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CASE REPORT

Anti-SARS-CoV-2 antibodies important in diagnostics of acute hepatitis in children

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ABSTRACT

The most common causes of acute hepatitis in children are hepatitis A and autoimmune hepatitis. Hepatitis in the course of Wilson's disease is sporadically registered in adolescents.
An increase of activity of aminotransferases both in the course of multisystem inflammatory syndrome in children (MIS-C) and in the course of COVID-19 has been observed. Hepatitis is common in children with MIS-C and is associated with a more severe presentation and persistent elevation of liver function tests.
To date, no cases of acute hepatitis in children due to COVID-19 have been reported.
We present 2 cases of acute hepatitis in children where the only cause seems to be a previous asymptomatic SARS-CoV-2 infection.

KEY WORDS:

hepatitis, SARS-CoV-2 infection, anti-SARS-CoV-2 antibodies, MIS-C.

INTRODUCTION

The main causes of acute hepatitis in children are hepatitis A virus (HAV) infection, rarely hepatitis C virus (HCV) and hepatitis B virus (HBV) infections. Hepatitis A is a classic "dirty hands disease" and is common in developing countries. Autoimmune hepatitis (AIH) is a form of chronic hepatitis and has a broad clinical spectrum including asymptomatic individuals with abnormal laboratory results, and clinical symptoms similar to those of acute viral hepatitis or even cirrhosis. Pediatric autoimmune liver diseases are diagnosed more frequently than in the past, because of enhanced awareness and a decrease in viral hepatitis-related diseases such as hepatitis C or B.

In acute SARS-CoV-2 infection and multisystem inflammatory syndrome in children (MIS-C), gastrointestinal manifestations may represent a relevant aspect of the clinical picture. According to Giannattasio *et al.*, acute COVID-19 liver involvement seems to affect mainly younger children (< 3 years of age); the prevalence of acute liver disease was higher in older MIS-C children [1]. They also hypothesized that the mechanisms contributing to liver damage are different in COVID-19 and MIS-C. In COVID-19, liver damage could be related to a direct cytopathic effect of the virus and higher expression of angiotensin-converting enzyme 2 receptors. In the case of MIS-C, they hypothesized a possible immunological factor. In the course of hepatitis, damage to hepatocytes results, inter alia, from blood circulation disorders, contributed to by damage to the endothelium. Endothelial damage is the result of, inter alia, the secretion of pro-inflammatory cytokines such as TNF-α and interleukin 6 observed in MIS-C. Hepatitis is common in children with MIS-C and is associated with a more severe presentation and persistent elevation of liver function tests [2].

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We observed 2 children with acute hepatitis without COVID-19 in the medical history and nasopharyngeal swab at the time of admission to the hospital negative for SARS-CoV-2 RNA. In the performed diagnostic process the only deviation in the laboratory tests was the presence of anti-SARS-COV-2 antibodies.

CASE REPORTS

CASE 1

An almost 8-year-old boy with Asperger's syndrome, not yet hospitalized, was sent to hospital due to periodic abdominal pain observed for 6 months and suspicion of ascariasis resistant to repeated anthelminthic treatments (presence of ascaris eggs in several studies, without expulsion of the parasite after the treatments). On admission to the hospital, the boy's general condition was good, with a slightly bloodshot throat, soft abdomen, no pain in palpation or pathological resistance. Nasopharyngeal swab was negative for SARS-CoV-2 RNA. Laboratory tests revealed low inflammatory markers, white blood cell smear with mild monocytosis and no eosinophilia, low IgE levels, and elevated activity of alanine aminotransferase (ALT) (6 × ULN) and aspartate aminotransferase (AST) (3 × ULN). On the basis of serological tests, HAV, HBV infection and leptospirosis were excluded. HCV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus (ADV), herpes simplex virus (HSV), varicella-zoster virus (VZV), human herpesvirus type 6,7 (HHV-6,7), entero- and parvoviral infections were excluded by PCR. The antinuclear antibody (ANA), antimitochondrial antibody (AMA), smooth muscle antibody (SMA) and liver kidney microsomal antibody (LKM 1) titers were negative.

