Extra-hepatic manifestations associated with hepatitis E virus infection: a comprehensive review of the literature

Fateh Bazerbachi1,†, Samir Haffar2,†, Sushil K Garg1 and John R Lake1,*

1Division of Gastroenterology and Hepatology, University of Minnesota, Minneapolis, MN 55455, USA and
2Department of Gastroenterology and Hepatology, University of Damascus, Damascus, Syrian Arab Republic

*Corresponding author. Division of Gastroenterology and Hepatology, University of Minnesota, 420 Delaware Street Southeast, Minneapolis, MN 55455, USA. Tel: +1-612-625-8999; Fax: +1-612-625-5620; Email: lakex009@umn.edu

†Fateh Bazerbachi and Samir Haffar contributed equally to this work and share first authorship.

Abstract

Background and aims: Hepatitis E virus (HEV) infection is a significant public health problem that afflicts almost 20 million individuals annually and causes acute liver injury in 3.5 million, with approximately 56 000 deaths. As with other viral hepatitis, extra-hepatic manifestations could represent an important aspect of this infection. The spectrum of these manifestations is still emerging. Acute pancreatitis and neurological, musculoskeletal, hematological, renal, and other immune-mediated manifestations have been described. The aim of this article is to comprehensively review the published literature of extra-hepatic manifestations associated with HEV infection.

Data sources: We searched the PubMed database using the MeSH term “hepatitis E” and each of the extra-hepatic manifestations associated with HEV infection. No language or date restrictions were set in these searches. Searches retrieving articles with non-A, non-B hepatitis were excluded. Additional articles were identified through the reference lists of included articles.

Results: Several extra-hepatic manifestations associated with HEV infection have been published. The temporal association between some extra-hepatic manifestations and HEV infection and the exclusion of other possible etiologies suggests that HEV infection could have caused some of them. According to the available data, HEV infection appears to be strongly associated with acute pancreatitis, neurological disorders (with primarily dominant peripheral nerve involvement, most commonly manifested as Guillain-Barre’s syndrome, followed by neuralgic amyotrophy), hematological diseases (hemolytic anemia due to glucose phosphate dehydrogenase deficiency, and severe thrombocytopenia), glomerulonephritis, and mixed cryoglobulinemia. More data are needed to clarify whether an association exists with musculoskeletal or other immune-mediated manifestations.

Conclusions: HEV infection should be considered in patients with acute pancreatitis, Guillain-Barre’s syndrome, neuralgic amyotrophy, hemolytic anemia due to glucose phosphate dehydrogenase deficiency, severe thrombocytopenia, glomerulonephritis, and mixed cryoglobulinemia. Alternatively, signs and symptoms of these conditions should be sought in patients with acute or chronic HEV infection. More data are needed to confirm the role of HEV in other extra-hepatic disorders.

Key words: hepatitis E virus; viral hepatitis; extra-hepatic manifestations; vaccine; primary prevention
Introduction

Hepatitis E virus (HEV) infection is an important public health problem in the developing world and presents two major issues. According to the fact sheet on hepatitis E, published by the World Health Organization (WHO) and updated in June 2014, there are each year 20 million hepatitis E infections, over 3 million acute cases of hepatitis E, and 56,000 hepatitis E-related deaths, with the highest prevalence in East- and southern Asia [1]. In the developed countries, hepatitis E infection is an emerging disease. It was traditionally thought to occur in individuals travelling to areas where the disease is endemic; however, cases of sporadic autochthonous hepatitis E have been reported in individuals with no history of recent travel [2]. In a recent analysis of the National Health and Nutrition Evaluation Survey (NHANES), the seroprevalence of hepatitis E in the USA was estimated at 6%, despite the rarity of reported cases of hepatitis E [3]. Its seroprevalence in blood donors in the United Kingdom is estimated to be 11% [4]. In the Toulouse region in south-west France—an area in which the disease is considered to be hyperendemic—the seroprevalence in blood donors was initially thought to be 16%, but rose to 52% using more sensitive assays [5].

