

# The Detection of Adenovirus Type 41 in Children with Acute Hepatitis of Unknown Etiology: The First Report from Southwest Iran

## Abstract

**Background:** Efforts continue to determine the cause of the rising number of instances of acute hepatitis of unknown etiology in healthy children nationwide. Human adenoviruses (HAdV), namely HAdV F-41, are proposed as potential causes. **Aim:** This research examined the link between HAdV and acute hepatitis of unknown etiology in children in southwest Iran. **Materials and Methods:** The study was conducted on children diagnosed with acute hepatitis of unknown etiology in the cities of Kerman and Yazd between February 20, 2023, and January 20, 2024. A standardized questionnaire was used to collect information on symptoms, and laboratory test results were also obtained. Blood and stool samples were obtained for viral detection using real-time polymerase chain reaction following DNA extraction. **Results:** This investigation consisted of 20 children diagnosed with acute hepatitis of unknown etiology. The children had a median age of  $6.8 \pm 5.7$  years, ranging from 8 months to 16 years, and 14 of these patients were male. Among the clinical symptoms, fever, diarrhea, and jaundice were the most common symptoms among patients. Aspartate aminotransferase and alanine transaminase testing revealed values above 500 IU/L in 70% of the individuals. The HAdV genome was found in the samples of 20% of the patients, with three of four HAdV-positive isolates confirming the presence of HAdV F-41. Finally, 17 patients were discharged, two had a liver transplant, and one patient passed away. **Conclusions:** A potential link between HAdV F-41 and acute hepatitis of unknown etiology is indicated. The results necessitate a revision of protocols to reduce complications.

**Keywords:** Adenovirus infections, adenovirus type 41, disease outbreaks, etiology, hepatitis, human

## Introduction

The acute inflammation of the liver tissue or damage to hepatocytes, which may lead to increased liver function markers, is called acute hepatitis. The disease can result from microbial agents such as viruses or other factors. When well-known causes of hepatitis are ruled out, the disease is classified as “acute hepatitis of unknown etiology.<sup>[1]</sup>”

A pediatric hospital in Alabama reported cases of severe acute hepatitis of unknown etiology from October to November 2021.<sup>[2]</sup> By March 31, 2022, 13 children under the age of 10 years had been diagnosed with acute hepatitis of unknown etiology in Scotland.<sup>[3]</sup> Since then, a substantial rise in cases has been observed, with 191 probable cases detected in several other countries.<sup>[4]</sup> The total number of recognized possible cases of acute hepatitis of unknown etiology now exceeds 1200.<sup>[5]</sup> If the patients

are children under 16 years old with aspartate aminotransferase (AST) or alanine transaminase (ALT) levels above 500 IU/L since October 1, 2021, and laboratory tests are negative for hepatitis A–E, reports classify them as probable epidemic cases.<sup>[1]</sup>

Prevention and management of this outbreak are only achieved through recognition of the underlying cause of the disease. Given that some children have needed liver transplants and, in some cases, have died following this disease, research in this area is of high importance.<sup>[6]</sup>

The human adenovirus (HAdV), with a linear, double-stranded DNA genome of 34–37 kb pairs and an icosahedral capsid shape, consists of multiple serotypes fitting species A–G.<sup>[7,8]</sup> The infection caused by these viruses is typically restricted to temporary upper respiratory, ocular, or gastrointestinal (GI) disorders unless the individual is immunocompromised. In that case, adenovirus has been linked with

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severe infections that affect several organs, leading to noteworthy illness and death. Children are the main targeted age group, and immunity from infection is exclusive to the specific serotype.<sup>[9]</sup>

Most of the patients reported in the current epidemic of severe acute hepatitis had a healthy background; however, many were positive for HAdV, especially adenovirus F-41.<sup>[3,4]</sup> To date, a decisive relationship between adenovirus infection and acute hepatitis in healthy children has not yet been proven. Nevertheless, results suggest that HAdV viral infection could be one of the most possible etiologies.<sup>[6]</sup>

