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Research Article

Abnormal liver function in children hospitalized with acute respiratory infection of adenoviruses: a retrospective study

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ABSTRACT

Human adenoviruses (HAdVs) can cause acute hepatitis in immunocompromised patients. However, it is unclear whether HAdVs are contributors to hepatitis in immunocompetent children. In this study, the liver function test (LFT) results were retrospectively analyzed among children hospitalized (age <14 years) between January 2016 and October 2019 for acute respiratory infection caused by adenoviruses. Alanine transaminase (ALT) and aspartate aminotransferase (AST) levels were elevated in 7.74% and 46.89% of patients, respectively. All patients with >2 folds of the upper limit of ALT or AST levels were infected with HAdV-7 or HAdV-55. Significantly higher levels of ALT, AST, γ-glutamyl transpeptidase (γ-GT), and lower albumin levels were observed in the HAdV-7 infection group than in the HAdV-3 infection group. HAdV-55 infection led to significantly higher γ-GT, total bilirubin, and direct bilirubin levels than the other infection types. The records of four patients with serial monitoring of the LFT results were further analyzed. Multiple indicators remained abnormal during the entire hospitalization in these patients. These results indicate that HAdV infection is often accompanied by abnormal liver function, and HAdV-7 and HAdV-55 might be under-recognized contributors to hepatitis among children.

1. Introduction

Human adenoviruses (HAdVs) are common pathogens that cause acute respiratory infections (ARI), gastroenteritis, and conjunctivitis in children. To date, more than 100 HAdV types have been identified, which are classified into seven groups (A–G) (HAdV Working Group, http://hadvwg.gmu.edu/). Among them, HAdV-3 and HAdV-7 are the major types associated with ARI in children (Chen et al., 2022). HAdVs cause acute hepatitis and liver failure in immunocompromised patients (Onda et al., 2021), and few cases have been reported in immunocompetent patients (Matoq and Salahuddin, 2016; Khalifa et al., 2022). Several early studies suggested the involvement of adenoviruses, directly or indirectly, in the etiology of infectious hepatitis (Alwen, 1973; Munoz et al., 1998; Peled et al., 2004; Ozbay Hosnut et al., 2008). However, it remains unclear whether HAdVs are a definite contributor to hepatitis in children. Recently, the World Health Organization (WHO) reported severe acute hepatitis of unknown etiology (SAHUE) in children. Most patients (78%, n = 327) were younger than 6 years of age. HAdV has been detected in at least 327 cases (Baker et al., 2022; WHO, 2022). These reports highlight the role of HAdVs in the etiology of hepatitis. Several recent reports suggested that the disease is related to co-infections involving adeno-associated virus type 2 (AAV2) and helper HAdV (Ho et al., 2023; Morfopoulou et al., 2023).

Upon review of clinical records, we noticed abnormal liver function test (LFT) results in some children with HAdV-associated ARI. Here, LFT results were analyzed among immunocompetent children (age < 14 years) hospitalized for acute respiratory diseases caused by adenovirus infection (Liu et al., 2022).

2. Materials and methods

2.1. Patient enrollment

To analyze the role of HAdV infection in liver function in children, we retrospectively analyzed the clinical data of 317 pediatric patients (age < 14 years) hospitalized for acute respiratory diseases caused by HAdV infection at the First Affiliated Hospital of Guangzhou Medical University between January 2016 and October 2019 in Guangzhou, southern China. All children had no underlying diseases such as immune insufficiency, leukemia, diabetes and hypertension before the onset of the disease.

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Alanine transaminase (ALT) and aspartate aminotransferase (AST), the two most important LFT indicators, were analyzed. Limited by the integrity of the clinical records, data of γ-glutamyl transpeptidase (γ-GT), albumin (Alb), total bilirubin (TBil), and direct bilirubin (DBil) were available from patients hospitalized between 2016 and 2018 but were partially missing in 2019. Lactate dehydrogenase (LDH) was only analyzed for patients hospitalized in 2019.

