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CASE REPORT Open Access

Transient sinus bradycardia caused by hepatitis A virus: a case report

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Abstract

Background: The most common cause of acute viral hepatitis is the hepatitis A virus (HAV). Millions of people are thought to be infected each year. It is transmitted either by the fecal-oral route or by consuming contaminated food. Extrahepatic complications, notably cardiologic ones, are infrequent. This case report was presented due to the development of HAV-related bradycardia without hypotension in an unvaccinated refugee patient.

Case presentation: A 9-year-old male presented with the complaint of jaundice and vomiting. There was no history of fever, diarrhea, or abdominal pain. A precise knowledge of suspected food intake is lacking. There was no pathological examination finding except jaundice. Total bilirubin, direct bilirubin, aspartate aminotransferase, and alanine aminotransferase levels were high. The coagulation test was normal. Anti-HAV-IgM/IgG was positive in the patient with suspicious viral hepatitis. In the follow-up, the heart rate decreased to 43 beats/min during sleep and 46 beats/min when awake. Cardiological examination and tests were within normal limits. Hypotension was not accompanied. In the follow-up, bradycardia and impaired liver function tests regressed. The patient was discharged on the 10th day.

Conclusions: Cardiologic complications are rare, and patients diagnosed with acute hepatitis A should be monitored. The most effective way of protection from the hepatitis A virus is vaccination.

Keywords: Bradycardia, Child, Hepatitis A, Refugee, Vaccine

Background

Hepatitis A virus (HAV) is a non-enveloped, single-stranded, positive-sense RNA virus belonging to the Picornaviridae family. It is thought that millions of people around the world are infected every year with HAV, which is known as the most common cause of acute viral hepatitis in developing countries [1]. HAV infection is among vaccine-preventable infectious diseases. The Advisory Committee on Immunization Practices recommends two doses (0–6 months) of vaccination for all children between 12 and 23 months and non-vaccinated individuals [2].

The course of HAV infection is highly variable. Symptomatic HAV infection can progress from an anicteric form with mild symptoms to fulminant hepatic failure that may cause mortality. Extrahepatic complications are not typical for HAV infection compared to other viral hepatitis [3]. Cardiologic complications are rare in the course of HAV. Bradycardia was detected during HAV infection in a refugee patient who fled from the chaotic environment in the Middle East and was learned to be unvaccinated and was presented because of an infrequent cardiological complication.

Case presentation

A 9-year-old male patient with no known disease complained of gradually increasing yellow coloring of the body and eyes that started 10 days ago and vomiting 3 days ago. There was no fever, diarrhea, or abdominal pain. He had no recent history of taking medications. However, clear information about eating suspicious food is lacking. There was not a member with similar complaints in the household. When the patient's vaccination

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was questioned, it was learned that the vaccines were missed. The patient's fever was 36.7 °C, and arterial blood pressure was 100/65 mm/Hg. The heart rate (HR) was 46 beats/min (Fig. 1).

No pathologic examination findings were detected except for the sclera's and skin's characteristic appearance. The patient's total bilirubin (TB) was 5.14 mg/dL (normal: 0–1.2 mg/dL), direct bilirubin (DB) was 4.36 mg/dL (normal: 0–0.3 mg/dL), aspartate aminotransferase (AST) was 361 U/L (normal: 0–51 mg/dL), alanine aminotransferase (ALT) was 699 U/L (normal: 0–39 U/L), alkaline phosphatase (ALP) was 540 U/L (normal: 142–335 U/L), gamma-glutamyl transferase (GGT) was 167 U/L (normal: < 31 U/L), lactic dehydrogenase (LDH) was 257 U/L (normal: 120–300 U/L), and albumin was 34.3 g/L (normal: 38–54 g/L). Complete blood count, coagulation tests, C-reactive protein, renal function tests, electrolytes, and cardiac enzymes (CK-MB/troponin I) were within normal limits. Electrocardiography (ECG) was compatible with sinus bradycardia (Fig. 2), and there was no pathological finding in echocardiography (ECHO). A pediatric cardiologist performed an echocardiogram and found no evidence of myocarditis, pericarditis, or cardiac complications. The abdominal