Despite the Tehran Children's Medical Center's published protocol of clinical guidelines and diagnostic algorithm for acute hepatitis with unknown origin in children, hepatitis caused by HAdV infection has not been systematically investigated in Iran.<sup>[1]</sup> As a result, there is limited information on whether incidences of hepatitis similar to those in other countries have happened in this country. However, a pediatric hospital in Tehran, Iran, has identified two 12-year-old children and a 6-year-old kid with severe acute hepatitis of unknown etiology from March 12, 2022, to May 8, 2022.<sup>[10]</sup> It is essential to immediately start monitoring children for HAdV, considering the possibility of acute severe hepatitis.

This study aimed to investigate the origin of acute hepatitis of unknown etiology in children in southwest Iran (Kerman and Yazd). Our goal was to explore any possible relationship between HAdV and acute hepatitis of unknown etiology.

## Materials and Methods

### Study population

From February 20, 2023, to January 20, 2024, blood and stool samples were gathered from 20 pediatric patients diagnosed with acute hepatitis at Afzalipour Hospital (Kerman University of Medical Sciences) and the Medical Centers of Yazd city. All patients provided informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kerman University of Medical Sciences (reference number: 1401.170, date: September 02, 2023).

Each patient's paraclinical test findings and assessments of disease-related parameters, such as ALT and AST levels, were documented.

Participants meeting the specified criteria were included: typical symptoms of acute hepatitis as reported by the World Health Organization (WHO) (vomiting, jaundice, diarrhea, and abdominal pain); liver enzymes (AST or ALT) increased to levels exceeding 500 IU/L; under the age of 16 years; and negative for hepatitis B surface antigen, hepatitis C virus antibody, ceruloplasmin serum, antinuclear antibody, anti-smooth muscle antibody, anti-LKM1, and serum protein electrophoresis tests.<sup>[11]</sup>

Patients with any of the following criteria were excluded: positive for any other viral hepatitis (A-E), infection with cytomegalovirus or Epstein-Barr virus, vascular causes of acute hepatitis, drug toxicities, metabolic diseases, immune deficiency, treatment with antiviral drugs, and failure to comply with cold chain transfer and sample isolation procedures.

### Data collection

A structured questionnaire was used to collect demographic information (age, sex, and place of residence) and clinical details of jaundice, vomiting, pale stool, diarrhea, abdominal pain, nausea, fever, respiratory symptoms, hepatomegaly, splenomegaly, acute liver failure (ALF), symptom duration, disease severity, and disease outcome. Laboratory test results (ALT, AST, alkaline phosphatase [ALP], total bilirubin, direct bilirubin, albumin, prothrombin time [PT], partial thromboplastin time [PTT], and international normalized ratio [INR]) were also collected.

### Collection of samples

Specimens of blood and stool obtained from individuals previously diagnosed with acute hepatitis were immediately delivered to the laboratory while ensuring the maintenance of optimal temperature conditions to facilitate molecular testing.

### Sample preparation and extraction of DNA

Following arrival, blood and stool samples were prepared. The FAVORGEN DNA extraction kit (Taiwan) was used to extract DNA from stool and whole blood samples, following the procedure provided by the manufacturer. The extracted genomes were preserved at  $-70^{\circ}\text{C}$ .

### Detection of human adenovirus in blood and stool samples

The detection of adenovirus genomes in stool and whole blood samples was accomplished by SYBR Green real-time polymerase chain reaction (PCR) utilizing particular primers for adenoviruses A-F. The reaction mixture included RealQ Plus 2× Master Mix, primers, water, and the genome. The real-time PCR protocol consisted of an initial denaturation step at  $95^{\circ}\text{C}$  for 15 min, followed by 45 cycles ( $95^{\circ}\text{C}$  for 10 s,  $55^{\circ}\text{C}$  for 30 s, and  $72^{\circ}\text{C}$  for 15 s).<sup>[12]</sup> Both positive and negative controls were included in the experiment to ensure accuracy. The quality of the results was then verified using electrophoresis on an agarose gel.