HEV can cause asymptomatic, icteric, or fulminant acute hepatitis [6]. Cases of chronic hepatitis E were first reported in 2008 [7]. Chronic hepatitis has been described in HEV genotype 3 infection, which occurs in western Europe and North America, almost exclusively among immunosuppressed individuals. Some patients with chronic hepatitis E develop progressive liver disease, resulting in advanced fibrosis or cirrhosis [8].

In immunocompetent individuals, acute hepatitis E is diagnosed, based on the detection of anti-HEV immunoglobulin M (IgM), increased titers of anti-HEV immunoglobulin G (IgG), or detection of HEV RNA in blood or stool. In immunocompromised individuals, acute hepatitis E is diagnosed, based on detection of HEV RNA in blood or stool [9]. Given that serological techniques vary in their accuracy [10], some authors recommend confirming serologically-detected cases with molecular techniques (HEV RNA) [11]. Chronic hepatitis E is defined by persistent HEV replication for more than 6 months, or more than 3 months in the setting of organ transplantation [12].

The number of papers published on HEV infection and indexed in PubMed has increased substantially during the last decade. Numerous extra-hepatic manifestations are reported in association with acute or chronic hepatitis E [13]. Although causality is uncertain [14], the temporal association between HEV infection and the extra-hepatic manifestations, plus the exclusion of other possible etiologies suggest that HEV infection may be causal. These extra-hepatic manifestations can overshadow the hepatic injury and HEV may not be suspected. The aim of this article is to comprehensively review the published literature on extra-hepatic manifestations associated with HEV infection.

Search strategy and selection criteria

Two independent investigators (FB and SH) searched PubMed on March 25, 2015 using the MeSH term “hepatitis E” AND each of the following MeSH terms: “pancreatitis”, “Guillain-Barre syndrome”, “brachial plexus neuritis”, “peripheral nervous system diseases”, “meningitis”, “encephalitis”, “myelitis”, “myositis”, “arthralgia”, “glucosephosphate dehydrogenase deficiency”, “anemia”, “thrombocytopenia”, “agranulocytosis”, “macrophage activation syndrome”, “monoclonal gammopathy”, “glomerulonephritis”, “renal insufficiency”, “cryoglobulinemia”, “Schönlein-Henoch purpura”, “myasthenia gravis”, “thyroiditis”, “hyperthyroidism”, and “myocarditis”. No language or date restrictions were set in these searches. Searches retrieving articles with non-A, non-B hepatitis were excluded. Additional articles were sourced manually by searching the bibliographies of relevant articles. The extra-hepatic manifestations associated with HEV infection found in these searches were classified into different categories as shown in Table 1. There were no disagreements between the two investigators regarding the search results. An example of inter-investigator discussion was the choice of acute pancreatitis classification (mild, moderately severe, or severe) based on Revision of the Atlanta classification. Another example was discussion of duplicated cases of neurological manifestations and making sure that no duplicates were added to the manuscript.

Acute pancreatitis

Acute pancreatitis (AP) in the setting of fulminant viral hepatitis is well recognized, and mortality depends on the severity of hepatitis, rather than pancreatitis [15, 16]. AP is rarely associated with non-fulminant viral hepatitis. Most frequently, these cases are attributed to hepatitis A virus (HAV), hepatitis B virus (HBV) or hepatitis C virus (HCV) [17]. The first documented case of non-fulminant HEV-associated AP was reported in 1999 by Mishra et al. [18], along with five other cases of HAV-related AP. To the best of our knowledge, at least 13 other case reports [19–31] and 4 case series [32–35] have been reported, with a total of 56 patients (Table 2). One study was in the form of an abstract [34], and all others were original articles. Two of the case series were prospective [33, 35], and the other two were retrospective [32, 34]. Three patients were excluded: one patient had other plausible causes of AP (including medications) [29], and two patients had fulminant acute hepatitis E according to the criteria in the position paper on acute liver failure, published by the American Association for the study of Liver Diseases [34–36]. All cases fulfilled the criteria of the American College of Gastroenterology for the diagnosis of AP [37].