2.2. Sample collection, test, and clinical presentation

As described previously, patients' respiratory samples (e.g., throat swabs, sputum, and bronchoalveolar lavage fluid) were collected to test for HAdV and 17 other common respiratory pathogens including influenza viruses A and B, respiratory syncytial virus, parainfluenza virus types 1–4, human metapneumovirus, human rhinovirus, enterovirus, four types of coronaviruses (HCoV-229E, -OC43, -NL63, and -HKU1), human bocavirus, mycoplasma pneumoniae (MP), and Chlamydophila pneumoniae simultaneously using TaqMan real-time quantitative polymerase chain reaction (Liu et al., 2022). The HAdV-positive samples were subjected to molecular typing. The clinical characteristics, treatments, and outcomes of the patients with HAdV infection were retrospectively collected from their medical records. The diagnosis of severe or non-severe illness was made by the attending physicians, as previously reported (Liu et al., 2022).

2.3. Statistical analysis

Statistical analysis was performed using GraphPad Prism 7.04 (GraphPad Software, San Diego, CA, USA). Differences between groups were calculated using the Mann-Whitney test or unpaired *t*-test and the χ^2 test. Two-tailed *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. ALT and AST levels were elevated in patients with HAdV infection

A total of 317 pediatric patients hospitalized with HAdV infection were enrolled, including 60, 34, 72, and 151 patients in 2016, 2017, 2018, and 2019, respectively. The median age of patients with HAdV infection was 3.0 (interquartile range: 1.1–4.2) years. The number of adenovirus infections peaked in July of each year. HAdV-7 replaced HAdV-3 as the predominant subtype after September 2017 (Fig. 1). The numbers of patients infected with HAdV-3, -7, -4, -55, and other types (or untyped) were 155, 128, 8, 5, and 21, respectively. The patients with co-infection of two or more HAdV types were excluded from further analysis. The indicator data of liver function were analyzed, and the numbers of patients with abnormal LFT results are shown in Table 1. Some data were missing in the clinical records of some patients, resulting in varied total numbers of patients for different tests. Abnormal levels of ALT, AST, LDH, γ-GT, and Alb were observed in 7.74%, 46.89%, 80.8%, 5.75%, and 16.09% of the patients, respectively (Table 1).

Of the 151 patients hospitalized in 2019, 108 (71.5%) were co-infected with at least one of the other common 17 pathogens of interest, as previously reported (Liu et al., 2022). For the levels of all four indicators (ALT, AST, LDH and AST/ALT), no significant difference was observed between patients with HAdV-coinfection and those with only HAdV infection (HAdV-single) (Table 2). This result indicated that HAdV infection, but not coinfection with the 17 other common respiratory pathogens, led to abnormal liver function.

The severe illness rate in patients with HAdV infection in 2019 was 34.4% (52/151). The proportion of patient with elevated levels of AST ($P = 0.0003$) or LDH ($P = 0.0092$) were significantly higher in patients with severe illness than in those with non-severe illness (Table 2).

Overall, children with HAdV infection were often accompanied by abnormal liver function.

3.2. Liver enzyme levels were higher in patients with HAdV-7 and HAdV-55 infection than in those with HAdV-3 infection

Of the 24 patients with elevated ALT levels, 17 (13.28%) and 2 (40%) were infected with HAdV-7 and HAdV-55, respectively; only 4 (2.58%) were infected with HAdV-3. Of the 143 patients with elevated AST levels, 84 (66.67%) and 3 (60%) were infected with HAdV-7 and HAdV-55, respectively (Table 1). The proportions of patients with elevated ALT or AST levels were significantly higher in those with HAdV-7 infection than in patients with HAdV-3 infection. Significantly higher levels of ALT, AST, γ-GT, and LDH and lower Alb levels were observed in patients with HAdV-7 infection than in those with HAdV-3 infection ($P < 0.01$) (Fig. 2). Patients with HAdV-55 infection possessed significantly higher levels of γ-GT, TBil, and DBil than those with other HAdV types ($P < 0.01$) (Fig. 2). Most importantly, all patients with more than two folds of the upper limit of ALT or AST levels were infected with HAdV-7 or HAdV-55. In summary, HAdV-7 and HAdV-55 infection may cause more severe hepatitis than HAdV-3 infection.

