hour recovery of appetite, resolution of dehydration and fever; she never presented vomiting or acholic stools. Hypotonia was no more evidenced at discharge on day 10.

During the following weeks, AST, ALT, ferritin and GGT levels decreased and returned to normal range after 21 days from the first biochemical evaluation (at admission).

## DISCUSSION

We report a novel pediatric case of acute liver injury in the course of SARS-CoV-2 mild infection, notable for the severe increased in serum aminotransferases without liver failure.

Children with COVID-19 are generally less severely affected than adults, unlike other respiratory diseases.<sup>1</sup>

**TABLE 1** Laboratory data trends of the infant with SARS-CoV-2 infection during hospitalization and follow-up

Variables	Reference range	Hospitalization			Follow-up
		On admission	Day 4	Day 9 (discharge)	At 21th day
Hemoglobin (g/dL)	8.6–15.0	12.1	13.5	11.1	10.0
White-cell count ( $\times 10^9/L$ )	5.0–19.5	9.6	12.5	15.2	11.2
Neutrophils	1.0–9.0	1.9	1.9	2.6	3.5
Lymphocytes	2.5–16.5	6.3	9.1	10.6	6.3
Platelet count ( $\times 10^9/L$ )	150–400	266	325	551	429
AST (U/L)	0–40	118	1147	183	40
ALT (U/L)	0–40	97	854	486	29
GGT (U/L)	0–40	–	353	429	37
Albumin (g/dL)	3.5–5.0	3.3	3.1	3.1	–
Ferritin (ng/mL)	12–180	620	4422	763	–
Bilirubin (mg/dL)					
Total	0.2–1.2	0.9	0.8	0.6	–
Direct	<0.40	0.3	0.3	0.2	–
D-dimer (ng/mL)	0–230	511	2176	608	–
PT (%)	70–130	110	99	109	–
INR	0.80–1.38	0.94	1.01	0.94	–
PTT (sec)	27–40	38	33	37	–
Creatinine (mg/dL)	0.2–1.3	0.32	0.23	0.25	0.2
Glucose (mg/dL)	70–110	71	–	–	91
CRP (mg/L)	0–6	10	6	3	–
LDH (U/L)	0–325	431	896	356	–
BNP (pg/mL)	1–100	–	12	–	–
IL-2-R (U/mL)	220–720	–	2572	–	–
IL-6 (pg/mL)	0–5.20	–	3.95	–	–
IL-10 (pg/mL)	0–9.10	–	8.70	–	–

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transferase; PT (%), prothrombin time activity; PTT (sec), partial thromboplastin time; INR, international normalized ratio; CRP, C-reactive protein; LDH, lactate dehydrogenase; BNP, brain-type natriuretic peptide; IL, interleukin; –, not tested.

However, some fatal cases are being reported in pediatrics, associated with extrapulmonary complications.<sup>7,8</sup> Liver injury, in particular has been described in infected children and adults.<sup>1</sup> It is usually associated with a longer hospital stay and more severe clinical course, but it is a common finding even during pauci-symptomatic infection with a mild elevation in AST and ALT.<sup>3,8</sup> Our case is singular for the severe hepatic cytolysis in the course of an uncomplicated infection, when the baby presented in good general conditions without relevant respiratory or gastrointestinal involvement.

The exact physio-pathological mechanisms of liver damage are not completely clarified yet, with potential role of direct virus injury and inflammatory damage.<sup>9,10</sup> Liver biopsy of infected adults previously evidenced that SARS-CoV-2 can replicate in the hepatocytes and cause direct liver damage, with histological evidence of massive hepatic apoptosis.<sup>10</sup> Zhou et al<sup>3</sup> reported on his pediatric case-series narrative review, that liver involvement could be prevalent in children aged 0–3 years, where mild hypertransaminasemia is common during acute infection.<sup>3</sup> An explanation could be that immaturity in liver tissue can predispose to a higher risk of direct viral injury.<sup>2,10</sup> On the other hand, uncontrolled release of cytokines could be responsible of greater liver injury in critical ill patients, in pediatric and adult age.<sup>1,2,9</sup>

There are few published pediatric cases that analyzed hepatic involvement and damage evolution during SARS-CoV-2 infection. A recent Greek case report showed a transient liver injury in a 5-years old child during a mild SARS-CoV-2 infection, without hepatic dysfunction nor need of intensive care.<sup>9</sup> On the other hand, an Iranian case of fulminant hepatic failure during COVID-19 has been described in 11 years-old boy without pre-existing liver disease.<sup>7</sup> In our case, despite the evidence of severe hypertransaminasemia, hepatic function was preserved: albumin, bilirubin levels and clotting assay were always in normal range according to age.

We can reasonably assume that severe hypertransaminasemia was not caused by immune mediated inflammation (levels of IL-6, CRP, ESR were normal and she was not long febrile),<sup>8</sup> nor by drug hepatotoxicity (she did not need a specific therapy and she was only supported with glucosalin rehydration). Hypoxic ischemic damage could also be ruled out, because she did not presented respiratory failure and Doppler signal at abdominal ultrasound was normal. Clinical history, microbial and metabolic investigations excluded a pre-existing liver disease. It is therefore likely that direct virus injury may be responsible of the transient severe liver injury that, in our case, spontaneously resolved after 3 weeks.

In conclusion, liver involvement should be taken into account even in patients with mild SARS-CoV-2 infection as it could be severe. Monitoring hepatic function until damage resolution is therefore desirable, to rule out persistent cytolysis or the development of a chronic disease.

## CONSENT FOR PUBLICATION

Consent for publication was obtained.

## CONFLICT OF INTEREST

There are no financial conflicts of interest to disclose, especially from the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI).

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