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ORIGINAL ARTICLE

Need for recognizing atypical manifestations of childhood sporadic acute viral hepatitis warranting differences in management

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Abstract

Various atypical manifestations have been described in acute viral hepatitis (AVH). We evaluated the prevalence, clinical features, response to treatment and outcome of various atypical manifestations of AVH in children. Consecutive children (≤ 18 years) with AVH due to hepatitis A, B, or E were studied while patients with acute or acute on chronic liver failure were excluded. Diagnosis of atypical manifestations was based on standard criteria. A total of 477 children with AVH (median age 7.0 (5–11) years, 74% boys) were seen; 22% ($n = 106$) had atypical manifestations. Prolonged cholestasis was the most common (11%), followed by ascites (7%), intravascular hemolysis (3%), relapsing hepatitis (2%), acute pancreatitis (1.3%), and thrombocytopenia (0.7%). Atypical manifestations were more common in HAV as compared to HBV (30% vs. 3%, $p = 0.00$) and HEV (30% vs. 15%, $p = 0.07$). Prolonged cholestasis was significantly more common in older children (20% in > 10 years vs. 9% in 6–10 years ; $p = 0.009$ and 5% in 0–5 years of age [$p < 0.000$]). Ascites was more common in younger children, although not significant. All patients recovered with supportive treatment.

Conclusions: Twenty-two percent of children with AVH have atypical manifestations, more often with HAV infection, and prolonged cholestasis is most common. Recognition of these manifestations ensures correct diagnosis and treatment.

What is Known:
- *Acute viral hepatitis is a major public health problem in developing countries.*
- *There is limited information about atypical manifestations which may lead to unnecessary investigations, delayed diagnosis and morbidity.*

What is New:
- *Atypical manifestations are common in children, seen most often with HAV infection, and prolonged cholestasis is most common.*
- *Prompt recognition of these manifestations helps in early diagnosis, appropriate management, and preventing unnecessary investigations.*
- *Ensure follow-up until complete recovery and not to miss underlying chronic liver disease.*

Keywords Atypical manifestations · Acute hepatitis · Cholestasis · Relapsing · Children

Abbreviations

ACLD	Acute on chronic liver disease
ACLF	Acute on chronic liver failure
AKI	Acute kidney injury
ALF	Acute liver failure
ALT	Alanine aminotransferase
AP	Acute pancreatitis
AST	Aspartate aminotransferase

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AVH	Acute viral hepatitis
CLD	chronic liver disease
CNNA	Culture negative neutrocytic ascites
G6PD	Glucose-6-phosphatase dehydrogenase
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HEV	Hepatitis E virus
IVH	Intravascular hemolysis
MNB	Monomicrobial non-neutrocytic bacterascites
SBP	Spontaneous bacterial peritonitis
UDCA	Ursodeoxycholic acid

Introduction

Acute viral hepatitis (AVH) is a major public health problem in developing countries. Hepatitis A (HAV), hepatitis E (HEV), and hepatitis B (HBV) viruses as single infection or in combination are responsible for majority of sporadic AVH in children and adults [6, 11, 18, 22]. Classical AVH is characterized by a prodromal phase followed by jaundice which gradually resolves over the next 2–3 weeks [6]. However, some patients have atypical manifestations like prolonged cholestasis, acute pancreatitis, relapsing jaundice, hemolytic anemia, thrombocytopenia, etc. Most of these manifestations have been described as small case series [5, 14, 18, 28]. Information about these is important as lack of awareness leads to unnecessary investigations, delayed diagnosis and morbidity. We evaluated the frequency, clinical features, natural history, and outcome of various atypical manifestations of AVH in children.

Materials and methods

Consecutive children (≤ 18 years of age) with AVH managed in our department from January 2000 to June 2012 either as inpatients or in the outpatient department were evaluated. Three authors did an independent search of the electronic records of hospital information system to identify the cases. Diagnosis of AVH was based on clinical features, > 3ULN increase in aminotransferases and positive serology (hepatitis A: IgM anti HAV; hepatitis E: IgM anti HEV; hepatitis B: IgM anti HBc with/without HBsAg). Atypical manifestations were selected based on published literature. Detailed history, clinical examination, and biochemical parameters for all children with atypical features, i.e., prolonged cholestasis, ascites, hemolysis, acute kidney injury, pancreatitis, thrombocytopenia, and relapsing jaundice were recorded. Children with ALF [3], ACLD/ACLF, acute hepatitis without positive viral serology, and on hepatotoxic drugs were excluded. Atypical manifestations found in our cases were defined as follows:

- AVH with ascites was defined as clinical and/or ultrasonography evidence of ascites. Spontaneous bacterial peritonitis [SBP], culture negative neutrocytic ascites [CNNA], or monomicrobial non-neutrocytic bacterascites [MNB] was diagnosed as per standard criteria [21].
- Prolonged cholestasis was defined as jaundice for ≥3 months with pruritus and serum bilirubin levels >10 mg/d [25].
- Hemolysis was defined as drop in hemoglobin level along with evidence of hemolysis on peripheral blood smear ± raised reticulocyte count. Hemolysis in presence of dark colored urine or increased plasma hemoglobin or urine hemosiderin supported the diagnosis of intravascular hemolysis. For etiological work up of hemolysis, glucose-6-phosphatase dehydrogenase (G6PD) level, direct Coomb's test, pyruvate kinase level, and serum ceruloplasmin levels were done. In patients who had received prior blood transfusion, G6PD levels were rechecked after 3 months in follow-up.
- Relapsing hepatitis was characterized by an episode of acute hepatitis followed by a remission of 4–16 weeks before a recurrence of symptoms [25].
- Thrombocytopenia was diagnosed when platelets were < 150,000/mm^3 with normal other cell lines (RBC/WBC), absence of splenomegaly, and other known causes of thrombocytopenia like dengue, malaria, or drugs.
- Acute pancreatitis (AP) due to AVH was diagnosed when the patient fulfilled the diagnostic criteria for AP, i.e., presence of ≥ 2 of the following three features: (i) abdominal pain suggestive or compatible with AP, (ii) serum amylase and/or lipase activity ≥ 3 times upper limit of normal (international units/liter), and (iii) imaging findings characteristic or compatible with AP and absence of other etiologies for pancreatitis like drugs, gall stones, hypercalcemia, hypertryglyceridemia or family history of pancreatitis [20].
- Acute kidney injury (AKI) was defined as increase in serum creatinine by > 0.3 mg/dl within 48 h or increase of > age appropriate level [16].

Ascites was treated with a salt-restricted diet, diuretics, and antibiotics for SBP/CNNA. Pruritus was managed with ursodeoxycholic acid (UDCA) and/or rifampicin and/or cholestyramine as per the clinical response till resolution of pruritus. Intravenous hydration, blood transfusion ((if Hb < < 6 g/dL), stopping any offending drug causing hemolysis in G6PD deficiency, and monitoring for urine output and hyperkalemia was done in patients with intravascular hemolysis. Pancreatitis was graded in severity and managed conservatively as per standard recommendations [33]. Acute kidney injury was managed as per guidelines with regular monitoring and renal support if required [24]. All cases were followed up on given scheduled appointments till resolution of clinical symptoms, regression of organomegaly, and normalization of liver function tests.

Ethical clearance with consent waiver was taken from the Institutional Ethics Committee.

Statistical methods

Data was analyzed using Statistical package for Social Sciences, version 23.0 (SPSS-23, IBM Chicago, USA). Continuous data were summarized as median and interquartile range and compared with Mann–Whitney U *t* test, while categorical variables were compared by chi-square or Fisher exact test as applicable. A $p < 0.05$ was considered significant.

Results

A total of 477 children of Indian origin with AVH, median age 7.0 (5–11) years (74% boys), were evaluated. Hepatitis A was the most common etiology ($n = 240$, 50.3%) followed by hepatitis B ($n = 93$, 19.5%), and hepatitis E ($n = 34$, 7.2%). Co-infection with multiple viruses was seen in 110 (23%) children [HAV + HEV in 95 (20%), HAV + HBV in 9 (1.8%), HEV + HBV in 6 (1.2%)]. Age group-wise distribution of etiology and atypical manifestations of AVH is shown in Fig. 1. One hundred twelve atypical manifestations of AVH were seen in 106 (22%) children and included prolonged cholestasis, ascites, intravascular hemolysis, relapsing hepatitis, pancreatitis, and thrombocytopenia. Table 1 shows the frequency of various atypical manifestations based on etiology of AVH. Comparison between children with atypical and typical manifestations showed that atypical features were significantly more common with HAV (Table 2).