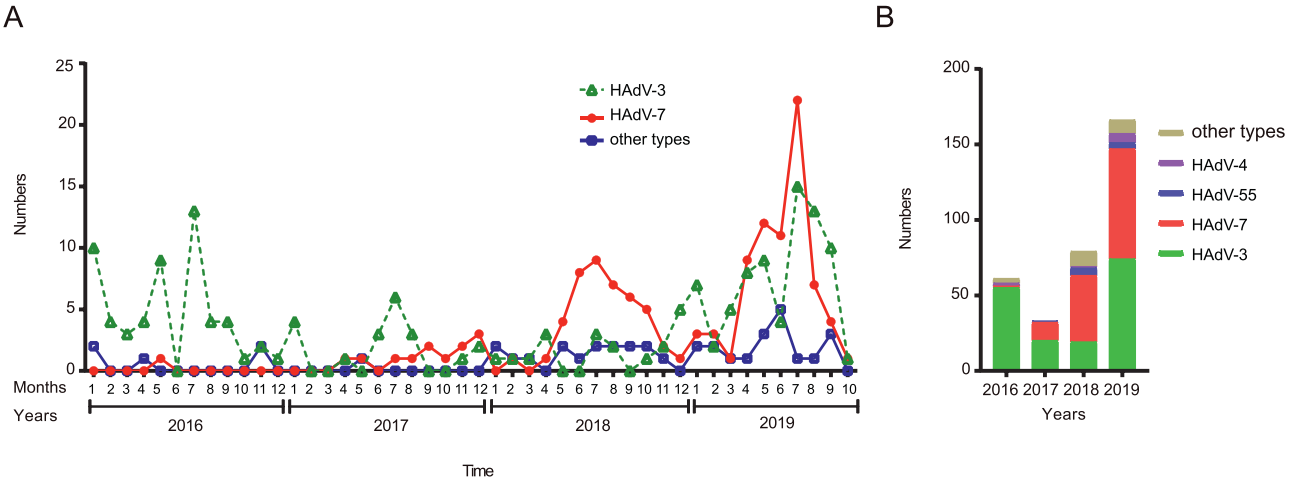

Fig. 1. Human adenovirus (HAdV) infection in children hospitalized with acute respiratory disease in Guangzhou, China between January 2016 and October 2019. **A** Monthly incidence and (**B**) annual incidence of HAdV types.

Table 1
Abnormal liver function in patients infected with adenoviruses.

HAdV types	Number of patients with abnormal levels of indicators/total number of patients (%)						
	ALT (>40 U/L)	AST (>40 U/L)	ALB (<35 g/L)	γ-GT (>50 U/L)	TBil (>22.2 μmol/L)	DBil (>6 μmol/L)	LDH (>255 U/L)
HAdV-3	4/155 (2.58)	48/153 (31.37)	4/97 (4.12)	1/97 (1.03)	2/97 (2.06)	0/96 (0.00)	54/97 (76.1)
HAdV-7	17/128 (13.28)	84/126 (66.67)	19/60 (31.67)	7/60 (11.67)	0/60 (0.00)	1/60 (1.67)	60/70 (85.7)
HAdV-4	1/8 (12.50)	4/8 (50.00)	0/2 (0.00)	0/2 (0.00)	0/2 (0.00)	0/2 (0.00)	5/6 (83.3)
HAdV-55	2/5 (40.00)	3/5 (60.00)	1/3 (33.33)	1/3 (33.33)	1/3 (33.33)	1/3 (33.33)	2/2 (100.0)
Other types	0/14 (0.00)	4/13 (30.77)	4/12 (33.33)	1/12 (8.33)	0/12 (0.00)	0/12 (0.00)	1/2 (50.0)
Total	24/310 (7.74)	143/305 (46.89)	28/174 (16.09)	10/174 (5.75)	3/174 (1.72)	2/173 (1.16)	122/151 (80.8)
P	0.0005	<0.0001	<0.0001	0.0149	0.0008	0.0872	0.4278

HAdV, human adenovirus; ALT, alanine transaminase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct bilirubin; γ-GT, γ-glutamyl transpeptidase; Alb, albumin; LDH, lactate dehydrogenase.
Statistical analysis was performed using GraphPad Prism 7.04 (GraphPad Software, San Diego, USA). Differences between groups were calculated using the chi-square test. *P*-values of <0.05 were considered statistically significant.