Of the 53 included patients, 51 were from southern Asia (India and Nepal) and 2 were from western countries, although both had recently travelled to southern Asia [20, 21]. The mean age of patients at diagnosis was 24.6 years (range 7–54) with a male-to-female ratio of 18:1. The diagnosis of acute HEV was based on the presence of anti-HEV IgM in 49 patients, anti-HEV IgG and anti-HEV IgM in 1 patient, and anti-HEV IgM and HEV RNA in 3 patients. Genotyping was performed in one patient and revealed type 1a [20]. It is presumed that all other patients were infected with genotype 1, which is prevalent in that area; it is possible that genotype 1 has high tropism for the pancreas. So far, no cases of AP have been reported in patients infected with other HEV genotypes. Although the presumption that all these patients were infected with genotype 1 may be justified, there is also a possibility that other genotypes may be associated with AP; however—as is the case of fulminant acute hepatitis E, which has been increasingly reported in western Europe, where genotype 3 is prevalent—AP related to acute hepatitis E may occur in these regions as well.

The mean interval between jaundice and AP-pain was 10 days (range 0–35). The mean hospital stay for AP was 9 days (range 2–35). We retrospectively classified these AP cases into mild, moderately severe, or severe, based on Revision of the Atlanta Classification [38], as it is currently the most widely accepted set of criteria. AP was mild or moderately severe in 44 patients (83%) and severe in 9 patients (17%). Mild
pancreatitis was not evaluated in a major prospective study of these cases [35], which may have resulted in a selection bias favoring the diagnosis of more severe cases. The overall mortality rate was 3.8% (2 of 53 patients) which is similar to the mortality rate observed for all other causes of AP.

The typical profile is a 25-year-old male residing in southern Asia, developing acute pancreatitis 10 days after the onset of jaundice, usually resolving with supportive treatment, with greater severity than previously thought, but with a similar mortality rate to other causes of AP.

Severe abdominal pain early in the course of acute hepatitis E should alert the clinician to the possibility of associated AP. Early diagnosis of AP complicating acute hepatitis E may help in reducing morbidity and mortality. Despite the rarity of the association between AP and non-fulminant acute hepatitis E, HEV infection should be added to the potential etiologies of AP in areas where the disease is endemic.

Neurological manifestations of HEV infection

Neurological manifestations of HEV infection were first reported by Soud in 2000 [39]. We are aware of 42 subsequent reports, involving a total of 77 patients, from regions where the disease is endemic and others where it is not, of neurological manifestations associated with HEV infection [40–81] (Table 3).

Neurological manifestations in patients with HEV infection are uncommon and have been reported as occurring in 7 cases of acute or chronic HEV infection (5.5%) over a 5-year period in a case series from Toulouse, France, and Cornwall, UK [40], and in 8 out of 106 cases of autochthonous acute and chronic hepatitis E (7.5%) over a 14-year period in a recent retrospective study from Cornwall, UK [41]. The spectrum of neurological injury is broad and can be divided into two clinical presentations: the dominant clinical presentation is peripheral nerve involvement—most commonly manifesting as Guillain-Barré syndrome (GBS)—followed by neuralgic amyotrophy (NA); the second and less frequent picture is central involvement in the form of meningitis, encephalitis, meningoencephalitis, or transverse myelitis. Although only genotype 3 was found among patients in developed countries, cases from southern Asia were not genotyped and many of these cases could have been infected with genotype 1.