### Adenovirus typing

Real-time PCR was used for adenovirus typing, using distinct primers for each type. The real-time PCR protocol consisted of an initial denaturation step at  $95^{\circ}\text{C}$  for 15 min, followed by 45 cycles ( $95^{\circ}\text{C}$  for 5 s,  $45^{\circ}\text{C}$  for 10 s, and  $72^{\circ}\text{C}$  for 5 s).<sup>[12]</sup> Positive and negative controls and appropriate quality control measures were used.

## Statistical analysis

The normal distribution was evaluated using the Kolmogorov–Smirnov test. Fisher’s exact test, *t*-test, ANOVA, Mann–Whitney *U*, and Kruskal–Wallis tests were used as appropriate. The correlation coefficient (Pearson and Spearman) was used to determine the strength of the linear relationship between variables. The significance threshold was established at 0.05, and data analysis was conducted using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA).

## Results

### Patient characteristics and clinical outcomes

This cross-sectional investigation included 20 children below the age of 16 who were diagnosed with acute hepatitis of unknown etiology and met the inclusion criteria. These children were admitted to the pediatric department of Afzalipour Hospital in Kerman and the medical centers in Yazd. The median age at admission was  $6.8 \pm 5.7$  years (with a minimum age of 8 months and a maximum of 15 years). Among admitted patients, 14 were male, with a median age of 5.5 years, and six were female, with a median age of 7.7 years. Most patients (16 children) resided in urban areas, while four lived in the neighboring villages [Table 1]. The average hospitalization period for

**Table 1: Demographic characteristics of the studied patients**

Parameters	<i>n</i>	<i>P</i>
Age (month)		
$\geq 1$ – $< 12$	2	0.074
$\geq 12$ – $< 24$	8	
$\geq 24$	10	
Gender		
Male	14	0.074
Female	6	
Place of residence		
Urban	16	
Rural	4	

the patients was 9 days. Most of the patients were admitted with severe medical issues, as shown in Tables 2 and 3. Ultimately, 17 patients recovered, two patients received a liver transplant, and one patient passed away.

### Clinical presentations

The most common clinical signs were fever, diarrhea, and jaundice observed in 16, 12, and 12 patients, respectively. Additional symptoms were vomiting, abdominal pain, pale stool (10 patients), and nausea (eight patients). Hepatomegaly, splenomegaly, and hepatic encephalopathy were examined as additional symptoms, as shown in Table 2.

### Laboratory test results

A range of laboratory tests, such as ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, PT, PTT, and INR, were conducted, as shown in Table 3. ALT and AST showed the most significant changes, with elevations exceeding 500 IU/L observed in 70% of the patients (14 out of 20 cases).

### Human adenovirus detection results

The HAdV genome was detected in the blood and stool samples of four of the 20 patients, with only one sample showing positive results for both blood and stool samples and three having positive results only for blood samples. Of the patients that tested positive for HAdV, two were female, the other two were male, and two were under 1 year old. Table 4 displays the clinical presentation and laboratory findings of individuals who tested positive and negative for HAdV. Distinct primers for individual HAdV types were used to identify the specific viral type. Molecular findings showed that three out of four HAdV-positive isolates were positive for HAdV F-41, a highly enteric strain that primarily transmits through the ingestion of feces. HAdV F-41 mainly affects the intestines and manifests symptoms such as fever, vomiting, and diarrhea.

## Discussion

Since October 2021, cases of severe acute hepatitis of

**Table 2: Clinical presentations of the studied patients**

Parameters	Age $< 24$ months ( <i>n</i> )	Age $\geq 24$ months ( <i>n</i> )	<i>P</i>	Male ( <i>n</i> )	Female ( <i>n</i> )	<i>P</i>
Jaundice	4	8	0.170	8	4	1.000
Vomiting	6	4	0.656	8	2	0.628
Diarrhea	8	4	0.170	8	4	1.000
Abdominal pain	2	8	0.023	8	2	0.628
Nausea	6	2	0.170	6	2	1.000
Fever	10	6		12	4	0.549
Respiratory manifestations	2	6	0.170	6	2	1.000
Hepatomegaly	6	2	0.170	6	2	1.000
Splenomegaly	0	0	N/A	0	0	N/A
ALF	6	2	0.170	6	2	1.000
Pale stool	8	2	0.023	6	4	0.628