Table 2
Abnormal liver function in different groups of patients hospitalized in 2019 with HAdV infection.

Group	Number of patients	Number of patients with elevated indicator (%)			
		ALT (>40 U/L)	AST (>40 U/L)	AST/ALT (>1)	LDH (>255 U/L)
HAdV-single	43	5 (11.6)	27 (62.8)	41 (95.3)	33 (76.7)
HAdV-coinfected	108	8 (7.4)	56 (51.9)	102 (94.4)	89 (82.4)
P		0.404	0.2227	0.8228	0.4253
Severe illness	52	6 (11.5)	39 (75.0)	49 (94.2)	48 (92.3)
Non-severe illness	99	7 (7.1)	44 (44.4)	94 (94.9)	74 (74.7)
P		0.3524	**0.0003**	0.8514	**0.0092**
Total	151	13 (8.6)	83 (55.0)	143 (94.7)	122 (80.8)

HAdV, human adenovirus; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.
Statistical analysis was performed using GraphPad Prism 7.04 (GraphPad Software, San Diego, USA). Differences between groups were calculated using the chi-square test. Two-sided *P*-values of < 0.05 were considered statistically significant.

3.3. Serial monitoring of the liver function in four pediatric patients

More indicators of liver function were analyzed in the 22 children with elevated ALT levels at admission (Table 3). All patients had more than three indicators elevated. γ-GT, TBil, and DBil levels increased in 10 (45.5%), 2 (9.1%) and 4 (18.2%) patients, respectively; Alb levels decreased in 11 (50%) patients. Then four patients with serial monitoring of the LFT results were further analyzed.

Patient 614803 was infected with HAdV-55 and presented with abnormal liver function, suggesting liver damage based on all six abnormal indicators (Table 3). The γ-GT and AST levels remained abnormally high during hospitalization until day 16 (Fig. 3A). ALT, TBil, and DBil levels continued to decrease. TBil and DBil levels returned to normal on day 3, and ALT levels returned to normal on day 12.

Patient 613809 was infected with HAdV-7 and presented with abnormal ALT, AST, and Alb levels at admission (Table 3). However, γ-GT levels continued to increase from day 1 to day 16, and ALT and AST levels remained high from day 1 to day 8 (Fig. 3B). ALT and AST levels decreased from day 8, but remained above the normal range until day 24.

Patient 645868 was infected with HAdV-7 and presented with abnormal liver function, suggesting liver damage (Table 3). γ-GT and ALT levels increased during the first 6 days (Fig. 3C). On day 20, γ-GT, AST, and ALT levels remained abnormal (259.7 U/L, 48 U/L, and 70.5 U/L, respectively). The patient received an infusion of gamma globulin (5 g and 10 g on day 1 and 3, respectively), methylprednisolone (1 mg/kg on day 1 and day 2), dexamethasone (10, 5, 2.5 mg/m^2 on day 3–16, 17–22, and 23–25, respectively), and was mechanically ventilated for 11 days.

Patient 653430 had elevated levels of six liver function indicators on day 1 in the hospital. The patient received treatment with fresh frozen plasma (on day 1), gamma globulin (1 g/kg on day 1 and 3), methylprednisolone (1 mg/kg on day 1–3), magnesium isoglycyrrhizinate injection (0.1–0.2 g/day on day 2–6), and mechanical ventilation for 3 days. However, γ-GT and ALT levels remained abnormal on day 9 (Fig. 3D).

The continuous monitoring further confirms the abnormal LFT results in HAdV-infected children and reminds us of the long-term effects of HAdV infection on liver function.

