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Research Article

Comparative Analysis of Hepatitis E and A in Children: Clinical Manifestations and Epidemiological Patterns in Kyrgyzstan

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A B S T R A C T

Introduction: Viral hepatitis E (HEV) poses a significant global health challenge with limited research on its impact on children. This retrospective study aimed to identify the clinical and laboratory features of HEV in children and compare them with those of hepatitis A virus (HAV) infections in the Kyrgyz Republic.

Methods: Clinical and laboratory data from children diagnosed with HEV (n=31) and HAV (n=42) at the three regional hospitals were analyzed.

Results: HEV cases were predominantly male (74.1%), aged 1-5 years (42%), and from rural areas (77.4%), while HAV showed no significant gender or urban-rural disparity. HEV patients experienced a more severe clinical course, with 13% classified as severe compared with 4.7% of HAV cases. HEV infection resulted in prolonged symptom duration during the pre-jaundice and jaundice phases, with longer periods of fever, weakness, decreased appetite, vomiting, and abdominal pain (P<0.05). Blood biochemistry revealed higher total and indirect bilirubin levels in HEV patients (P<0.05) and lower total protein levels in severe HEV cases (P<0.05). The mean hospitalization duration was longer for HEV (17.2±1.3 days) than HAV (12.7±1.2 days; P<0.05).

Conclusion: The study found the clinical manifestations of children with HEV were severe and longer in duration as compared to children with HAV. These findings highlight the importance of timely diagnosis of HEV and preventive measures, particularly in rural areas.

Keywords: Viral Hepatitis E, Acute Viral Hepatitis, Hepatitis A Virus, Children, Seroprevalence

Introduction

Viral hepatitis E (HEV) presents a critical challenge for healthcare systems worldwide.[1–6] The symptoms of the disease range from asymptomatic and mild to severe, with a fatality rate of approximately 1%.[7,8]

HEV is a non-enveloped RNA-containing pathogen that induces both acute and chronic hepatitis. HEV has four distinct genotypes; HEV1 and HEV2 are primarily waterborne and affect individuals in developing nations. HEV1 is prevalent in Asia, whereas HEV2 is common in Africa and Mexico.[1,9] Globally, up to 20 million cases of Acute viral hepatitis C (HCV) infection have been reported annually, resulting in 70,000 fatalities.[2,3]

HEV1 and HEV2 cause anthroponotic hepatitis E, whereas HEV3 and HEV4 are zoonotic infections transmitted via the fecal-oral route in animals. Infection often occurs through consumption of undercooked pork liver, pork meat, or deer. HEV4 may also spread via aquatic transmission.[10,11]

In developed countries, acute viral hepatitis A (HAV) tends to manifest more severely in middle-aged and elderly men,[10,12] with patients in England averaging 63.5 years old.[13] Hepatitis caused by HEV3 and HEV4 is asymptomatic in 67–98% of cases.[11]

Research on HEV infection in children is limited because most studies have focused on adults. Clinically evident forms of HEV infection are uncommon in children. However, during epidemics in Uganda, HEV-related deaths in children under two years of age reached 25%.[14] In one-third of newborns, HEV infection can be extremely severe and potentially fatal.[15]

A regional study from Egypt found HEV infection to be common among preschool children, particularly those in rural areas with animal contact.[16] Conversely, Argentina has reported a low prevalence of HEV among urban children.[17]

In the Kyrgyz Republic, an analysis of HEV infection seroprevalence among HV cases from to 2015 - 2020 revealed that 16.2% (n=25 out of 154) of the examined children aged 0 to 14 years were seropositive. The highest seroprevalence was observed in children aged 1–5 years (8.4%), decreasing with age: 7.8% in 6–10 years and 4.5% in 11–15 years.[18]

All epidemiological studies on HEV infection in the Kyrgyz Republic were conducted at the Scientific and Practical Center for Viral Infection Control for scientific purposes. Comprehensive epidemiological and clinical studies of the general population have not been performed because of the unavailability of HEV verification test systems. Consequently, this disease has not been officially registered in the country.

Research on the clinical presentation of HEVs in children is limited. In the Kyrgyz Republic, HEV monitoring is challenged by limited screening programs and diagnostic capabilities. Despite seroprevalence studies indicating HEV circulation among children, there is no national registry available. The effects of HEV on children remain unknown, and the lack of clinical studies has hindered the development of prevention and management strategies. HAV is endemic to the area, making it essential to distinguish between HEV and HAV in children for proper diagnosis and treatment. Although HAV is a recognized cause of pediatric hepatitis, the clinical differences between HEV and HAV infections have not been thoroughly examined. In light of this, the current study, which examines the clinical and laboratory characteristics of HEV infection in children and compares them to HAV infection in the present context, is timely and necessary.