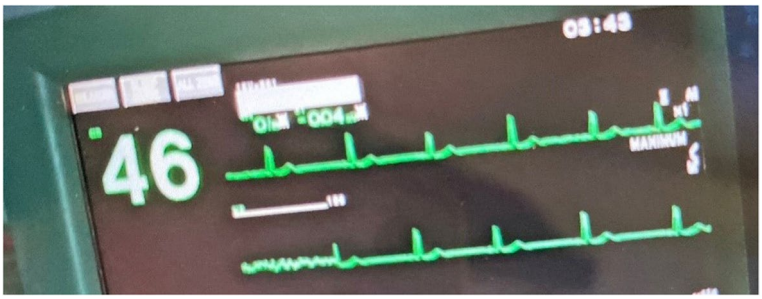

Fig. 1 The patient's heart rate while awake (46/min)

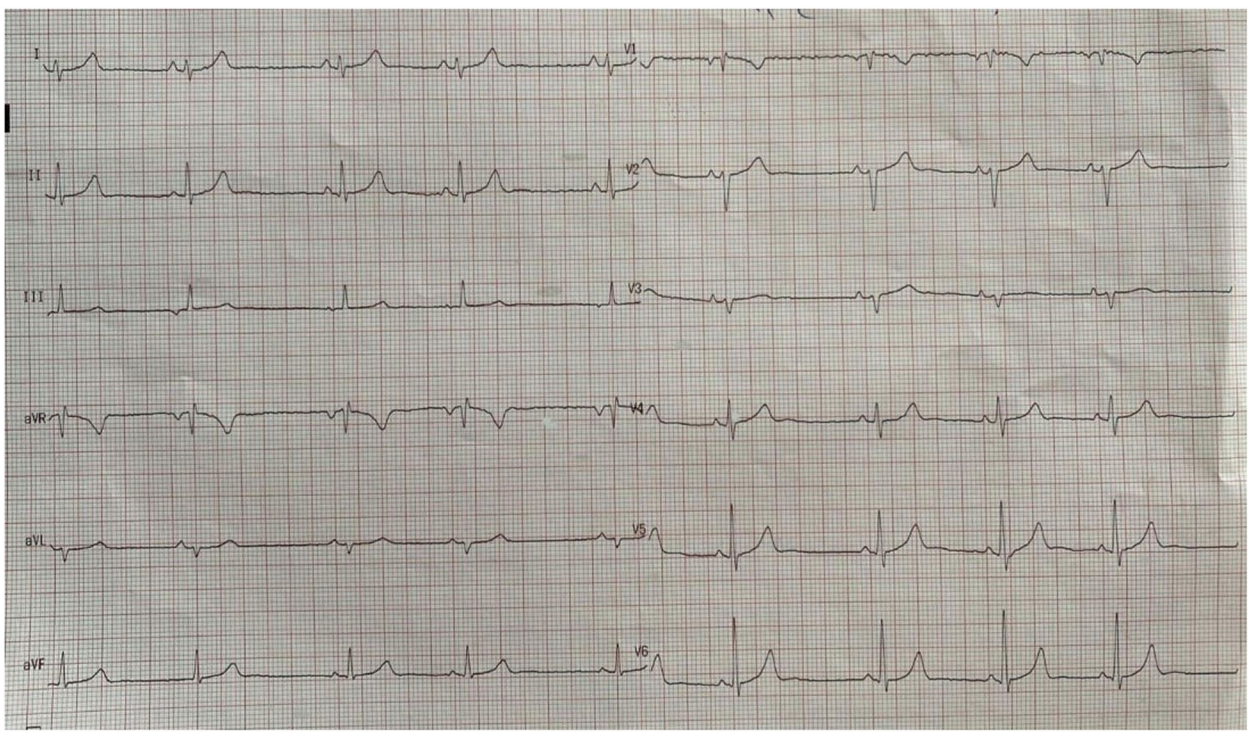

Fig. 2 Electrocardiogram displaying sinus bradycardia in the patient with hepatitis A while awake

ultrasonography was compatible with cholestasis. The patient was admitted to the hospital, and intravenous fluid therapy was given as treatment. Symptomatic treatment was administered to the patient, and no antiviral or antibiotherapy was required.