The others parameters of the autoimmune process such as IgG and gamma globulin levels were normal. The concentration of ceruloplasmin was normal. The presence of anti-SARS-CoV-2 S1/S2 IgG was detected (97.6 AU/ml). Abdominal ultrasound revealed no enlargement of the parenchymal organs. Due to the appearance of epigastric pain and vomiting, gastroscopy was performed, excluding gastric mucosa inflammation. Due to a quiet systolic murmur on the right side of the sternum, an electrocardiogram was performed describing disturbances in interventricular conduction. The parasitological examination of the stool revealed the presence of several roundworm eggs. Albendazole treatment was performed, without expelling the roundworm. Further multiple stool tests performed in two laboratories showed no evidence of parasite presence. In the following days of hospitalization, an increase in the activity of liver enzymes was observed to the values ALT 2331 U/l (58 × ULN), AST 2005 U/l (40 × ULN), gamma-glutamyl transpeptidase (GGTP) 149 U/l (9 × ULN) – and a decrease in the prothrombin index to 65% (Table 1, Figures 1A, B). Hepatoprotective and choleretic treatment was used in the therapy. Due to the risk of liver failure, steroids were added to the treatment – initially intravenously, in follow-up orally with dose reduction. After a significant improvement in liver function tests, the boy was discharged home in good general condition.

TABLE 1. Laboratory results of Patient's 1

Parameters	Day of hospitalisation										
	Reference values	0	8	10	11	12	13	14	16	21	23	28
ALT [U/l]	0–39	242	421	1091	1524	2111	2331	1672	1125	822	710	223
AST [U/l]	0–52	163	392	1097	1448	2005	1780	813	341	364	248	90
GGT [U/l]	7–17	39		57	73	96	122	110	119	149	135	44
Prothrombin index (%)	83–125	85	82	79	73	65	75	74	89	91	96	94

ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGPT – gamma-glutamyl transfpeptidase

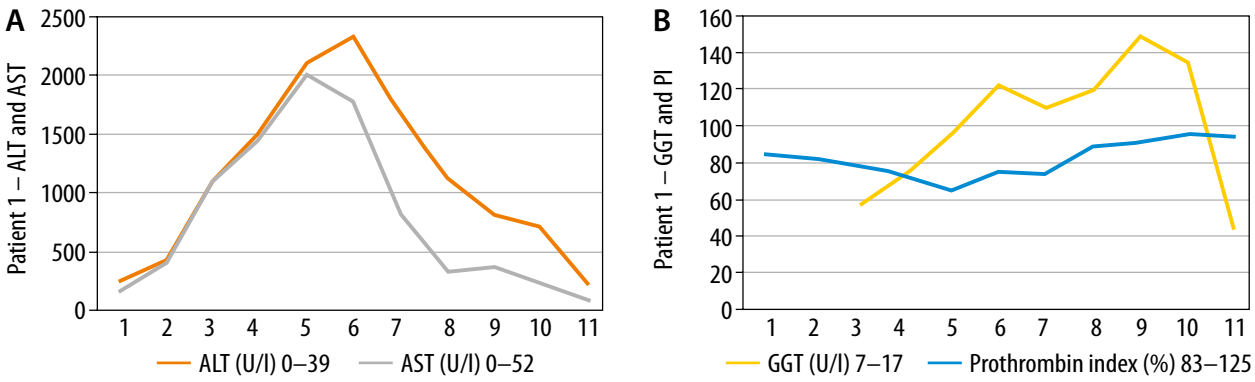

FIGURE 1. Changes of alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase activity and PI value in Patient 1

ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – gamma-glutamyl transpeptidase