Materials and Methods

A retrospective analysis was conducted of clinical and laboratory data from children diagnosed with HEV (n=31) and HAV (n=42) at the Department of Infectious Diseases in three regional hospitals located in Osh, Jalal-Abad, and Batken, Bishkek, Kyrgyzstan.

This study focused on children aged 0-14 diagnosed with HEV or HAV. The diagnosis was verified through serological tests: HEV by anti-HEV IgM and HAV by anti-HAV IgM. Eligible participants were admitted to infectious disease units at the Osh, Jalal-Abad, and Batken Regional Clinical Hospitals. Only cases with comprehensive clinical, epidemiological, and laboratory data were included in this analysis.

This study excluded patients with coinfections of other viral hepatitis types (B, C, and D), as confirmed by serology. Children with chronic liver conditions, metabolic disorders, congenital liver anomalies, or immunosuppression were omitted because of their potential impacts on disease progression and laboratory results. Cases lacking complete medical records or definitive laboratory confirmation of HEV or HAV were not considered. Patients who had undergone antiviral treatment before hospitalization were excluded to prevent confounding effects on disease course and laboratory findings.

HEV in pediatric cases was verified through serological tests that detected HEV infection markers in the serum of patients with HV (n=5765) who were negative for hepatitis A, B, D, and C markers. These data were gathered from 2000-2008 as part of the sentinel epidemiological surveillance in the Republic in partnership with the United States Centers for Disease Control and Prevention during seasonal spikes of HV in endemic areas of the Republic.

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Blood serum samples were examined using enzyme immunoassay (EIA) methods to identify various markers, traveled beyond the southern Kyrgyz Republic or had contact with patients with HV. All participants reported occasional consumption of unboiled water and unwashed fruits. In contrast, 69.0% of HAV-infected children reported contact with patients in organized groups, whereas 31.0% could not identify the infection source.

Regarding disease severity, 65% of HEV cases were classified as moderate, 13% as severe, and 22% as mild (Figure 1). For HAV, moderate cases also predominated (59%), but severe cases were less frequent (4.7%), and mild cases were more common (36.3%).

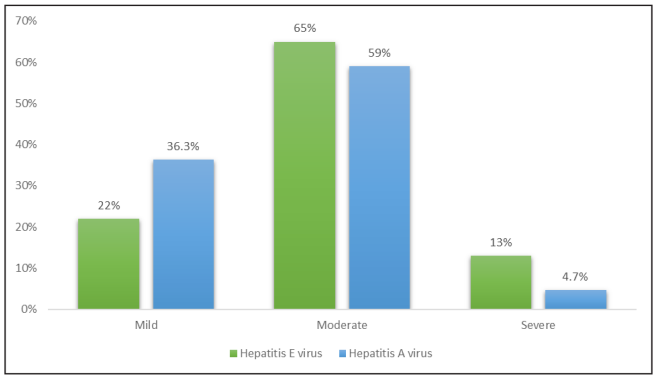

Figure 1. Severity of HEV and HAV infection in children

In 42% of children with HEV, the disease progressed slowly, while 58% experienced sudden onset. The initiation was similar to that of HAV. Both HEV and HAV in children exhibit cyclic pattern characteristics of HV. Comparing the pre-icteric phase in children with HEV to those with HAV, a specific prevalence of certain symptoms was noted, as illustrated in Table 1.

During the pre-jaundice stage of HEV and HAV, patients exhibited symptoms of intoxication and dyspeptic disorders with similar frequencies of fever, headache, reduced appetite, vomiting, anorexia, and nosebleeds. However, patients with HEV experienced significantly longer durations of certain symptoms than those with HAV. These included headache (3.0±0.1 vs 2.7±0.1 days, $p<0.05$), weakness (5.0±0.4 vs 3.0±0.2 days, $p<0.001$), decreased appetite (4.6±0.3 vs 3.2±0.5 days, $p<0.05$), vomiting (3.1±0.2 vs 2.0±0.2 days, $p<0.05$), abdominal pain (4.1±0.2 vs 1.7±0.2 days, $p<0.001$), joint pain (3.0±0.3 vs 1.7±0.2 days, $p<0.005$), nosebleeds (2.1±0.2 vs 1.4±0.1 days, $p<0.05$), and epigastric pain (4.1±0.2 vs 1.8±0.2 days, $p<0.001$). As the pre-jaundice period concluded, patients noticed changes in urine and fecal color. This period was longer in HEV (6.2±0.3 days) than in HAV (5.3±0.2 days, $p<0.05$).

