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CASE REPORT

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Acute hepatitis A complicated by encephalitis: a case report and literature review

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Abstract

Background Hepatitis A is the most common cause of acute hepatitis around the globe, especially in developing countries. It often presents with signs and symptoms related to the gastrointestinal system. However, it rarely presents extrahepatic manifestations, which can be more common in adults than in children.

Case presentation We report a unique case of hepatitis A presenting with encephalitis that was resolved conservatively. Before attributing the neurological features to hepatitis A, we had to rule out other etiologies with similar presentations.

Clinical discussion Many viruses cause encephalitis, such as herpes simplex virus types 1 and 2, varicella zoster virus and enteroviruses. A few cases of hepatitis A complicated by encephalitis have been reported in the literature. In our case, developing a tonic-clonic seizure with no past seizure history demanded more investigations to exclude other etiologies. Ultimately, clinical signs and laboratory investigations led us to consider hepatitis A as the main cause of the patient's symptoms of encephalitis.

Conclusion Hepatitis A virus may present with extrahepatic manifestations more than expected, so more studies and research should be done to increase physicians' knowledge of these manifestations, make early diagnosis, and administer the effective treatment.

Highlights

- Encephalitis is a rare extrahepatic manifestation of HAV.
- Encephalitis presenting with a tonic-clonic seizure and loss of consciousness in an icteric patient.
- Differential diagnosis is important to exclude other etiologies of encephalopathy.

Keywords Hepatitis A, Encephalitis, Convulsion, Hepatic encephalopathy, Status epilepticus

Introduction

Hepatitis A virus (HAV) is an RNA virus transmitted by the fecal-oral route or the consumption of contaminated food and water. It has an incidence rate of about 1.4 million annually [1]. Clinical manifestations of hepatitis A range from asymptomatic infection to acute liver failure in rare cases. It usually presents with fatigue, weakness, nausea, jaundice and abdominal discomfort [2].

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There have been rare cases of extrahepatic manifestations of hepatitis A, including hemolytic anemia, pleural or pericardial effusion, acute reactive arthritis and neurologic complications [3].

Although the hepatitis A virus was identified in the early 1970s, there are not enough studies assessing such unusual manifestations [4].

Encephalitis associated with hepatitis A is rare and has been reported in a few cases. The purpose of this paper is to introduce the first case report of encephalitis due to HAV in Syria with a review of the literature and differential diagnosis.

Case presentation

A 19-year-old male with no previous medical or drug intake history complained of fever, chills, abdominal pain, vomiting and dark urine. The detection of IgM antibodies against HAV in the serum of the patient confirmed the diagnosis of hepatitis A. Five days later, the patient presented with a generalized tonic-clonic seizure for 5 min accompanied by cyanosis. He could not be awakened and remained unconscious after the seizure ended. The vital signs were temperature: 37.5 °C, respiratory rate: 16/min, blood pressure: 110/60 mm Hg and pulse rate: 80/min.

On physical examination, the patient was unresponsive with partially dilated pupils that reacted sluggishly to light. The Glasgow coma score (GCS) was 9/15, head and neck examination revealed scleral icterus with no nuchal rigidity or focal neurologic signs. The deep tendon reflexes were normal with flexor plantar responses bilaterally. No lymphadenopathy or hepatosplenomegaly were detected. Otherwise, no apparent infectious source was found except the recent HAV. Blood tests revealed white blood cell (WBC) counts of 6180 cells/μL. Glucose 147 mg/dl, aspartate aminotransferase (AST) 757 U/L, alanine aminotransferase (ALT) 2397 U/L, alkaline phosphatase (ALP) 172 U/L, total bilirubin and direct bilirubin levels (7.65 mg/dL and 6.34 mg/dL, respectively). The abdominal ultrasound showed a normal-sized homogenous liver with no focal lesion or any sign of bile ducts dilation, the gall bladder's wall also appeared normal in diameter with no sign of gallstone cholecystitis.

Hepatic encephalopathy due to acute hepatic failure was ruled out since the serum ammonia levels and prothrombin time internal normalized ratio (INR) were normal. We administered IV diazepam and phenytoin when status epilepticus was considered before the electroencephalogram (EEG) showed a very slow background indicative of a severe encephalopathy without epileptiform discharges. A brain computed tomography (CT) scan showed no abnormality. Cerebrospinal fluid (CSF) analysis demonstrated leukocytes of 12 cells/ μL (80% lymphocytes), erythrocytes of 120 cells/μL, protein levels of 19.8 mg/dl and normal glucose levels (66 mg/dL) which revealed viral encephalitis. We initiated IV acyclovir because of the suspicion of herpes. Serologic tests and polymerase chain reaction specific for herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein - Barr virus (EBV), hepatitis E virus, hepatitis B virus and hepatitis C virus of the CSF were negative. The serum was only positive for anti HAV IgM.