Prolonged cholestasis was the most common atypical presentation (52, 11%) with a median age of 10 (6–12) years and 81% (42) being boys. The median duration of jaundice was 110 (99–188) days. All of them had pruritus; the interval between jaundice to onset of pruritus being 20 (15–30) days. Five patients each had pale stools and relapsing hepatitis also. Prolonged cholestasis was significantly more common in hepatitis A vs. hepatitis B (Table 1) and older children (> 10 years) (Table 3).

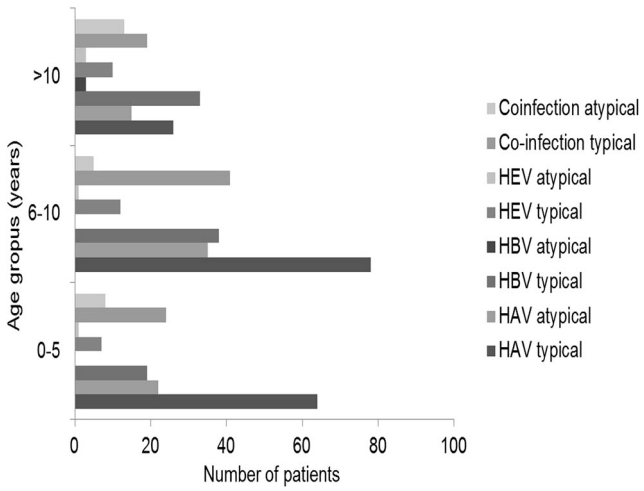

Fig. 1 Etiology of acute viral hepatitis and proportion with atypical manifestations in different age groups

Prolonged cholestasis with pruritus was treated with UDCA in all for 40 (30–60) days, rifampicin in 15 (29%) for 36 (30–60) days, and cholestyramine in 3 (6%) for 23 (11–24) days. Pruritus settled in all over 55 (36–73) days. Another 32 children (median age 8.5 (6–13) years, 19 boys) also had pruritus during the icteric period, but both jaundice and pruritus subsided within 12 weeks of onset on UDCA treatment. If we include these cases, cholestasis was seen in 84 (17.6%) cases.

Ascites was the second most common atypical presentation seen in 33 (7%) children (26 boys). Ascites was diagnosed on clinical examination in 16 patients, while in 17 cases, it was found only on ultrasound. The median age of these children was 6 (3.5–8.5) years, which was significantly less compared to those without ascites 8 (5–11) years, ($p = 0.03$). Ascites was more frequent in the younger (0–5 years) than the older children, but the difference was not significant (Table 3).Children with ascites had lower serum protein and albumin [7.1 (6.0–7.5) g/dL and 3.7 (2.7–4.3) g/dL respectively] compared to those without ascites [7.5 (7–8.1) g/dL and 4.0 (3.6–4.4) g/dL, respectively], $p = 0.005$ and $p = 0.02$ respectively. Three (9%) children had SBP, all were below 5 years of age, and two of them were boys. One had HAV and two had co-infection with HAV and HEV. SBP resolved with oral third generation cephalosporin in all cases. Ascites was managed with salt restriction in all and diuretics in 16/33 (48%) for 9.5 ± 4.5 days. Ascites resolved over 7 days in 26 (79%), 14 days in 3 (9%), and 21 days in 4 (12%) children. Serum protein and albumin normalized in all over the next 56 (33–78) days.

Intravascular hemolysis (IVH) was detected in 14 (3%) cases, 9 (64%) being boys. There was no difference in terms of underlying etiology and age group in children having hemolysis (Tables 1 and 3). All children presented with anemia, dark colored urine, and deep jaundice. Liver function showed significantly higher peak serum bilirubin than those without intravascular hemolysis [24.5 (18–30) vs. 6 (3.3–12.9) mg/dL, $p < 0.00$]. Hemolysis was supported by increased plasma hemoglobin and urine hemosiderin. Etiological workup for hemolysis found G6PD deficiency in 5 (36%), direct Coomb's test positivity in 1 (7%), and idiopathic in 5 (36%). In the remaining 3 (21%) cases, work up was inadequate. In one child with G6PD deficiency, hemolysis was precipitated by intake of chloroquine. Two (14%) children had pigment nephropathy and manifested as AKI with oliguria and increased serum creatinine. Both were managed conservatively and improved without renal replacement therapy.