CASE 2

A 6.5-year-old girl, hospitalized in the past due to diarrhea and allergic rash, was admitted due to jaundice, preceded by a three-day deterioration in well-being, loss of appetite, nausea, abdominal pain and vomiting. On admission, the girl's general condition was fairly good, with slightly yellow skin and non-enlarged parenchymal organs. Nasopharyngeal swab was negative for SARS-CoV-2 RNA. Laboratory tests revealed low inflammatory markers, elevated aminotransferase activity (ALT 2356 U/l, AST 1883 U/l), hyperbilirubinemia with predominance of conjugated bilirubin, high bile acid concentration, and normal levels of prothrombin index (Table 2). The ANA, AMA, and LKM 1 titers were negative. IgG, gamma globulin levels and ceruloplasmin concentration were normal. There was a positive titer of SMA antibodies. HAV, HBV, CMV, EBV infection and toxoplasmosis were serologically excluded and HCV, Herpesviridae and enterovirus infection were excluded in molecular tests. The presence of anti-SARS-CoV-2 S1/S2 IgG (27AU/ml) was detected. Due to the repeated presence of occult blood in the stool, colonoscopy was performed under short-term general anesthesia, excluding intestinal inflammatory pathology. Abdominal ultrasound shows a slight increase in the echogenicity of the liver. Hepatoprotective and choleretic drugs were used in the treatment, which resulted in a gradual resolution of jaundice and improvement in liver tests. Due to the slow decline in the activity of transaminases steroids were used systemically, and from the third week of hospitalization a rapid improvement in liver tests was observed (Table 2, Figures 2A, B). After a month of hospitalization, the patient was discharged home in good condition.

DISCUSSION

In the study by Cantor *et al.* hepatitis was present in 19/44 subjects (43%) with MIS-C. Children with hepatitis had significantly higher rates of shock at presentation, greater respiratory support requirement, and longer hospitalization times [2]. Wanner *et al.*, on the basis of clinical, histopathological, molecular and bioinformatic studies for the hepatic tropism of SARS-CoV-2, revealed that liver injury, indicated by a high frequency of abnormal liver function tests, is a common clinical feature of COVID-19. Furthermore, they identified transcription-, proteomic- and transcription factor-based activity profiles in hepatic autopsy samples, revealing similarities to the signatures associated [3]. In the retrospective study by Perez *et al.* of patients ≤ 21 years of age and positive for SARS-CoV-2 PCR, elevated ALT was detected in 36% of the 291 patients, 31% with COVID-19, and 51% with MIS-C. Elevated ALT in COVID-19 was associated with obesity ($p < 0.001$), immunocompromised status ($p = 0.04$), and chronic liver disease ($p = 0.01$). In the regression models, elevated ALT in COVID-19 was associated with higher CRP. Children with elevated ALT and MIS-C were more often boys ($p = 0.001$). Children with elevated ALT in both cohorts had significantly higher multiorgan dysfunction, longer

TABLE 2. Laboratory results of Patient's 2

Parameters	Day of hospitalisation													
	Reference values	0	2	4	5	7	11	13	17	21	23	27	29	33
ALT [U/l]	0–39	2356	2366	1903	1599	839	1101	939	1011	988	765	280	161	103
AST [U/l]	0–52	1883	1758	1206	983	512	843	735	738	636	359	59	38	40
GGT [U/l]	7–17	151	141	121	106	60	105	91	97	83	80	63	54	52
Prothrombin index (%)	83–125	79	85	82	86	75	86	85	88	83	88	91	102	104

ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGPT – gamma-glutamyl transfpeptidase

