CASE REPORT

Hepatitis E virus infection in a patient with suspected drug-induced liver injury

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SUMMARY

A 58 years old woman, known case of multiple sclerosis, was referred to the acute medical assessment unit for worsening liver function. She was recently started on a new drug (fingolimod) for multiple sclerosis. After excluding common causes of acute hepatitis in the community, a working diagnosis of drug-induced liver injury was made. When liver enzymes kept rising, further investigations were carried out, which revealed acute hepatitis E virus (HEV) infection. This finding was unexpected, as this patient had no risk factor to acquire HEV infection and there was not a single case of HEV diagnosed in our hospital since long time. This case report highlights certain issues like, considering rarest possible diagnosis when meeting such clinical case, concern over the infections which were once thought confined to the developing countries and inclusion of HEV workup in the cases of acute hepatitis when baseline workup is inconclusive.

BACKGROUND

Drug-induced liver injury (DILI) and rising number of hepatitis E virus (HEV) seropositivity are two different issues, but the recent discovery of HEV cases in those patients who were initially labelled as DILI has created an interesting relation between both these disorders. Unfortunately literature about these issues is scarce. Through this case report we have tried to highlight the importance of DILI and growing incidence of HEV in the developed countries.

CASE PRESENTATION

This patient was managing well on interferon for primary progressive multiple sclerosis for several years. She had no disability, living a normal life without any assistance. She had not travelled anywhere in the past 12 months. She is very particular with her food, usually eats chicken and fish cooked at home. She does not smoke or drink alcohol. She has not had contact with any person with hepatitis in the recent past.

In October 2015, interferon was changed with a new immunomodulator (fingolimod) on her own request as she wanted to get rid of injections. Her medications at the time of admission in our service were fingolimod (0.5 mg once daily), carbamazepine, atorvastatin, pregabalin, baclofen, fesoteridone, dosulepin and modafanil.

On 13 January 2016 she had her routine liver function test (LFT) checked at general practitioner (GP) practice. The test showed derangement of liver function (>5 times of normal). She was

completely asymptomatic at that stage. The GP contacted her neurologist who advised to continue fingolimod and repeat the LFT after 2 weeks. Repeated LFT on 27 January 2016 showed worsening results, though she was completely asymptomatic (table 1).

Fingolimod and atorvastatin were discontinued at this stage after discussion with the neurologist. Over the next few days she started feeling unwell and noticed yellowish discolouration of the skin and sclera. She was referred to the acute medical assessment unit of the Letterkenny university hospital on 5 February 2016. She reported about tiredness, loss of appetite, nausea and generalised pruritus. LFTs on admission showed severe transaminitis and hyperbilirubinaemia. She denied abdominal pain, fever or any other symptoms. On examination she was fully alert and oriented but deeply jaundiced affecting skin, sclera and mucous membranes. Her abdomen was soft, non-tender, not distended and no organomegaly was found. Other systemic examinations were unremarkable; there were no signs of chronic liver disease. The patient was admitted in our service under the care of consultant physician. Hepatitis A, B, C and autoimmune screenings were negative. Renal function test, coagulation profile and full blood count were normal. Ultrasound scan of the liver showed normal liver and adjacent viscera. At this stage we presumed that her acute hepatitis was due to DILI. Though she was not showing features of fulminant hepatic failure or fulfilling the criteria for liver transplant but due to significant rise in liver enzymes, the case was referred to the liver unit in the tertiary hospital as per advice of the gastroenterologist. The hepatologist in the tertiary hospital advised for observation and further workup including serology for HEV, adenovirus, herpes simplex virus, leptospirosis, Epstein-Barr virus, cytomegalovirus and CT scan of the liver. Liver enzymes kept rising for few days, followed by gradual decline. CT scan of the liver was reported normal. On day 8 of admission the team was notified for high titres of antihepatitis E IgM and IgG. Later PCR also confirmed presence of hepatitis E RNA in high titres. Genotyping of HEV could not be carried out for some technical reasons. The patient was managed conservatively and discharged home after achieving a good clinical improvement with significant decline in liver enzymes (table 2).

DIFFERENTIAL DIAGNOSIS

1. Acute HEV infection
2. DILI

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Table 1 LFTs before hospitalisation

	11 November 2015	13 January 2016	27 January 2016
AST	21	253	953
ALT	14	335	1215
Alk. P	56	81	158
Total bilirubin	07	09	61
GGT	36	160	375
Total protein	65	66	65
Albumin	44	44	41
Globulin	21	22	24

Alk. P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transferase; LFT, liver function test.

Table 2 LFTs trend from hospitalisation until last follow-up

	5 February 2016	8 February 2016	11 February 2016	15 February 2016	9 March 2016
AST	2831	2715	739	180	32
ALT	2722	2542	1126	433	23
Alk. P	146	130	116	110	72
Total bilirubin	203	258	275	200	44
GGT	232	181	159	125	49
Total protein	63	58	57	65	66
Albumin	39	37	35	38	43
Globulin	24	21	20	27	26
INR	1.3	1.3	1.2	1.0	–

Alk. P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transferase; INR, international normalised ratio; LFT, liver function test.

OUTCOME AND FOLLOW-UP

She was followed up in the clinic after 4 weeks, where repeated PCR for HEV showed complete clearance of HEV.

She had returned to her baseline. Fingolimod was not started again and she is planning to see her neurologist to discuss options for multiple sclerosis treatment in the future.

DISCUSSION

Hepatitis E

HEV is making its way into the developed countries. Though its mode of transmission and genotypes are different than in developing countries, today's fact is that HEV is now nearly endemic here.¹ The worrisome part is that in a large number of developed countries HEV infection remains under-rated and is not under surveillance.