Thirty-seven cases of GBS were reported in 16 case reports and 2 case-controlled studies. In these case-controlled studies of GBS of all etiologies—involving 100 patients in Bangladesh and 201 patients in the Netherlands—acute HEV infection was associated with this syndrome in 11% and 5% of patients, respectively [42]. The mean age of the reported patients was 44.5 years (range 20–73) with a male-to-female ratio of 9:4. The mean delay between acute hepatitis E and neurological symptoms was 6 days (range 0–40). In 16 cases for which details of treatment were available, intravenous immunoglobulin (IVIG) was used in 13, mechanical ventilation in 5, plasmapheresis in 3 cases, and ribavirin in 1. Neurological recovery was complete in 13 cases and partial in the remaining three within a period ranging from 1 week to 18 months.

Neuralgic amyotrophy (NA), also known as brachial neuritis or Parsonage-Turner syndrome, is an acute monophasic brachial plexus disorder of unknown cause, although preceding infections have commonly been reported. Eighteen cases of NA were reported in 17 case reports and 1 case series. In this case series of 47 NA patients of all etiologies from the UK and the Netherlands, acute hepatitis E was associated with this.

| Table 1. Extra-hepatic manifestations of HEV infection |
| --- |
| Manifestation | Type |
| Acute pancreatitis | Central nervous system diseases |
| Neurological | Meningitis - encephalitis - meningoencephalitis |
| | Ataxia |
| | Pyramidal syndrome |
| | Pseudotumor cerebri |
| | Acute transverse myelitis |
| Peripheral nervous system diseases | Guillain-Barre syndrome |
| | Neuralgic amyotrophy |
| | Cranial nerve diseases: Bell palsy - oculomotor palsy |
| Musculoskeletal | Necrotizing myositis |
| | Pyomyositis |
| Hematological | Hemolytic anemia |
| | Aplastic anemia |
| | Pure red-cell aplasia |
| | Severe thrombocytopenia |
| | Hemophagocytic syndrome |
| | MGUS |
| Renal | Decreased eGFR |
| | Glomerulonephritis ± cryoglobulinemia |
| | Membranous glomerulonephritis |
| | Membranoproliferative glomerulonephritis |
| | IgA nephropathy |
| | Nephroangiosclerosis |
| Other immune-mediated | Thyroiditis |
| | Myocarditis |
| | Henoch–Schönlein purpura |
| | Myasthenia gravis |

eGFR = estimated glomerular filtration rate; G6PD = glucose-6-phosphate dehydrogenase; MGUS = monoclonal gammopathy of uncertain significance
| Authors/year | Country | No. of cases | Age/sex | HEV diagnosis/genotype | Days to APa | Days in hospital for APb | Severity of AP | Treatment of AP | Outcome |
|--------------|---------|--------------|---------|------------------------|-------------|--------------------------|----------------|----------------|---------|
| **Case report** | | | | | | | | | |
| Mishra 1999 [18] | India | 1 | 14/M | IgM/NT | 10 | 4 | Mild | Supportive | Recovery |
| Majumder 1999 [25] | India | 1 | 32/M | IgM/NT | 15 | NM | Moderately severe | Surgery | Recovery |
| Borgohain 2000 [19] | India | 1 | 18/M | IgG-IgM/NT | 0 | 9 | Mild | Supportive | Recovery |
| Maity 2002 [24] | India | 1 | 18/M | IgM/NT | 30 | 35 | Severe | Hemodialysis | Recovery |
| Makharia 2003 [26] | India | 1 | 45/M | IgM/NT | 0 | NM | Mild | Supportive | Recovery |
| Jarozewicz 2005 [21]c | Poland | 1 | 28/M | IgM/NT | 15 | 6 | Mild | Supportive | Recovery |
| Thapa 2009 [31]d | India | 1 | 7/M | IgM/NT | 12 | 29 | Mild | Supportive | Recovery |
| Somani 2009 [30] | India | 1 | 35/M | IgM/NT | 7 | 20 | Severe | Hemodialysis | Death |
| Deniel 2011 [20]e | France | 1 | 26/M | IgM-PCR/1a | 21 | NM | Moderately severe | Supportive | Recovery |
| Javid 2012 [22] | India | 1 | 36/M | IgG-IgM/NT | 7 | 5 | Mild | Supportive | Recovery |
| Rudrajit 2013 [28] | India | 1 | 24/M | IgM/NT | 16 | 6 | Mild | Supportive | Recovery |
| Nayak 2013 [27] | India | 1 | 16/M | IgM-PCR/NT | 8 | 9 | mild | Supportive | Recovery |
| Karanth 2014 [23] | India | 1 | 27/M | IgG-IgM-PCR/NT | 28 | 14 | severe | Supportive | Recovery |
| **Case series** | | | | | | | | | |
| Jain 2007 [33] | India | 4 | mean 26 | IgM/NT | 4 (2–5) | 6 (3–12) | 4 mild | 4 supportive | Recovery |
| Bhagat 2008 [32] | India | 4 | mean 21 | IgM/NT | 15 (12–17) | 12 (7–23) | 2 mild | 3 supportive | Recovery |
| Sudhamshu 2011 [35] | Nepal | 17 | NM | IgM/NT | NM | NM | 16 mild/moderate severe | 1 drainage | Recovery |
| Mohindra 2013 [34] | India | 15 | mean 25 | IgM/NT | 8 (0–35) | 7 (2–30) | 5 mild | 16 supportive | 16 recovery |
| **Total** | | 51 southern Asia 1 France 1 Poland | mean 24.6 35M/2F | 49 IgM 1 IgG + IgM 3 IgM + PCR | 10 (0–35) | 9 (2–35) | 44 mild/moderate severe 9 severe | 47 supportive 2 surgery | 2 deaths 51 recovery |