Therefore, acyclovir was stopped and we concluded that the encephalitis was an extrahepatic manifestation of HAV. The patient was managed conservatively, and during the next 24 h the patient regained consciousness and improved significantly.

Over the next six months, the patient had been seizure-free with normal serological tests, ALT: 25 U/L, AST: 17 U/L, total bilirubin and direct bilirubin levels 0.5 and 0.1 mg/dL respectively, and EEG recordings.

Discussion

Hepatitis A virus is the most important cause of acute hepatitis, it can lead to acute liver failure and mortality in severe cases. Most HAV infections occur in developing countries and low-income regions, and the diagnosis is confirmed by the detection of the serum IgM antibody to HAV in symptomatic patients [1, 2].

The spectrum of clinical symptoms depends on the age of the patient as clinical presentations are more severe in adults than in children [5]. Some patients show atypical features of HAV such as relapsing hepatitis or prolonged cholestatic hepatitis, as well as extrahepatic manifestations [2]. However, HAV rarely causes neurological manifestations, especially encephalitis. The pathogenesis is attributed to the metabolic disturbances and disturbed detoxification process caused by the damaged liver [6]. A few cases of HAV-associated encephalitis have been reported, we present a literature review of those in (Table 1). It demonstrates a comparison between numbers of variables that had a role in the diagnosis. Almost half of the patients were young and adolescents, as was the patient in our case. The neurological manifestations of encephalitis caused by HAV included decreased levels of consciousness, confusion, combativeness and focal signs. Convulsions were present in six patients. In most cases, liver enzymes were elevated and jaundice was obvious at admission. Nuchal rigidity was also common.

In our case, the patient had previously been diagnosed with hepatitis A before developing the neurological manifestations. He presented with a seizure and loss of consciousness with no meningeal irritation or focal deficits. Because many disorders cause these nonspecific features, differential diagnosis was very important. According to our patient's past medical history, hepatic encephalopathy was our initial potential diagnosis and due to the

Table 1 Literature review of HAV-associated encephalitis

Authors	Patient's age	Neurological manifestations of encephalitis	Jaundice at admission	Nuchal rigidity	Plantar reflexes	Liver enzymes at admission
Bromberg K et al. 1982 [7]	56	Decrease mental status, mental dullness and confusion	Presence	Presence	Extensor	Elevated
Hammond GW et al. 1982 [8]	34	Disorientation, combativeness and restlessness	_	Absence	_	Elevated
Hodges JR. 1987 [9]	17	Convulsion, drowsiness and focal hemisphere signs	presence	presence	_	normal
Dollberg S et al. 1990 [10]	8 / 4	Convulsion	Presence / absence	_	_	Elevated
Matsushima K et al. 1992 [11]	39	Convulsion	Absence	Presence	Extensor	Elevated
Davis LE et al. 1993 [12]	7	Confusion, combativeness and incoherence	Presence	Absence	Flexor	Elevated
Cam S et al. 2005 [13]	5	convulsion	presence	presence	_	Elevated
Ghorbani G et al. 2008 [14]	21	confusion	_	presence	_	_
Davoudi S et al. 2010 [15]	14	headache, photosensitivity, weakness of lower extremities and dysarthria	Absence	Presence	flexor	Elevated
Hegazi MA et al. 2011 [16]	11	Coma	Absence	Absence	_	Elevated
Lee JJ et al. 2011 [6]	27	Convulsion	Absence	presence	_	Elevated
Mathew T et al. 2012 [17]	11	convulsion	Presence	Presence	Extensor	Elevated
Guillaume M et al. 2019 [18]	42	Hemiparesis, hemianopia and bilateral reactive mydriasis	Absence	_	_	normal

patient's age and the characteristics of convulsion, we also considered status epilepticus as a rational cause. Although some infections can manifest with confusion and altered mental status but not seizures, we could not find any other infectious source in our patient except the recent HAV.

Ultimately, laboratory and radiographic investigations demonstrated viral encephalitis and we, like other authors, considered HSV, hepatitis B, C and E, EBV and CMV as potential etiologies.

The only positive serological test was anti HAV IgM which confirmed the HAV-associated encephalitis.

Although Syria has a high prevalence of HAV, it is uncommon to present with encephalitis. To our knowledge, this is the first reported case of hepatitis A presented with this manifestation during the acute phase of the disease in Syria, and we hope that it will make physicians more aware of this rare presentation of HAV in future clinical practice.

Conclusion

Although HAV- associated encephalitis is rare and reported in a few cases, it can be more common than we expect, so more studies should assess the accurate incidental rates of this presentation in order to be early detected and treated.