3.4. The pediatric patient with extremely high liver enzyme levels

Patient 656900 had extremely high liver enzyme levels, indicating severe liver damage (Table 3). Epstein-Barr virus (EBV) DNA, immunoglobulin G (IgG), and IgM were detected in the diagnosis of infectious mononucleosis. After 3 days of hospitalization, the LFT indicators remained at high levels: ALT, 864.9 U/L; γ-GT, 206.6 U/L; TBil, 29.9 μmol/L; and DBil, 12.6 μmol/L. This case suggests a possible role of co-infection of EBV and HAdV-7 in severe liver injury.

4. Discussion

HAdVs may cause fatal respiratory tract infections in immunocompetent children and young adults. In clinical practice, damage to other organs by HAdVs has not received enough attention. This study presents the first statistical analysis of LFT indicators, specifically in children with respiratory HAdV infection. We found that patients with respiratory HAdV infection often had abnormal LFTs, and HAdV-7 or HAdV-55 infection may increase the risk of hepatitis in children. These data may help us to understand hepatitis of unknown cause.

Few cases of hepatitis caused by HAdVs have been previously reported in immunocompetent patients; however, most HAdVs were not typed. In this study, significant differences in abnormal LFT results in patients infected with different HAdV types were reported. HAdV-7 leads to higher levels of liver enzymes, which also contribute to more severe diseases, compared with HAdV-3 (Fu et al., 2019; Liu et al., 2022). In this study, only hospitalized pediatric patients with ARI were included. The association between HAdV types (e.g., HAdV-F41) causing gastrointestinal diseases with hepatitis is also worth further studying. In addition, novel HAdVs that