Viral hepatitis was considered due to the missed childhood vaccines. While hepatitis B and hepatitis C serology were negative, anti-HAV-immunoglobulin (Ig)M and IgG were positive. The patient did not have vomiting since the 2nd day of his hospitalization. In the patient's cardiac monitoring follow-up, the bradycardia frequency decreased while he was asleep and awake. As of the 5th day of his admission, bradycardia was no more observed, and HR was within the normal range. A decrease was observed in elevated transaminase and bilirubin levels. Blood parameters and HR levels checked during the patient's follow-up are shown in Table 1. During the follow-up, blood pressure remained within normal limits. The patient was discharged on the 10th day of hospitalization. We followed the patient in the inpatient service. The patient was monitored and followed up, and symptomatic treatments were applied (hydration) during the follow-ups, and there was no need to use cardiac agents and antiviral agents. In the follow-ups, the patient was discharged on the 10th day. The patient was followed in the outpatient clinic for 3 months; the laboratory finding was in the normal range on the second month of the follow-up. The patient's parents' and two siblings' HAV serologies were evaluated at the outpatient clinic; their anti-HAV-IgG was positive.

Discussion

Millions worldwide encounter HAV yearly, usually by ingesting contaminated food and water or contacting an infected person. Low-income countries have high HAV incidence rates. In addition, most refugees are considered at risk due to unsuitable living conditions. Another reason is that children avoid routine vaccination schedules [4]. The patient was deprived of the vaccination schedule. The patient's parents conveyed that they neglected vaccination due to the family's delay in the registration process. Although the registration system for refugee children is successfully implemented and essential health services such as vaccination are carried out in our country, sometimes people cannot be reached.

Young children who are exposed to the virus are often asymptomatic. With increasing age, the risk of acute liver failure increases in the pediatric population. However, older children and adults are at risk of acute liver failure and death. While jaundice and fever are prominent in typical HAV infection, nausea, vomiting, dark urine, abdominal pain, anorexia, and weakness are other complaints. On physical examination, hepatomegaly is often found [3]. Patients frequently have elevated ALT, AST, TB, and DB and decreased albumin levels. In addition, coagulopathy is expected [5]. Our patient presented with complaints of jaundice and vomiting. Other symptoms, such as fever and abdominal pain, were absent. There were no findings other than icterus and bradycardia on examination. Except for coagulopathy, our patient's results were compatible with the literature.

In patients with clinically and laboratory-proved hepatic damage, suspicion is essential for diagnosing HAV infection. Because there are many causes of hepatitis, such as infectious causes (viral, bacterial, and fungal infections), metabolic diseases, immune diseases (such as autoimmune hepatitis), hepatic perfusion and oxygenation problems, drugs, toxins, alcohol, and some plants [6], our patient did not have a history of suspected medicine, substance use, or food poisoning. There was also no acute phase-reactant elevation for severe bacterial infection and no predisposing factors for fungal infection such as immune deficiency. Given the patient's age and lack of vaccination, viral hepatitis diagnosis came to the

Table 1 Laboratory and heart rate beats per minute on the 1st, 3rd, 6th, and 10th day of admission

Admission	ALT (U/L)	AST (U/L)	GGT (U/L)	TB (mg/dL)	DB (mg/dL)	HR awake (beat/minute) (minimum)	HR asleep (beat/minute) (minimum)
Day 1	699	361	167	5.14	4.36	46	43
Day 3	548	303	151	3.49	2.61	50	48
Day 6	271	159	80	1.45	1.29	65	60
Day 10	251	129	32	1.08	0.71	75	70
Day 13	170	89	30	1.00	0.42	90	-
Day 20	70	55	24	1.00	0.22	87	-
Day 45	42	34	20	1.00	0.13	92	-

ALT alanine aminotransferase. *AST* aspartate aminotransferase, *GGT* gamma-glutamyl transferase, *TB* total bilirubin, *DB* direct bilirubin, *HR* heart rate. (The patient was discharged on the 10th day. The heart rate asleep could not be evaluated during outpatient controls)

fore. The diagnosis of acute HAV infection is made with positive serum anti-HAV-IgM. Anti-HAV-IgG positivity shows the immune response that develops with a previous HAV infection or vaccination [1]. Our patient was diagnosed with anti-HAV-IgM positivity. Anti-HAV-IgG of the parents and two siblings were positive, while anti-HAV-IgM was negative in the household screening. This result shows that other family members had the disease before or were vaccinated.