When jaundice began, children with HEV displayed intensified intoxication symptoms, unlike those with HAV. Table 2 shows the frequency and duration of clinical symptoms during the jaundice period in children with both HEV and HAV.

Examination of the jaundice phase revealed that the symptoms lasted longer in the HEV cases than in the HAV cases. Table 2 indicates significantly extended durations of elevated body temperature (3.6±0.2; 2.7±0.1 $P<0.05$), fatigue (5.2±0.4; 3.0±0.1 $p<0.01$), reduced hunger (4.3±0.4; 3.0±0.2 $P<0.05$), emesis (4.1±0.3; 2.1±0.1 $p<0.05$), and discomfort in the right upper abdominal region (5.2±0.4; 3.0±0.3 $p<0.05$).

During the jaundice stage of HEV, a slight negative correlation was observed between increased body temperature and pruritus ($r= -0.35$), whereas a weak positive correlation was noted with epistaxis ($r= 0.37$).

In children with HEV, jaundice was classified as mild in 22%, moderate in 65%, and severe in 13%, persisting for 16.8±1.0 days. Liver enlargement was detected in 93% of the affected children, with over half (61.2%) experiencing tenderness upon palpation and a predominantly soft consistency, while 38.8% had a firm, elastic liver. Spleen enlargement was noted in 45.1% of the patients, extending 1.5-2.0 cm below the rib cage. The jaundice phase in children with HEV lasted longer than in HAV, spanning 15.8±1.4; 11.6±1.3 days ($p<0.05$).

Blood count analyses for patients with HEV and HAV showed no substantial deviation from normal values.

Analysis of blood biochemistry showed that children with HEV had significantly higher total bilirubin levels than those with HEV (98.1±8.5 vs 74.3±6.2; $p<0.05$) (Table 3). Additionally, indirect bilirubin was also elevated in HEV cases (39.0±3.5 vs 18.9±2.1; $p<0.05$).

Liver enzymes and thymol levels were elevated in both HEV and HAV patients, but no significant differences were found between the groups. Total protein and prothrombin index were evaluated in patients with HEV and HAV according to illness severity. The total protein index was significantly lower in HEV compared to HAV - 58.7±3.0 and 72.0±2.5, respectively ($p<0.05$). Total bilirubin levels showed a moderate negative correlation with total protein levels ($r= -0.62$) and prothrombin index ($r= -0.71$).

During their hospital stay, the patients received standard care, including a prescribed diet and regimen. Severe cases of both HEV and HAV were treated using detoxification therapy. None of the patients required antiviral therapy. The mean duration of hospitalization was 17.2±1.3 days for HEV patients and 12.7±1.2 days for HAV patients ($p<0.05$). After receiving basic therapy, all children with HEV and HAV infections were discharged from the hospital in satisfactory condition.

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Table 1. Clinical manifestations and duration of symptoms in the pre-jaundice period in HEV and HAV-infection in children

Clinical symptoms	Frequency of symptoms (%)		Duration (in days m±SD)				p-value
	HEV	HAV	HEV	95% CI	HAV	95% CI	
Increase in body temperature	87.0	80	2.7±0.2	2.3-3.1	2.5±0.1	2.3-2.7	>0.05
Headache	70.0	71	3.0±0.1	2.8-3.2	2.7±0.1	2.5-2.9	<0.05*
Weakness	90.3	66.6	5.0±0.4	4.2-5.8	3.0±0.2	2.6-3.4	<0.001
Decreased appetite	84.0	80	4.6±0.3	4.0-5.2	3.2±0.5	2.2-4.2	<0.05*
Anorexia	16.0	14.0	1.7±0.4	0.9-2.5	1.1±0.2	0.6-1.4	>0.05
Nausea	71.3	69.0	3.2±0.2	2.8-3.6	2.5±0.3	1.9-3.1	>0.05
Vomiting	61.0	59.5	3.1±0.2	2.7-3.5	2.0±0.2	1.6-2.4	<0.05*
Itchy skin	9.6	21.4	3.3±0.4	2.5-4.1	2.0±0.2	1.6-2.4	>0.05
Abdominal pain	74.2	50.0	4.1±0.2	3.7-4.5	1.7±0.2	1.3-2.1	<0.001
Catarrhal phenomenon	12.0	23.8	3.0±1.3	0.4-5.6	2.7±0.3	2.1-3.3	>0.05
Joint pain	38.7	14.2	3.0±0.3	2.4-3.6	1.7±0.2	1.3-2.1	<0.05*
Nosebleeds	13.0	11.0	2.1±0.2	1.7-2.5	1.4±0.1	1.2-1.6	<0.05*
Epigastric pain	76.2	42.8	4.1±0.2	3.7-4.5	1.8±0.2	1.4-2.2	P <0.001