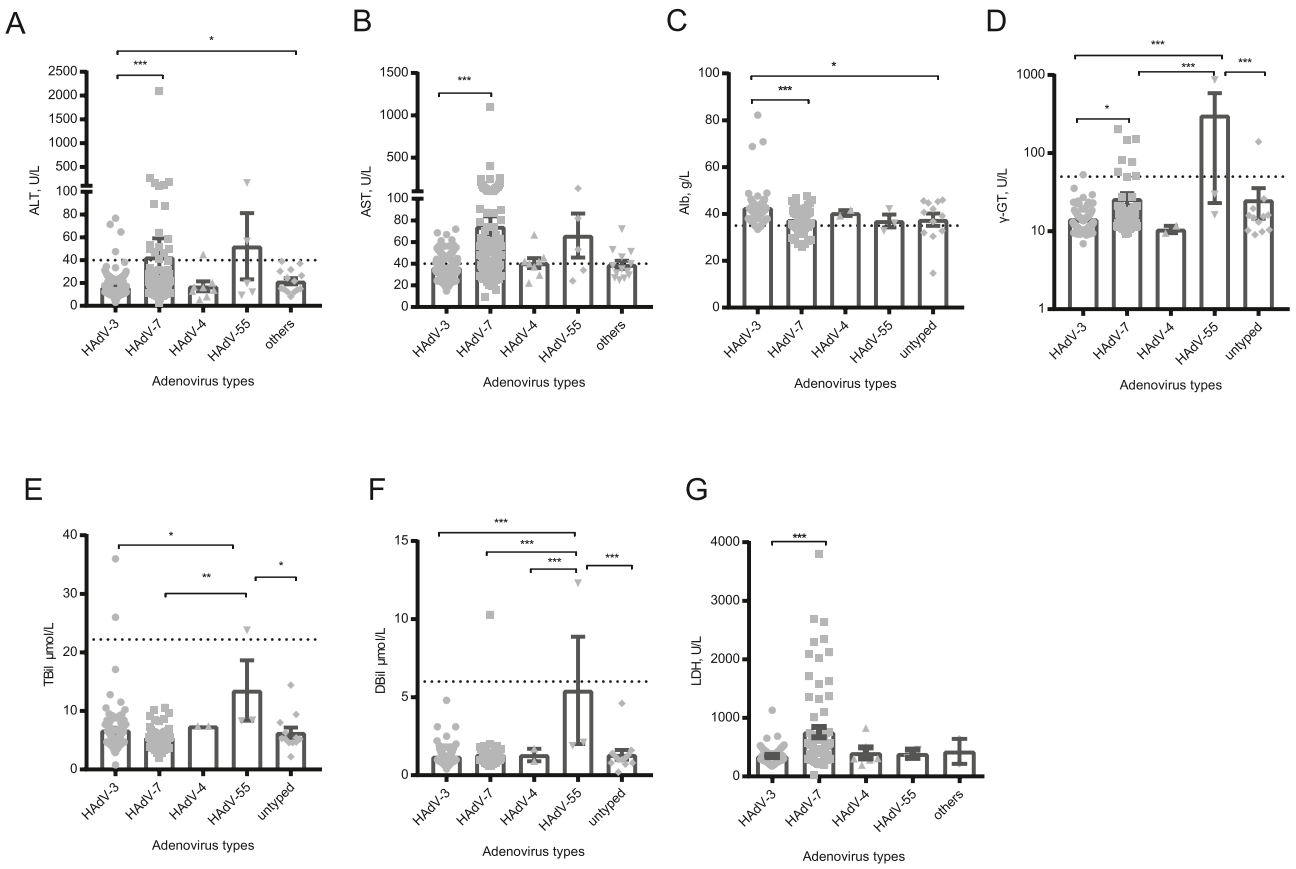

Fig. 2. Liver function test results in immunocompetent children hospitalized for acute respiratory infection of adenovirus. The levels of ALT (**A**), AST (**B**), Alb (**C**), γ-GT (**D**), TBil (**E**), and DBil (**F**) in pediatric patients infected with different HAdV types are shown. Bar represents mean with SEM. Statistical analysis was performed using the two-tailed Mann Whitney test. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ns, no significant difference. ALT, alanine transaminase; AST, aspartate aminotransferase; Alb, albumin; γ-GT, γ-glutamyl transpeptidase; TBil, total bilirubin; SEM, standard error of the mean; HAdV, human adenovirus.

Table 3
Liver function test in patients with elevated alanine transaminase (ALT).

Patient No.	Age (year)	HAdV (types, Ct)	Co-infection	ALT (U/L)	AST (U/L)	γ-GT (U/L)	TBil (μmol/L)	DBil (μmol/L)	Alb (g/L)
656900	5	7 (24.7)	EBV	2090	1094.4	312.9↑	34.4↑	15.8↑	39.9
653521	1.08	7 (22.3)	HBoV	259.3	397.2	14.6	5	0.9	36.3
652453	3	7 (23.12)	n	176.9	202	305.3↑	3.9	1.8	32.2↓
624650	2	7 (25.24)	n	163.4	124	150.8↑	6.2	1	31.8↓
613809	1	7 (24.23)	n	112.3	245.6	11.3	3.4	0.7	31.6↓
573067	2.83	7 (26.85)	n	103.1	172.7	27.6	6.1	1.3	34↓
637487	0.75	7 (27.47)	n	89.2	102.9	45.9	4.4	1.1	40.1
653430	6	7 (19.48)	MP	87.8	208	94↑	6.5	2.1	29.2↓
649542	9	7 (22.86)	n	64.3	134	56.9↑	7.5	2.1	29.1↓
647242	0.33	7 (24.1)	n	58.8	58.9	150.8↑	4.1	0.5	35.4
620768	15	7 (29.37)	n	51.7	15.4	81.1↑	5	1.2	26↓
617889	0.67	7 (26.05)	n	53.2	107.8	12.4	3.6	0.9	34.6
642523	4	7 (19.13)	n	50.2	89.7	18.4	6.5	1.8	37.8
645868	1	7 (16.12)	n	50	241	285.7↑	16.7	10.5↑	30.7↓
620090	1.25	7 (27.12)	n	47.6	57.1	18.4	5.3	1	41
651737	1	7 (22.12)	n	46.1	256.3	28.8	8.5	1.5	27.7↓
614803	0.92	55 (26.17)	n	163.4	137	865.8↑	23.8↑	12.3↑	32.8↓
660175	2.83	55 (24.39)	MP	56.6	82	93.3↑	9.3	2.3	38.5
536891	3.33	4 (24.81)	n	44.9	42	11.7	7.4	1.7	41.6
654143	2.08	3 (25.46)	n	68.6	64.7	5.8	1.4	43.7↑	11.4↓
652708	1.75	3 (22.2)	n	47.5	71.9	9.1	6	1.3	42.2
544089	0.42	3 (21.85)	n	71.4	49.3	22.5	6.5	1.8	43.1