Abbreviations

HAV Hepatitis A virus
WBC White blood cell
AST Aspartate aminotransferase
ALT Alanine aminotransferase
ALP Alkaline phosphatase
INR Internal normalized ratio
EEG Electroencephalogram
CT Computed tomography
CSF Cerebrospinal fluid
HSV Herpes simplex virus
CMV Cytomegalovirus
EBV Epstein - Barr virus

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Not applicable.

Authors' contributions

A.M is the supervisor of the case, did the examinations and made the diagnosis. The literature search was done by R.A, R.I and A.M. The manuscript was written by R.A and R.I. A.M revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate
Not required for case reports at our hospital, because this article does not contain any studies with human or animal subjects.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Competing interests
None.

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References

1. Abutaleb A, Kottilil S (2020) Hepatitis A: epidemiology, natural history, unusual clinical manifestations, and prevention. Gastroenterol Clin North Am 49:191–199. https://doi.org/10.1016/j.gtc.2020.01.002
2. Shin EC, Jeong SH (2018) Natural history, clinical manifestations, and pathogenesis of hepatitis A. Cold Spring Harb Perspect Med 8:a031708. https://doi.org/10.1101/cshperspect.a031708
3. Jeong SH, Lee HS (2010) Hepatitis A: clinical manifestations and management. Intervirology 53:15–19. https://doi.org/10.1159/000252779
4. Guenifi W, Gasmi A, Lacheheb A (2022) Les manifestations extra-hépatiques de l'hépatite A [Extra hepatic manifestations of hepatitis A]. Rev Med Interne 43:603–607. https://doi.org/10.1016/j.revmed.2022.07.007
5. Jung YM, Park SJ, Kim JS et al (2010) Atypical manifestations of hepatitis a infection: a prospective, multicenter study in Korea. J Med Virol 82:1318–1326. https://doi.org/10.1002/jmv.21822
6. Lee JJ, Kang K, Park JM, Kwon O, Kim BK (2011) Encephalitis associated with acute hepatitis A. J Epilepsy Res 1:27–28. https://doi.org/10.14581/jer.11005
7. Bromberg K, Newhall DN, Peter G (1982) Hepatitis A and meningoencephalitis. JAMA 247:815. https://pubmed.ncbi.nlm.nih.gov/6276580/#:~:text=G%20Peter-,PMID%3A%206276580,-No%20abstract%20available
8. Hammond GW, MacDougall BK, Plummer F, Sekla LH (1982) Encephalitis during the prodromal stage of acute hepatitis A. Can Med Assoc J 126:269–270. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc1862821/
9. Hodges JR (1987) Hepatitis A and meningo-encephalitis. J Neurol 234:364. https://doi.org/10.1007/bf00314299
10. Dollberg S, Hurvitz H, Reifen RM, Navon P, Branski D (1990) Seizures in the course of hepatitis A. Am J Dis Child 144:140–141. https://doi.org/10.1001/archpedi.1990.02150260018010
11. Matsushima K, Niwa K, Fujita H, Yamamoto M, Shinohara Y (1992) Acute hepatitis A (HA) presenting findings of meningoencephalitis. Rinsho Shinkeigaku 32:441–443. https://pubmed.ncbi.nlm.nih.gov/1395333/#:~:text=expand-,PMID%3A%201395333,-Abstract
12. Davis LE, Brown JE, Robertson BH, Khanna B, Polish LB (1993) Hepatitis A post-viral encephalitis. Acta Neurol Scand 87:67–69. https://doi.org/10.1111/j.1600-0404.1993.tb04078.x
13. Cam S, Ertem D, Koroglu OA, Pehlivanoglu E (2005) Hepatitis A virus infection presenting with seizures. Pediatr Infect Dis J 24:652–653. https://doi.org/10.1097/01.inf.0000168754.24478.6d
14. Ghorbani G, Ameli J, Ghadimi HR (2008) Meningoencephalitis of hepatitis A in adult man: a case report. Hepat Mon 8:313–316
15. Davoudi S, Soudbakhsh A, Emadikouchak H, Nikbakht G, Modabbernia A (2010) Meningoencephalitis associated with hepatitis A infection: a case report and review of literature. Trop Doct 40:176–177. https://doi.org/10.1258/td.2010.090424
16. Hegazi MA, Mansor I, Rahman FA, El-Sayed M (2011) Hepatitis A virus presenting as fatal encephalitis in a child. Pediatr Infect Dis J 30:1012. https://doi.org/10.1097/inf.0b013e3182270020
17. Mathew T, Aroor S, Nadig R, Sarma G (2012) Focal meningoencephalitis of hepatitis A: a clinico-radiologic picture. Pediatr Neurol 47:222–223. https://doi.org/10.1016/j.pediatrneurol.2012.05.023
18. Guillaume M, Mouna L, Coustillères F et al (2019) Invasive meningoencephalitis as the first manifestation of hepatitis A. J Viral Hepat 26:1330–1333. https://doi.org/10.1111/jvh.13177

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