HEV is a RNA virus with four human infecting genotypes (HEV 1–4). In developing countries where HEV is endemic, genotypes 1 and 2 infect humans via faecal oral route (contaminated water). These genotypes produce an acute self-limiting disease except in pregnant women, who can be seriously ill with a case fatality of nearly 25%.² But there are no reported cases of chronic hepatitis caused by these viral strains.

In Europe and other parts of the developed world initially HEV was thought to be a disease of international travellers returning from Asia and Africa, but now it is being realised that it is endemic in Europe, where along with the waterborne strains carried by travellers, zoonotic transmission of the HEV 3

and 4 occurs via consumption of raw or undercooked pork produce autochthonous cases.¹ Therefore, in Europe HEV carries features of autochthonous and imported infections.³ HEV 3 and 4 are not only confined to human but can also infect pigs and other mammals. In humans, these genotypes produce acute self-limiting hepatitis similar to HEV 1 and 2.⁴ HEV 3 is more notable as it can cause chronic hepatitis (persistence of virus in serum or stool for 6 months or more) in immunosuppressed patients.⁵

Despite the fact that HEV is endemic in Europe and it has chances of progression into chronic infection in immunosuppressed patients, documentation and reporting of HEV is not satisfactory in most parts of the Europe.⁶ It is difficult to get the correct estimation of seroprevalence rate in Europe, a few studies have suggested that it is <5% but the true number could be higher, given the fact that in the Toulouse region of south-west France initially seroprevalence of HEV in the blood donors was thought to be 16% but more sensitive assays showed a much higher rate of 52%.⁷

In Ireland until recently (2015) HEV was not a notifiable disease,⁶ but due to significant changes in HEV epidemiology, it is now notifiable and introduced in the routine panel of tests performed for acute hepatitis.⁸ In 2015, 30 cases of HEV were reported to the national virus reference laboratory of Ireland.⁶ This recent change in the reporting system and inclusion of HEV in the workup of acute hepatitis could help us to estimate the real number of HEV cases in the next few years, which might be higher than it was expected in the past.

Drug-induced liver injury

DILI is one of the common causes of acute liver failure, which resulted in usage restriction, prescription warning and in extreme cases disapproval and market withdrawal of certain drugs.⁹ There is no set parameter, laboratory or radiological finding to diagnose DILI; and the diversity of its clinical presentation makes it even more difficult.¹⁰ Therefore, DILI is usually dealt as a diagnosis of exclusion after careful elimination of common causes such as viral hepatitis, bile duct obstruction, autoimmune hepatitis, alcoholic hepatitis, and certain metabolic and genetic causes.

The casual relation between HEV and DILI is an interesting finding which came under the spotlight when a number of patients who were initially diagnosed as DILI were rather found to have HEV infection as a causative agent for elevated liver enzymes.^{11 12} Findings of DILI network showed among 318 patients of suspected DILI, 50 (16%) were positive for anti-HEV IgG and 9 (3%) for anti-HEV IgM.¹¹

Fingolimod

Fingolimod is a sphingosine 1 receptor modulator, used for relapsing-remitting multiple sclerosis. It is relatively a new drug in the clinical practice and in Europe it was licensed during 2011. There are over 400 drugs known to interact with fingolimod, whereas atorvastatin also interacts with more than 200 drugs. But no interaction is reported yet between both agents, neither there is any data that one potentiates the hepatotoxicity of other. Elevation of liver enzymes and reduction in peripheral blood lymphocyte counts were among the most common adverse events reported in phases II, III and extension studies. The drug label requires discontinuing the drug if liver enzymes increase by ≥ 5 .¹³ The rise in liver enzymes looks dose dependent, as seen in the placebo-controlled phase III trial of fingolimod, where elevation of liver enzymes were reported in 0.5% of participants receiving 1.25 mg daily dose and in none of the

participants receiving the 0.5 mg daily dose.¹⁴ To date, the European and American guidelines recommend periodic monitoring of liver enzymes and peripheral blood complete blood count and discontinuation of treatment if the LFTs increased by $\geq 5 \times \text{ULN}$. It is not yet clear when to resume the drug, and what if there is recurrence of lymphopenia or liver injury.¹⁵

CONCLUSION

It is extremely difficult to conclude a firm diagnosis in such cases, where multiple causative agents are in question. DILI cannot be completely ruled out, given the fact that multiple hepatotoxic drugs were in use. But in this case we witnessed a close correlation between elevation of liver enzymes and detection of HEV RNA and IgM antibodies. Presence of HEV RNA and IgM antibodies in high titres during acute phase, followed by complete clearance of the virus with the normalisation of liver enzymes points more towards the diagnosis of acute HEV infection.

Learning points

- ▶ Hepatitis E virus (HEV) is an emerging fact in developed countries and should be considered in all the patients with acute hepatitis besides hepatitis A, B and C.
- ▶ An integral reporting system could be introduced in all developed countries to estimate the real number of HEV cases.
- ▶ Drug-induced liver injury needs a careful assessment and should be dealt as diagnosis of exclusion unless obvious reason (paracetamol poisoning).

Contributors AM, after obtaining consent from the patient, collected related information through interview with the patient and review of case notes. He designed and drafted the report for publication, used PubMed to search for related articles and case reports. He did a thorough review of available literature before

presenting it to the consultant for review. JM brought up the idea for writing a case report on this particular case. This patient was admitted under his care and his generous expert opinion helped in to finalise the report. He supported enormously throughout the analysis of data and drafting of report.

Competing interests None declared.

Patient consent Obtained.

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