aDays between jaundice and acute pancreatitis
bDays in hospital after diagnosis of AP
cIndian patient living in Poland with recent travel to India
dG6PD deficiency patient
ePakistan-French patient living in France with recent travel to Pakistan
NM=not mentioned; NT=not tested
Table 3. Neurological manifestations associated with HEV infection

| Authors/year | Country        | No. of cases | Age/sex | Neurological manifestations | Delay hepatitis neurological disorders | IgM | HEV RNA | HEV genotype | ALT (IU/L) | Treatment       | Recovery/delay |
|--------------|----------------|--------------|---------|----------------------------|----------------------------------------|-----|---------|--------------|------------|-----------------|----------------|
| Acute hepatitis E – Peripheral manifestations |
| Sood 2000 [39] | India          | 1            | 50/M    | GBS                        | 5 days                                 | +   | NT      | NT           | 114        | Supportive      | Full/1 month   |
| Kumar 2002 [45] | India          | 1            | 35/M    | GBS                        | 17 days                                 | +   | NT      | NT           | 752        | MV/IVIG         | Full/2 weeks   |
| Kamani 2005 [46] | India          | 1            | 58/F    | GBS                        | 9 days                                  | +   | NT      | NT           | 1448       | IVIG/PP         | Full/12 days   |
| Khanam 2008 [47] | Bangladesh     | 1            | 20/M    | GBS                        | 10 days                                 | +   | NT      | NT           | 2509       | MV              | Full/12 days   |
| Loly 2009 [48]  | Belgium        | 1            | 66/M    | GBS GM2+                   | Few days                                | +   | NT      | NT           | 1813       | IVIG            | Full/3 months  |
| Chalupa 2010 [49] | Czech Rep      | 1            | 65/M    | GBS                        | No delay for all                        | +   | NT      | NT           | 1600       | IVIG            | Full/4 months  |
| Kamar 2011 [50] | France         | 1            | 60/F    | GBS                        | Concomitant                             | +   | Serum+CSF-| 3f           | 384        | IVIG            | Partial/18 months |
| Cronin 2011 [51] | Ireland        | 1            | 40/M    | GBS GM2+                   | Concomitant                             | +   | NT      | NT           | 57         | MV/IVIG/PP      | Full/6 months  |
| Maurissen 2012 [52] | Belgium       | 1            | 51/F    | GBS GM1 & 2+               | Concomitant                             | +   | Serum+  | NT           | 2074       | IVIG            | Full/1 week    |
| Tse 2012 [53]   | Hong Kong      | 1            | 60/F    | GBS                        | 3 days                                  | +   | NT      | NT           | 2858       | PP              | Full/1 month   |
| Del Bello 2012 [54] | France       | 1            | 65/M    | GBS                        | Concomitant                             | +   | Serum+  | 3f           | 2000       | MV/IVIM/Riba  | partial/1 month |
| Santos 2013 [55] | Portugal       | 1            | 58/M    | GBS                        | 17 days                                 | +   | Serum+  | 3a           | 2320       | IVIG/MV        | partial/2 months |
| Sharma 2013 [56] | India          | 1            | 27/M    | GBS                        | 40 days                                 | +   | NT      | NT           | NM         | IVIG/IVIG       | Full/4 months  |