Table 1 Comparison of various atypical manifestations between the different etiological groups

Atypical manifestation	Hepatitis A ($n = 240$)	Hepatitis B ($n = 93$)	Hepatitis E ($n = 34$)	Co-infection ($n = 110$)	p value
Any atypical manifestation	72 (30%)	3 (3%)	5 (15%)	26 (24%)	0.00*, 0.07$^{\$}$, 0.02^
Prolonged cholestasis	36 (15%)	1 (1%)	3 (9%)	12 (11%)	0.00*, 0.4$^{\$}$, 0.06^
Hemolysis	7 (3%)	1 (1%)	0	6 (10.5%)	0.4*, 0.6$^{\$}$, 1.0^
Relapsing hepatitis	9 (4%)	0	0	1 (0.9%)	0.07*, 0.4$^{\$}$
Pancreatitis	1 (0.4%)	0	1 (3%)	0	1.0*, 0.2$^{\$}$,0.3^
Ascites	22 (9%)	1 (1%)	1 (3%)	9 (8%)	0.009*, 0.3$^{\$}$, 1.0^
Thrombocytopenia	0	0	0	1 (0.9%)	–

*Hepatitis A vs. B

$^{\$}$ Hepatitis A vs. E

^ Hepatitis B vs. E

Relapsing hepatitis was observed in 10 (2%) cases, majority (7, 70%) being boys. All of them had two episodes of jaundice. HAV was the etiology of AVH in all, only HAV in 9 (90%) and co-infection with HAV and HEV in 1 (10%) case. Jaundice re-occurred after 1 month in 5 (50%), after 2 months in 4 (40%), and after 3 months in 1 (10%). Five (50%) of them also had pruritus (2 in first episode and 3 in second episode). Jaundice resolved by 4 months following the relapse in all. Occurrence of relapsing jaundice was similar across the age groups (Table 3).

Two children had mild acute pancreatitis. One of them was a 16-year-old boy who presented with epigastric pain suggestive of pancreatitis and found to have anicteric hepatitis (high serum alanine aminotransferase (2912 IU/dL) with normal serum bilirubin) due to HEV. The other child was a 10-year-old boy with AVH due to HAV and developed abdominal pain on day 14 of jaundice. Both had raised serum amylase with ultrasound evidence of bulky and edematous pancreas. Conservative management was done, and pain resolved over next 4 days in both. There was no recurrence of pancreatitis over 1 and 3 months follow-up.

Thrombocytopenia was seen in an 8-year-old child on day 7 of AVH with HAV and HEV co-infection. Although asymptomatic, the lowest platelet count documented was 43,000/mm^3 which normalized by day 10. Etiological workup including dengue antigen and antibody, malarial antigen, and blood culture were negative, and the child had no evidence of sepsis or disseminated intravascular coagulation. There was no exposure to any drugs known to cause thrombocytopenia. Bone marrow was not done as the child had spontaneous improvement in platelet count.

Other atypical manifestations including vasculitis, arthritis, optic neuritis, transverse myelitis, etc. were not seen in any of our patient.

Discussion

We found atypical manifestations in 22% cases in a large cohort of 477 children with AVH from North India. The other pediatric studies reported atypical manifestations in 4–49% of cases (Table 4), which is similar to our findings.

Prolonged cholestasis was the most common atypical manifestation seen in 11% of children, and all had pruritus. Children in the second decade of life and underlying HAV as etiology were significantly more likely to have prolonged cholestasis. The occurrence of prolonged cholestasis in AVH has

Table 2 Comparison of children with and without atypical manifestations of AVH

	AVH with atypical ($n = 106$)	AVH without atypical ($n = 371$)	p value
Age group			0.20
0–5 years	31	114	
6–10 years	41	169	
> 10 years	34	88	
Male	82 (77%)	272 (73%)	0.4
HAV	72 (68%)	168 (45%)	<0.001
HBV	3 (3%)	90 (24%)	<0.001
HEV	5 (5%)	29 (8%)	0.3
Co-infection	26 (25%)	84 (22%)	0.7

AVH Acute viral hepatitis, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HEV* hepatitis E virus

Table 3 Comparison of atypical manifestations between different age groups

Atypical manifestations	Prolonged cholestasis	Hemolysis	Relapsing hepatitis	Pancreatitis	Ascites
0–5 years ($n = 145$)	8 (5%)	6 (4%)	3 (2%)	0	15 (10%)
6–10 years ($n = 210$)	20 (9%)	7 (3%)	4 (2%)	1 (0.5%)	11 (5%)
> 10 years ($n = 122$)	24 (20%)	1 (0.8%)	3 (2.5%)	1 (0.8%)	7 (6%)
p value	0.2*, 0.009$, 0.000^	0.7*, 0.3$, 0.1^	1.0*, 1.0$, 1.0^	1.0*, 1.0$, 0.5^	0.07*, 0.8$, 0.2^