The normal reference value: ALT, 5–40 U/L; AST, 5–40 U/L; γ-GT, 5–50 U/L; TBil, 1.7–22.2 μmol/L; DBil, 0–6 μmol/L; and Alb, 35–55 g/L.
HAdV, human adenovirus; EBV, Epstein-Barr virus; HBoV, human bocavirus; MP, mycoplasma pneumoniae; ALT, alanine transaminase; AST, aspartate aminotransferase; TBil, total bilirubin; DBil, direct bilirubin; γ-GT, γ-glutamyl transpeptidase; Alb, albumin.
n, negative. ↑ and ↓ represent values outside the normal reference range.

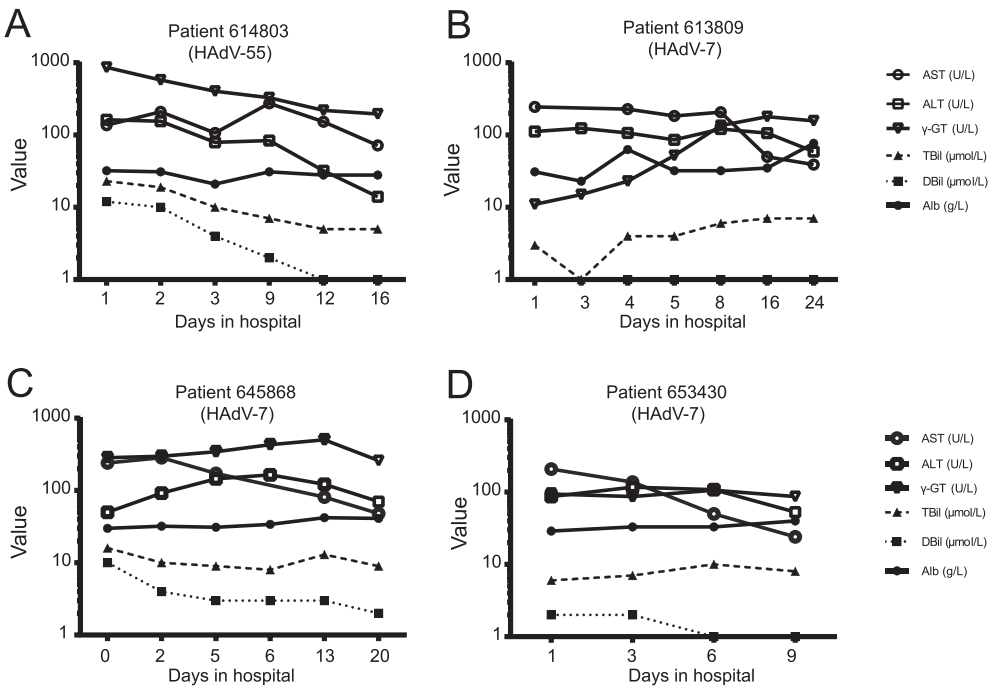

Fig. 3. Serial monitoring of the liver function test results in four children infected with adenovirus type 55 (**A**) or type 7 (**B**–**D**).

lead to acute hepatitis could emerge through recombination. Enhanced testing for adenovirus is required to identify the existing rare outcome that has not been previously detected due to a lack of diagnosis.