ALF: Acute liver failure, N/A: Not available

**Table 3: Laboratory tests results of the studied patients**

Parameters	Mean±SD
ALT (IU/L)	3236±4464
AST (IU/L)	5136±10,472
ALP (IU/L)	534±200
Total bilirubin (mg/dL)	3.8±2.5
Direct bilirubin (mg/dL)	2.6±2.6
Albumin (g/dL)	3.5±0.4
PT (s)	29±20
PTT (s)	59±38
INR	2.6±1.9

ALF: Acute liver failure, ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio, SD: Standard deviation

unknown etiology have started to increase around the globe.<sup>[2]</sup> The outbreak revolves around children with no prior health issues and under 16 years old. The main features include liver enzymes increasing to levels above 500 IU/L, with negative results for hepatitis A-E.<sup>[1]</sup> In the current research, the origin of acute hepatitis of unknown etiology in children in southwest Iran was investigated. The study focused on investigating the connection between HAdV and the disease.

Adenoviruses are not commonly associated with hepatitis and typically cause self-limited illnesses, especially in immunocompetent individuals.<sup>[13]</sup> Nevertheless, the high number of HAdV-positive cases in different countries introduced adenoviruses, particularly the HAdV F-41 serotype (which causes gastroenteritis in children and can be fatal in infants), as a possible origin of the outbreak.<sup>[14-16]</sup>

In the current study, four out of 20 cases were positive for HAdV, and three HAdV-positive cases were positive for HAdV F-41. These findings further suggest the possibility of HAdV F-41's association with the outbreak. The management protocol for patients in our study primarily involved supportive care, which included managing symptoms, maintaining fluid and electrolyte balance, and closely monitoring for complications such as coagulopathy and encephalopathy. In severe cases where ALF developed and supportive care and intensive care unit admission were insufficient, liver transplantation was considered a life-saving option.

Despite the relatively small study population size and the limited geographical scope of the investigation, the findings highlight the importance of considering HAdV infections in diagnosing acute hepatitis of unknown etiology. Cases that tested positive for HAdV suggest a potential link between adenovirus infections and acute hepatitis of unknown etiology. However, the cause of this link is still unknown, so more research is needed.

The prevalence of acute hepatitis of unknown etiology in the southwest of Iran, with the identification of 20 patients,

**Table 4: Demographic characteristics and clinical symptoms of the studied patients based on the presence and absence of adenovirus**

Parameters	Adenovirus positive cases (n)	Adenovirus negative cases (n)	p
Age (month)			
≤24	2	8	1.000
≥24	2	8	
Gender			
Male	2	12	0.459
Female	2	4	
Place of residence			
Urban	4	12	0.056
Rural	0	4	
Jaundice	4	8	0.068
Vomiting	2	8	1.000
Diarrhea	4	8	0.068
Abdominal pain	4	6	0.025
Nausea	2	6	1.000
Fever	4	12	0.263
Respiratory manifestations	2	6	1.000
Hepatomegaly	2	6	1.000
Splenomegaly	0	0	N/A
ALF	2	6	1.000
Pale stool	2	8	1.000
Death	1	0	N/A
Need for liver transplantation	2	0	N/A
ALT (IU/L)	2345	3458	0.28
AST (IU/L)	1731	5987	0.22
ALP (IU/L)	549	528	0.8
Total bilirubin (mg/dL)	6.2	3	0.74
Direct bilirubin (mg/dL)	4.7	1.9	0.1
Albumin (g/dL)	2.5	3.4	0.053
PT (s)	16.8	33.6	0.051
PTT (s)	32.5	68	0.05
INR	1.2	3.1	0.00