*0–5 years vs. 6–10 years

$ 6–10 years vs. > 10years

^ 0–5 years vs. > 10 years

been reported in 1–25% of cases with predominant HAV infection, which is similar to our study [5, 14, 18, 28]. Majority (82%) of patients responded to UDCA, and a small proportion required rifampicin (18%) and cholestyramine (4%). Our treatment protocol was based on previous studies and guidelines recommending the use of UDCA as first line agent for treatment of pruritus in children with cholestasis [2, 4]. Steroids have been shown to have benefit in patients' refractory to other choleretic agents [17, 27]. A standard regimen utilizes prednisone in a dose of 1 mg/kg/day gradually tapered over, at least, a 4–8-week period. However, data is very limited, and definite role is unclear.

Other causes of cholestasis in children include extrahepatic biliary obstruction due to stones, choledochal cyst, etc. These can be suspected in the presence of right-sided abdominal pain and should in all cases be excluded by abdominal ultrasound. Benign recurrent intrahepatic cholestasis is another self-limiting condition seen usually in adolescents which has a similar presentation with pruritus and jaundice. However, the pruritus usually precedes jaundice by 2–4 weeks [19]. History of recurrent episodes of cholestasis (if present) and normal gamma-glutamyl transferase along with normal or near normal aminotransferases during an episode of cholestasis supports the diagnosis of benign recurrent intrahepatic cholestasis [19].

Ascites was found in 7% of children with AVH. Previous studies reported an incidence of 10–30% [22, 34]. Children with ascites had significantly lower levels of serum protein and albumin which leads to decrease in the oncotic pressure, thereby promoting ascites formation. SBP was seen in a small number (9%) without any adverse outcome which is similar to the observation by Yachha et al. [34]. Ascites in a case of AVH may also be a manifestation of acute on chronic liver disease (ACLD). Two studies from India showed that CLD was diagnosed for the first time in 82–86% children during their presentation with a superimposed acute insult, which was AVH in

Table 4 Summary of the studies on atypical manifestations of acute viral hepatitis in children

Study	Kumar A. J ^GastroenterolHepatol* 2006[1]	Samanta T. ^Ind J Gastroenterol* 2010[5]	Kamath S. ^Indian Pediatrics* 2009[6]	Cetinkaya B J Infect DevCtries$ 2014	Present study
Number of cases	122	229	138	427	477
Age (year)	2–14	–	1 month–15 years	1–17y	7 (5–11)
Male (%)	70%	–	–	216 (50.6)	74%
Etiology of AVH	Hepatitis A, E, and B	Hepatitis A	Hepatitis A	Hepatitis A	Hepatitis A, E, and B
Atypical features	60 (49%)	32 (14%)	63 (45.6%)	16 (3.7%)	106 (22%)
Prolonged cholestasis#	30 (24.5%)	10 (4%)	33 (24%)	4 (0.9%)	52 (11%)#
Ascites	12 (10.6%)	8 (3%)	30 (21%)	–	33 (7%)
IV hemolysis	5 (4%)	3 (1.3%)	–	–	14 (3%)
Relapsing jaundice	13 (10.6%)	8 (3%)	–	1 (0.2%)	10 (2%)
Pancreatitis	–	–	–	–	2 (1.3%)
Thrombocytopenia	–	2 (0.9%)	–	11 (2.6%)	1 (0.7%)

All values given as number (percentage)

*Duration of jaunidce for defining prolonged cholestasis is not given

$ Cholestasis defined as total bilirubin level higher than 10 mg/dL over a 4-week period

Another 32 (7%) cases also had pruritus, but jaundice and pruritus subsided within 12 weeks

30–97% cases [1, 11]. All efforts to look for features of CLD on clinical examination and investigations should be made. In addition, adequate follow-up should continue until all liver tests normalize and re-evaluation is recommended in those with persistent abnormality.