| Geurtsvan-Kessel 2013 [57] | Bangladesh | 11           | 24/NM   | GBS                        | Concomitant                             | +   | Serum+ in 1 | 1 in 1 | 1461       | IVIG/IVIG       | Full/12 months |
| Scharn 2014 [58] | Netherlands    | 10           | Mean: 54 6M/4F | GBS GM1 & 1B+ | Concomitant                             | +   | Serum+CSF-| 3c           | 334        | IVIG            | Full/5 months  |
| van den Berg 2014 [59] | Netherlands | 5            | Mean: 54 6M/4F | GBS GM2+ & 1B+ | Concomitant                             | +   | Serum+ in 3 | 3f           | 795         | NM             | partial/4 months |
| Chen 2014 [60]   | China          | 1            | 64/M    | GBS                        | 5 days                                  | +   | NT      | NT           | 31         | Supportive      | Full/2 months  |
| Comont 2014 [61] | France         | 1            | 73/M    | GBS                        | Concomitant                             | +   | Serum+CSF+| 3f           | 822        | IVIG            | Full/2 months  |
| Fong 2009 [62]   | UK             | 1            | 53/M    | Bilateral NA               | Concomitant                             | +   | NT      | NT           | 2547       | Physiotherapy   | Full/2 years   |
| Rianghavan 2010 [63] | Thailand   | 1            | 49/M    | Bilateral NA               | Concomitant                             | +   | Serum+  | 3f           | 769        | NM             | partial/4 months |
| Kamar 2011 [64]  | UK             | 1            | 38/M    | Bilateral NA               | 3 days                                  | +   | Serum+  | 3e           | 1160       | Supportive      | partial/18 months |
| Carl 2012 [65]   | France         | 1            | 30/M    | Left NA                    | 5 days                                  | +   | Serum+  | 3f           | 1158       | Steroid         | Full/slow      |
| Inghilleri 2012 [66] | France     | 1            | 28/M    | Bilateral NA               | Concomitant                             | +   | NT      | NT           | 1007       | NM             | Full/10 months |
| Cheung 2012 [67] | UK             | 1            | 56/M    | Bilateral NA               | Concomitant                             | +   | NT      | NT           | 300        | NM             | Partial/10 months |
| Motte 2014 [68]  | France         | 1            | 52/M    | Bilateral NA               | 7 days                                  | +   | Serum+  | 3f           | 590        | NM             | Partial/2 months |
| Meoisset 2014 [69] | France        | 1            | 36/M    | Bilateral NA               | 7 days                                  | +   | Serum+  | 3f           | 1707       | IVIG/Riba       | Partial/6 months |
| Deroux 2014 [70] | France         | 1            | 38/M    | Left NA                    | Concomitant                             | +   | NT      | NT           | 1612       | NM             | Partial/4 months |
| van Eijk 2014 [71] | Netherlands | 5            | 36’4M/1F | Bilateral NA | Concomitant                             | +   | NT      | NT           | 34–313      | NM             | Partial in 5/6 months |
| Woolson 2014 [72] | UK             | 1            | 38/M    | Bilateral NA               | NM                                      | +   | Serum+  | 3            | 319        | Supportive      | Partial/12 months |
| Theochari 2015 [73] | UK             | 1            | 39/M    | Bilateral NA               | NM                                      | +   | Serum+  | 3           | 27         | Supportive      | Partial/12 months |