ALT: Alanine transaminase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio, ALF: Acute liver failure, N/A: Not available

is less than that of several regions in the world, such as the United States and the United Kingdom, and more than regions like Rome.<sup>[4,17]</sup> Among the 20 patients identified in 1 year, 17 were finally discharged, two patients received a liver transplant, and one patient died. The patient died due to ALF, kidney failure, cerebral edema, elevated intracranial pressure, infection, and GI bleeding following adenovirus-associated hepatitis. According to the reports of various studies and the WHO, the average death rate for this infection is between 1% and 2%. However, the mortality rate was slightly higher (5%) in our study. According to the latest report from the WHO, among cases identified worldwide, 5% have undergone liver transplantation, and 2% have died.<sup>[18]</sup> In this study, liver transplantation was

considered for two cases due to the significant and rapid liver failure, coagulopathy, and hepatic encephalopathy that did not improve after supportive treatment.

The median age for admission in this study was reported to be 6.5 years. The results highlight the young age of the affected children. In general, acute hepatitis of unknown etiology occurs more often at younger ages.<sup>[19]</sup> The young age of patients can suggest the role of exposure to infectious agents and genetic background in this disease. Adeno-associated virus 2 (AAV2) infection (which needs HAdV as a helper virus to support AAV2 replication) association with the class II HLA allele HLA-DRB1 \* 04:01 in acute hepatitis of unknown etiology has been reported in the past.<sup>[20]</sup> Although more research needs to be done, this hypothesis gives us a different way to look at how HAdV might have been involved in this outbreak. It suggests an indirect rather than a direct cytopathic effect, which is more likely for HAdV.<sup>[21]</sup>

Scleral icterus, hepatomegaly, jaundice, vomiting, pale stool, diarrhea, abdominal pain, and nausea were the most common symptoms in patients with acute hepatitis of unknown etiology reported in previous studies.<sup>[2,3,22]</sup> The symptoms observed in this research aligned with those observed in other studies. However, fever, an uncommon symptom in acute hepatitis of unknown etiology, was the most common presentation observed. Of course, the increase in liver enzymes and factors was expected. However, ALT, AST, total bilirubin, and direct bilirubin were particularly increased, consistent with findings from other reports of this outbreak.<sup>[1]</sup> In addition, it was observed that nearly half of the patients without adenovirus developed ALF, whereas two adenovirus-positive patients showed ALF. ALF was identified based on signs of the liver's synthetic function loss, including a rapid onset of severe liver dysfunction within days to weeks, elevated liver enzyme levels (AST and ALT typically exceeding 500 U/L), coagulopathy with an INR >1.5, the presence of hepatic encephalopathy, hypoalbuminemia, hypoglycemia, and hyperbilirubinemia. Previous studies have found no significant link between adenovirus-positive results and ALF.<sup>[23]</sup> Moreover, the specific population in southwest Iran, where the study was conducted, may have distinct epidemiological or genetic factors that influence the progression of hepatitis. However, further studies are necessary to examine outcomes in larger sample sizes and more diverse populations in order to gain a better understanding of the underlying reasons for the progress of hepatitis of unknown origin toward ALF.

In conclusion, while the association of HAdV with acute hepatitis of unknown etiology is not yet fully proven, our results propose a probable connection. A review of the diagnostic and management protocols for such cases and consideration of adenovirus infections is needed to help better understand the disease and manage and prevent

complications resulting from the disease, such as liver transplantation and death.

## Conclusions

The study suggests a connection between HAdV, in particular the HAdV F-41 subtype, and the ongoing outbreak of acute hepatitis of unknown etiology in children younger than 16 years old. The symptoms reported in our study were in line with earlier reports, with some discrepancies, such as fever. High levels of ALT, AST, total bilirubin, and direct bilirubin align with the main factors reported in this outbreak, further supporting a potential connection to HAdV. Although the association between HAdV and acute hepatitis of unknown etiology needs additional proof, the results of this study highlight the requirement for a revision of diagnostic and management procedures to prevent complications such as liver transplantation and death.

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## Conflicts of interest

There are no conflicts of interest.

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