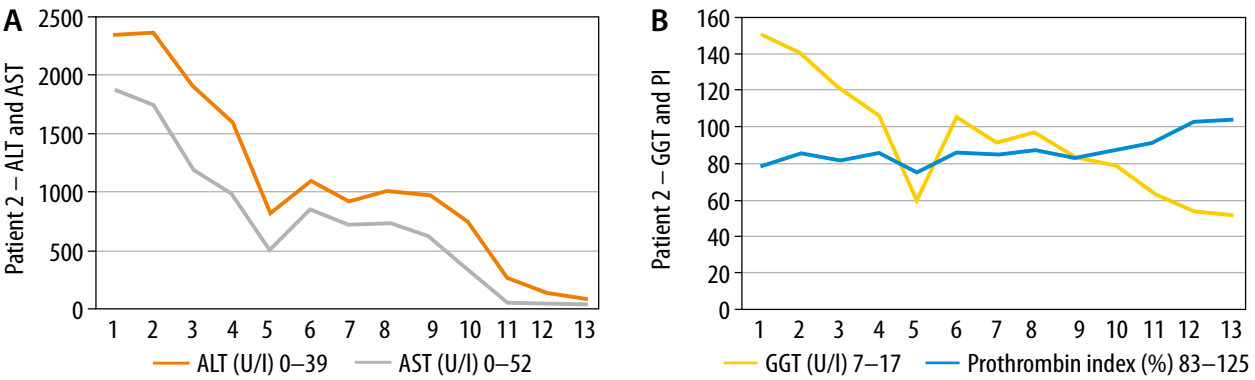

FIGURE 2. Changes of alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase activity and PI value in Patient 2

ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – gamma-glutamyl transpeptidase

hospitalization, and Intensive Care Unit stay. Children with MIS-C had 2.3-fold increased risk of ALT increase compared to children with COVID-19 [4].

Brisca *et al.* suggested an unreported association between acute SARS-CoV-2 infection and acute hepatitis in children, thus supporting the notion that evaluation of liver enzymes during hospitalization for SARS-CoV-2 infection is also indicated in pediatric age [5].

By 20th May 2022, more than 450 cases of acute hepatitis of unknown origin in children had been reported worldwide. The hypotheses indicate several potential causes of these cases. One of them points to an association between adenovirus infection in immunocompetent children and acute hepatitis [6, 7]. In our patient ADV infection was excluded by the PCR method but there is a possibility of SARS-CoV-2 superantigen-mediated reactivation of immune cells and induction of acute hepatitis [7]. The second hypothesis for the cause of acute hepatitis of unknown origin in children is an autoimmune disease. SARS-CoV-2 virus like HAV may rarely act as a trigger for autoimmune hepatitis, owing to immune mimicry, and induce AIH by initiating self-perpetuating immune-mediated liver inflammation [8].

The high burden of the population with the Omicron variant (B1.1.529) is associated with the appearance of severe hepatitis of unknown etiology in children [9]. Patients described in our article were hospitalized before October 2021 and the World Health Organization criteria for definition of severe hepatitis of unknown etiology in children include cases of acute hepatitis with ALT/AST activity > 500 IU/ml, not due to hepatitis A–E viruses, in children aged < 16 years reported since October the first, 2021. Omicron variant domination has been observed since the last months of 2021.

Most children with SARS-CoV-2 infection have a mild form of the disease; only a small proportion develop MIS-C and symptoms of long-COVID. In Ludvigsson's study the most common symptoms 2 months after the onset of COVID-19 were fatigue, dyspnea and heart palpitations or chest pain [10]. Cooper *et al.* reported 2 distinct patterns of potentially long COVID-19 liver manifestations in children, acute liver failures in infants and hepatitis with cholestasis in adolescents, with common clinical, radiological, and histopathological characteristics after a thorough workup excluded other known etiologies [11].

CONCLUSIONS

We presented 2 cases of acute hepatitis in children in whom the only deviation in etiologic laboratory tests was the presence of anti-SARS-CoV-2 antibodies. Those children did not have symptomatic COVID-19 or PIMS/MIS-C. They had not been vaccinated with SARS-CoV-2. The course of acute hepatitis was mild with full recovery, although both children had indications for the use of corticosteroids.

It seems that SARS-CoV-2 may be the cause of hepatitis in children; therefore, in the etiological diagnosis of acute hepatitis in children, testing for the presence of anti-SARS-CoV-2 antibodies should be included.

DISCLOSURE

The authors declare no conflict of interest.

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