| Decard 2015 [74] | Switzerland    | 1            | 47/M    | Bilateral NA               | Concomitant                             | +   | NT      | NT           | 1368       | Prednisolone   | Full/10 months |
| Kamar 2011 [75]  | UK             | 1            | 42/M    | PRN                        | Concomitant                             | +   | Serum+CSF-| 3e           | 623        | NM             | Full/3 months  |
| Despierres 2011 [76] | France      | 1            | 49/M    | PRN                        | Concomitant                             | +   | Serum+  | 3            | 78         | Supportive      | Full/2 weeks   |
| Peri 2013 [77]   | Italy          | 1            | 53/M    | PRN                        | Concomitant                             | +   | Serum+Stool+| 3            | 1768       | Supportive      | Full/3 months  |
| Authors/year | Country | No. of cases | Age/sex | Neurological manifestations | Delay hepatitis neurological disorders | IgM | HEV RNA | HEV genotype | ALT (IU/L) | Treatment | Recovery/delay |
|-------------|---------|--------------|---------|-----------------------------|----------------------------------------|-----|---------|-------------|-----------|-----------|---------------|
| Yadav 2002 [72] | India | 1 | 13/F | Oculomotor palsy | 3 days | + | NT | NT | 382 | Supportive | Minimal |
| Dixit 2006 [73] | India | 1 | 32/M | Bell's palsy | 7 days | + | NT | NT | 1000 | Supportive | Full/3 weeks |
| Jha 2012 [74] | India | 1 | 28/M | Bell's palsy | 10 days | + | NT | NT | 1200 | Physiotherapy | Full/3 weeks |
| Woolson 2014 [41] | UK | 1 | 92/F | Vestibular neuritis | Concomitant | + | Serum+ | 3 | 1504 | Supportive | Full/7 days |
| Coulibaly 2014 [42] | France | 1 | 92/F | Neuromyopathy | Concomitant | + | Serum+ | NT | 285 | Supportive | Partial/nm |
| UK | 1 | 34/M | Small-fibre neuropathy | 2 months | - | Serum+CSF- | NM | – | Gabapentin | No response |
| Bennett 2015 [75] | UK | 1 | 77/F | Paresthesia | Concomitant | + | Serum+ | NT | 1606 | Supportive | Full/3 weeks |
| Kejariwal 2001 [76] | India | 1 | 28/W | Meningo-encephalitis | Concomitant | + | NT | NT | 1890 | Supportive | Full/3 weeks |
| Deroux 2014 [67] | France | 1 | 41/M | Encephalitis | Concomitant | + | Serum+CSF+ | 3f | 479 | Nm | Full/12 weeks |
| Despierres 2011 [70] | France | 1 | 54/F | Meningitis Diffuse neuralgic pain | Concomitant | + | Serum+CSF+ | 3 | 566 | Ceftriaxone/acyclovir | Full/2 weeks |
| Naha 2012 [77] | India | 1 | 33/M | Aseptic meningitis | 10 days | + | NT | NT | 400 | Supportive | Full/nm |
| Mandal 2006 [78] | India | 1 | 12/F | Acute transverse myelitis | 20 days | + | NT | NT | 400 | Supportive | Full/10 days |
| Thapa 2009 [79] | India | 1 | 7/M | Pseudotumor cerebri | 2 days | + | NT | NT | 654 | Supportive | Full/3 days |
| Chronic hepatitis E – Neurological manifestations | | | | | | | | | | | |
| Kamar 2010 [44] | France | 1 | 44/M | Pyramidal syndrome, PN | 33 months | + | Serum+CSF+ | 3f | 105 | Reduce TAC/IVIG | Death/3 months |
| Kamar 2011 [40] | France | 1 | 60/M | Ataxia, confusion, PN | 60 months | + | Serum+CSF+ | 3f | 171 | Change TAC to sirolimus | Partial/10 months |
| France | 1 | 35/M | Encephalitis | 3 years | + | Serum+CSF+ | 3f | 110 | MMF/Riba | Full/2 months |
| Maddukuri 2013 [80] | USA | 1 | 48/M | Sensory PN | NM | + | Serum+CSF+ | 3a | 195 | PegIFN/Riba | Full/7 months |
| de Vries 2014 [81] | Netherlands | 1 | 66/F | Ataxia, cognitive decline, PN | 12 months | + | Serum+ | 3 | 362 | Reduce TAC/ PegIFN | Death/48 months |