Values are expressed as the % and mean (m)±standard deviation (SD). HEV – Hepatitis E Virus, HAV – Hepatitis A Virus, CI – confidence interval. *p <0.05

Table 2. Frequency of clinical symptoms and their duration in the jaundice period in children with HEV and HAV-infection

Clinical symptoms	Frequency of symptoms (%)		Duration (in days m±SD)				p-value
	HEV	HAV	HEV	95% CI	HAV	95% CI	
Increase in body temperature	38.7	26.1	3.6±0.2	3.2-4.0	2.7±0.1	2.5-2.9	<0.05*
Weakness	77.4	35.7	5.2±0.4	4.4-6.0	3.0±0.1	2.8-3.2	<0.01
Decreased appetite	71.0	23.8	4.3±0.4	3.6-5.1	3.0±0.2	2.6-3.4	<0.05*
Nausea	48.3	33.3	5.0±2.3	0.4-9.6	3.0±0.1	2.8-3.2	>0.05
Vomiting	41.2	26.0	4.1±0.3	3.5-4.7	2.1±0.1	1.9-2.3	<0.05*
Itchy skin	35.4	31.0	3.6±0.4	2.8-4.4	3.2±0.3	2.6-3.8	>0.05
Nosebleeds	22.5	16.6	2.5±0.4	1.7-3.3	2.0±0.2	1.6-2.4	>0.05
Sleep disorders	16.0	14.2	3.2±0.3	2.6-3.8	2.8±0.1	2.6-3.0	>0.05
Pain in the right hypochondrium	71.0	38.0	5.2±0.4	4.4-6.0	3.0±0.3	2.4-3.6	<0.05*

Values are expressed as the mean (m)±standard deviation (SD). HEV – Hepatitis E Virus, HAV – Hepatitis A Virus, CI – confidence interval. *p <0.05

Table 3. Changes in biochemical parameters in children with HEV and HAV-infection

Laboratory parameters	HEV		HAV		p-value
	m±SD	95% CI	m±SD	95% CI	
Aspartate Aminotransferase	9.7±0.64	8.42-10.98	8.3±0.78	6.74-9.86	>0.05
Alanine Aminotransferase	11.8±0.97	9.86-13.74	10.8±0.88	9.04-12.56	>0.05

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Total bilirubin:	98.1±8.5	81.1-115.1	74.3±6.2	61.9-86.7	<0.05*
-direct	59.1±5.0	49.1-69.1	55.4±4.1	47.2-63.6	>0.05
-indirect	39.0±3.5	32.0-46.0	18.9±2.1	14.7-23.1	<0.05*
Thymol test	14.0±1.2	11.6-16.4	13.0±2.7	7.6-18.4	>0.05
The prothrombin index	60.8±4.0	52.8-68.8	62.5±3.0	56.5-68.5	>0.05
Total protein	58.7±3.0	52.7-64.7	72.0±2.5	67.0-77.0	>0.05

Values are expressed as the mean (m)±standard deviation (SD). HEV – Hepatitis E Virus, HAV – Hepatitis A Virus, CI – confidence interval. *p <0.05

Discussion

This study investigated the clinical characteristics of HEV in children and compared them to those of HAV. The findings revealed distinctions in epidemiological data, clinical presentations, and laboratory results between HEV and HAV infections.