Is a high level LFT indicator due to disseminated infection or an inflammatory response in immunocompetent children infected with adenovirus? Adenovirus DNA has been detected in serum samples from 40% to 4.2% of HAdV-7- and HAdV-3-infected children, respectively (Chen et al., 2021). Our recent reports indicate that HAdV-7 and HAdV-55 infections cause more severe disease and deaths than HAdV-3 infection which may be associated with stronger inflammatory responses (Chen et al., 2022; Liu et al., 2022; Zhang et al., 2022). Therefore, we speculate that HAdV-7 not only causes multi-organ immune damage through inflammatory storms but may also lead to direct liver damage through systemic disseminated infection. In future research, blood and liver tissue samples should be collected to validate this hypothesis. In the four patients with serial monitoring of the LFT results, multiple indicators remained abnormal during the entire hospitalization, which reminds us of the long-term effects of adenovirus infection on liver function.

During April to July 2022, outbreaks of severe acute hepatitis of unknown etiology in children were reported in 35 countries. Some studies have suggested an association with HAdVs (Gao et al., 2022). Several recent reports further suggested that the disease is related to co-infections involving AAV2 and HAdV, which is required as a "helper virus" to support AAV2 replication (Ho et al., 2023; Servellita et al., 2023). The high levels of abnormal AAV2 replication products aided by HAdV and in severe cases human herpesvirus 6B may have triggered immune-mediated hepatic disease in genetically and immunologically predisposed children (Morfopoulou et al., 2023). The WHO defined a probable case of acute hepatitis of unknown etiology as acute hepatitis (non-A–E hepatitis) with a serum transaminase level >500 IU/L (AST or ALT). In this study, patient 656,900 presented with an ALT level of 2090.8 U/L, and AST level of 1094.4 U/L, and was positive for EBV. In a recent report, six of nine patients with acute hepatitis of unknown etiology tested positive for EBV DNA (Baker et al., 2022). The present case highlights the role of co-infection of EBV with HAdV-7 on severe liver injury. We found that respiratory HAdV coinfection with other pathogens including MP may contribute to the development of more severe diseases (Liu et al., 2022). Our results highlight the potential role of respiratory adenoviruses, especially HAdV-7 and -55, in acute hepatitis of unknown etiology. Some studies have suggested the role of HAdV-41 in the etiology of SAHUE. However, most studies have not identified HAdV types. Therefore, whether co-infection of respiratory HAdV-7 or -55 with AAV2 may cause severe acute hepatitis should be investigated in the future.

In this study, the sample size of children infected with HAdV-55 was small. More attention should be paid to patients with HAdV-55 infection. In our previous study, a tree shrew animal model intranasally infected with HAdV-55 was established (Li et al., 2021). We retrospectively reviewed the liver pathology section and biochemical examination of liver function for the tree shrews infected with HAdV-55. The ALT, AST, TBil, and DBil levels in one of six tree shrews infected with HAdV-55 were significantly increased (213 U/L, 175 U/L, 1.3 μmol/L, and 0.6 μmol/L, respectively). This animal showed widespread and patchy necrosis with minimal inflammatory cell infiltration and eosinophilic nuclear changes in hepatocytes, indicating hepatitis (Supplementary Fig. S1A–C). It is unclear whether the hepatitis was caused by the inflammatory response or direct damage by the virus. Tree shrews may be a suitable model for a better understanding of the pathogenesis of hepatitis induced by HAdV, as they have been used as an animal model for hepatitis viruses (e.g., hepatitis B virus, hepatitis C virus, hepatitis E virus).

5. Conclusions

Our results highlight that respiratory HAdV infection, especially HAdV-7 and HAdV-55, often leads to abnormal LFT results in children. Thus, more attention should be paid to liver damage caused by co-infection involving respiratory HAdVs and AAV2 or more viruses in future work.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

The study was approved by the First Affiliated Hospital of Guangzhou Medical University Ethics Committee. Next of kin, caretakers, or guardians provided written informed consent for participation in the study on behalf of all minors/children.

Author contributions

Xingui Tian: conceptualization, methodology, funding acquisition, visualization, writing-original draft and editing. Xiao Li: data curation, investigation. Shuyan Qiu: investigation, data curation. Rong Zhou: supervision. Wenkuan Liu: software, validation, writing-reviewing and editing.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.virs.2023.07.007.

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