We found that 3% of AVH children had IVH. Almost one-third had G-6PD deficiency. The frequency is comparable to the other pediatric studies (Table 4), but the etiology of IVH was not well described in these studies [18, 28]. IV hemolysis in G-6PD-deficient patients can be precipitated by vitamin K [8] and may result in AKI requiring renal replacement therapy. Fat soluble vitamin K (phytonadione) is a safe alternative in such patients with AVH [15]. Presence of anemia in a child with AVH should be taken seriously and evaluated according to standard diagnostic work-up, particularly remembering causes like hemolysis and hemophagocytic lymphohistiocytosis (HLH).

Relapsing jaundice was seen in 2% of children, and 50% of them also had prolonged cholestasis. This is similar to published studies showing incidence of 0.2–10%, with HAV as the predominant etiological agent [5, 18, 28]. The first phase of jaundice is indistinguishable from any other acute hepatitis which generally lasts for less than 3 weeks followed by remission for 1.5–18 weeks. Relapse phase persists for 1–4 months. Prolonged cholestasis is a predominant feature in the second phase. The pathogenesis of relapsing hepatitis is thought to be either due to persistent HAV infection or altered immune response to HAV infection [32]. The prognosis is good as all of our patients recovered and none developed chronic hepatitis. Autoimmune liver disease can present with recurrent hepatitis and can mimic relapsing AVH. In fact, there have been several case reports of autoimmune hepatitis triggered after few months by acute hepatitis A [9, 23, 30]. Thus, in a given case of relapsing hepatitis, these conditions should be considered and excluded by appropriate investigations.

Acute pancreatitis (AP) has been reported in 5.6–12% of adults with AVH [12, 13] but is rare in children. We found it in 0.5% of cases, and other pediatric studies have not reported this. All hepatotropic viruses have been reported to cause AP [12] similar to our study having one case each with HAV and HEV. Mechanism of pancreatitis in AVH is unknown and may be multifactorial. Documentation of hepatitis B surface antigen and core antigen in the pancreatic acinar cells and pancreatic juice supports the hypothesis of direct viral invasion through blood or bile ([7, 29]). Thus, children with AVH having significant upper abdominal pain necessitate evaluation for associated conditions like AP, acalculous cholecystitis or drug-induced gastritis, etc. Simple investigations like serum amylase/lipase and ultrasound abdomen are helpful in this setting.

Association of thrombocytopenia and AVH is not very well known and described mostly as case reports [5, 10, 31]. Our only patient had co-infection with HAV and HEV while previous reports showed association with HAV [5, 10, 31]. Thrombocytopenia was attributed to the viral hepatitis as other causes were ruled out including use of Chinese herbs. Treatment with oral steroids in adults results in improvement in platelet count within 48 h [26]. As there is no established protocol for management of AVH-related thrombocytopenia, it seems worthwhile to evaluate the cause with daily monitoring of platelet counts. Platelet transfusion is advised if platelets are $< 20{,}000/mm^3$ or if there is bleeding.

As prevention is always better than cure, efforts at increasing immunization of children against hepatitis A and B should be a priority. Improvement in sanitation is the only way at present for hepatitis E protection.

One of the limitations of our study is its retrospective nature spanning over a decade. As there was no protocol-based evaluation for children with AVH, we did not have the serial serum creatinine value in all patients. Thus, the children meeting the criteria of AKI based only on the rise in creatinine irrespective of oliguria might have been missed. Also, we could have missed the milder or anicteric variant of AVH attending the outpatient clinic due to lack of suspicion and appropriate testing for viral markers. We did not test for other co-infections (EBV, CMV, enterovirus, parvovirus B19) in children with hemolysis. Lastly, as our hospital is a tertiary care center, patients with more severe symptoms are likely to form the major bulk of the study population which may overestimate the true prevalence of atypical manifestations in AVH.

Conclusions

Atypical manifestations of AVH are common in children, seen most often with HAV infection and prolonged is most common. Prompt recognition of these manifestations helps in early diagnosis, appropriate management, and preventing unnecessary investigations. Care should be taken to ensure follow-up until complete recovery and not to miss cases with underlying chronic liver disease.

Authors' contributions SKS collected and analyzed the data drafted the manuscript. VB collected and analyzed the data and drafted the manuscript. AS designed and supervised the study, analyzed the data, and co-drafted the manuscript. AM collected and analyzed the data and co-drafted the manuscript. SKY designed the study and revised the manuscript for important intellectual content. UP analyzed the data and revised the manuscript for important intellectual content. All authors have read and approved the final version to be published.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent For this type of study, formal consent is not required.

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