Acute HEV predominantly affected male children (74.1%), while HAV infection showed no significant gender disparity. The 1-5-year-old group, primarily from rural areas (77.4%), was most susceptible to HEV infection, aligning with the high seroprevalence data for this demographic. A literature analysis indicates a notably higher prevalence of viral hepatitis E markers in children under 6 years of age, particularly in Egypt, causing acute self-limiting hepatitis. The study also notes significant correlations with animal contact (p=0.001) and rural residence (p=0.001).[16] In contrast, only 2% of children aged 2-4 years in Southwestern France, a hyperendemic region, were seropositive for HEV.[23] Other studies have reported low HEV seropositivity in children under 10 years of age in Morocco and Turkey (5%).[24] Large-scale research confirms that less than 10% of children under 10 years and less than 5% of European children are seropositive for viral hepatitis.[15]

In contrast, this study found that primary school-aged children were highly susceptible to HAV, with no substantial differences between urban and rural patients. This disparity may stem from different transmission routes and epidemiological factors, such as the consumption of unboiled water in rural areas, where HEV cases predominate. Unlike VHE, 69.0% of children with HAV infection reported contact with patients with HV in organized groups.

These findings underscore the importance of timely HEV diagnosis and the development of preventive measures, including access to safe drinking water and improved sanitation, especially in rural areas.

Both HEV and HAV infections in children follow a cyclical course that is typical of viral hepatitis. However, clinical data revealed a more severe progression of HEV infection than of HAV infection. Severe cases were reported in 13% of children with HEV, which was significantly higher than that of HAV (4.7%). HEV infection also resulted in a longer symptom duration during the pre-jaundice and jaundice periods. As jaundice onset occurred, children with VHE experienced increased symptoms of intoxication, unlike those with HAV. Symptoms such as fever, weakness, decreased appetite, vomiting, and right hypochondrium pain were more prevalent and lasted significantly longer in children with HEV infection than in those with HAV infection (p<0.05).

Biochemical analyses revealed that HEV infection had a more significant effect on liver bilirubin metabolism than HAV infection did. In HEV cases, overall bilirubin and its indirect components were significantly elevated, whereas total protein levels were reduced in severe instances, indicating more extensive liver impairment. Importantly, HEV RNA was not detected in any serum sample where anti-HEV IgM was present. Research suggests that RNA-HEV decreases quickly and becomes undetectable in serum approximately 20 days after symptoms begin.[25]

Studies in developing countries have reported vertical transmission from infected mothers to unborn children and infants. In one-third of these cases, HEV infection in newborns evolved into a fulminant course with lethal outcomes.[15] Research from Argentina provides vital evidence that HEV infection can result in symptomatic or more severe acute hepatitis in children when it occurs alongside other infectious agents or in patients with underlying conditions.[26]

In addition to typical liver involvement, HEV infection in children can present extrahepatic manifestations, affecting the central nervous system, kidneys, and hematological systems.[27–31] Studies indicate that children undergoing immunosuppressive treatment, those with nephrotic syndrome, autoimmune disorders, or intestinal inflammation are at a higher risk of developing chronic hepatitis E,[32,33] particularly those with weakened immune systems (3.2%).[34,35]

Despite our clinical observations and the aforementioned studies, reviews of several international investigations

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have suggested that overt forms of HEV infection in children are rare.[36,37] This aligns with conclusions from other researchers who proposed that HEV infection, while common in children, is typically asymptomatic and mild, often progressing without jaundice. As a result, they frequently go undetected.[7,38]

In this study, all hospitalized patients received standard treatments, including dietary and lifestyle adjustments. Detoxification therapy was administered only to children with severe forms of both viral hepatitis types. No antiviral medication was administered. Some recent studies advocate a three-week course of the antiviral drug ribavirin in immunocompetent patients with severe HEV infection, suggesting that it may lower serum transaminase activity.[39]

These results confirm HEV circulation during inter-epidemic periods and call for further research into its epidemiological and clinical features. They also highlighted the importance of prompt HEV diagnosis in children, especially when the viral hepatitis agent remains unidentified.

This study has notable constraints, including a restricted sample size and data confined to the southern areas of the Kyrgyz Republic, which potentially limits the applicability of the findings to other regions and nations. Despite these limitations, the study's outcomes significantly contribute to the understanding of HEV epidemiology and clinical manifestations in children, emphasizing the importance of continued investigations in this field.

Conclusions

HEV infection in children presents a more severe clinical course compared to hepatitis A. The primary affected group consisted of male children between 1 and 5 years old from rural areas. Children infected with HEV experience prolonged symptom duration during both the pre-jaundice and jaundice phases. Additionally, HEV-infected children exhibit more significant alterations in biochemical markers, including elevated total bilirubin levels and decreased total protein levels, than those with HAV infection. These findings indicate that HEV has a more substantial effect on liver function than HAV.

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Conflict of Interest: None

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