Acute HAV is usually self-limiting and does not lead to chronic disease. Complications include cholestatic hepatitis, recurrent hepatitis, and autoimmune hepatitis, which rarely progress to liver failure. Extrahepatic complications include rash (urticarial/maculopapular), acute kidney injury, glomerulonephritis, autoimmune hemolytic/aplastic anemia, thrombocytopenia, reactive arthritis, acute pancreatitis, mononeuritis, Guillain-Barre syndrome, pleural/pericardial effusions, polyarteritis nodosa, and cryoglobulinemia. Presentation with cardiac signs and symptoms depending on the cardiac affinity of HAV is hardly expected. Allen et al. presented the first case of HAV-induced myocarditis in the USA in 2018 [7]. Botero et al. presented a postoperative HAV-induced cardiomyopathy case who developed acute liver failure due to HAV and underwent liver transplantation [8]. Soleimani et al. demonstrated the first association of HAV-induced hypotension and bradycardia in an adolescent patient [9]. Atabek et al. presented a 16-year-old adolescent patient with acute HAV infection because of bradycardia, hypotension, and progressive cholestasis developed in the patient and emphasized that this association was the first pediatric presentation [10]. Indeed, in the literature, cardiac involvement of HAV has not been documented in large series but in sporadic cases; we have reviewed some (Table 2) [9–13]. There was no finding suggestive of myocarditis in our patient. Bradycardia was not accompanied by hypotension. Our case is rare, in which HAV-induced bradycardia and mild cholestasis were found in a pediatric patient.

The mechanism of bradycardia in the course of hepatitis A is not fully understood. Sinus bradycardia is associated with circulating bile salts and the severity of jaundice [14]. It has been reported that sinus node dysfunction and bradycardia can be seen, especially in cases with obstructive jaundice, assuming that bilirubin depresses the sinoatrial node via vagal centers. Supporting this hypothesis, Tanır et al. presented a hospitalized patient (TB: 3.36 mg/dL, DB: 1.78 mg/dL) diagnosed with HAV infection because of bradycardia developed on the 3rd day of hospitalization and lasted for 4 days. They reported that bradycardia was associated with deep hyperbilirubinemia (TB: 6.74 mg/dL, DB: 3.64 mg/dL), and the higher the bilirubin levels are, the lower the heart rate [13]. In a patient who was followed up due to gall bladder malignancy, it is reported that arrhythmia occurred as biliary tract obstruction developed, it has been shown that HR returned to normal, and arrhythmias disappeared as bilirubin levels decreased with the drainage of the bile ducts. Also, it has been suggested that sinus bradycardia may be present in professional athletes and associated with various clinical conditions such as intracranial hypertension, cervical tumor, myxedema, and hypothermia [15]. Our patient did not do sports regularly. There was no respiratory distress suggestive of intracranial hypertension. Except for the presence of HAV, there were no additional symptoms, finding, or diseases to explain the bradycardia. The bradycardia was detected at the time of admission on the 10th day after his complaints when his TB level was 5.14 g/dL, and DB level was 4.36 mg/dL. Sinus bradycardia was thought to have developed due to the increase in vagal stimulation associated with the increase in parasympathetic activation from autonomic cardiovascular reflexes after mechanical distension of the biliary tract or the direct effect of cardiac viral load on the sinoatrial node. Again, we think that increased bilirubin level may cause sinus bradycardia by directly affecting the sinoatrial node when the serum bilirubin level is high and sinus bradycardia is prominent (TB; 5.14 mg/dL while the pulse is 46/min); heart rate normalized after bilirubin level decreased (TB; 1.08 mg/dL = pulse 75/min).

Table 2 Brief literature review of sporadic cases of acute HAV infection cases with cardiac manifestations

Case report	Age (years), gender	Cardiac manifestation
Soleimani G. et al. [9]	14, F	Bradycardia with hypotension
Atabek M. E. et al. [10]	16, M	Bradycardia with hypotension
Khan A. et al. [11]	10, F	Bradycardia
	13.5, M	Bradycardia with hypotension
Cheemma H. et al. [12]	1–15 (3 cases), n/a	Miyocarditis, pericardial effusion
Tanır G. et al. [13]	9, F	Bradycardia

Conclusions

Today, because of vaccination and mainly ensuring hygienic conditions in society, HAV is often not encountered. A sporadic case of HAV-induced bradycardia reminded us that patients with acute HAV infection should be closely monitored for cardiovascular effects. It should be aimed at preventing the complications of HAV infection by ensuring the vaccination of risk populations.

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None.

Authors' contributions
ÖK, DİK, and EF contributed to the conception and design of the work. Analysis and interpretation of data were performed by all authors. All authors were involved in drafting of the work, and it was revised by all authors. The authors read and approved the final manuscript.

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Availability of data and materials
None.

Declarations

Ethics approval and consent to participate
The need for ethics approval was waived by the institutional ethics committee.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report.

Competing interests
The authors declare that they have no competing interests.

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