ALT = alanine aminotransferase; CSF = cerebrospinal fluid; GBS = Guillain-Barré syndrome; IS = immunosuppressants; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; MV = mechanical ventilation; NA = neuralgic amyotrophy; NM = not mentioned; NT = not tested; PN = peripheral neuropathy; PegIFN = pegylated interferon; PP = plasmapheresis; PRN = polyradiculoneuropathy; Riba = ribavirin; TAC = tacrolimus
neurological disorder in 10% of patients [43]. The mean age of reported patients with NA was 50 years (range 28–65) with a male-to-female ratio of 8:1. The delay between acute hepatitis E and neurological symptoms ranged from 0–7 days. NA was bilateral in 16 cases and unilateral in 2 cases (88%). In eight cases for which details of treatment were available, steroids were used in two, physiotherapy in two, IVIG and ribavirin in one case, and the treatment was supportive in three cases. Neurological recovery was complete in three cases after follow-up periods of 10–24 months, and partial in 14 cases after follow-up periods of 2–24 months.

The finding that hepatitis E is associated with both GBS and NA may suggest that these syndromes reflect differing parts of the same spectrum of neurological immune-mediated diseases [43].

Six cases have been reported of neurological manifestations of chronic hepatitis E following solid organ transplantation (five cases) and HIV infection (one case). HEV RNA has been found in both the serum and the cerebrospinal fluid (CSF) in the five tested patients, which suggests that HEV replication may occur in this compartment. Analysis of such HEV RNA in one patient shows that the variants differed from those observed at the same time point in the serum, which suggests the presence of neurotropic quasispecies [44]. The first-line therapy for chronic HEV in solid organ transplant recipients is to reduce immunosuppressants when possible. The second-line therapy in these patients is the administration of ribavirin. Full neurological recovery following treatment was noted in one patient, partial recovery in two and death, related to decompensated cirrhosis and neurological deterioration, in two. Full neurological recovery was observed in the sixth patient with HIV infection following treatment with peginterferon and ribavirin.

It is recommended that clinicians consider the possibility of HEV infection in patients with neurological disorders and concurrent transaminase elevation, especially those with peripheral nerve involvement. The diagnosis may be suggested by HEV serology but should be confirmed with molecular testing in serum, CSF, or both. The recognition of HEV infection in a patient presenting with neurological manifestations could present an opportunity to treat active HEV infection with antivirals before chronic damage takes place, but further studies are needed to clarify their role in this setting.

### Musculoskeletal manifestations of HEV

Several musculoskeletal manifestations associated with the acute phase of HEV infection have been reported: (i) asymptomatic elevation of creatine phosphokinase (CK) of MM type indicating skeletal muscle damage [82], (ii) acute polyarthritis lasting for 3 months and resolving spontaneously [83], (iii) necrotizing myositis associated with GBS in a liver-transplant patient resolving after ribavirin administration [53], (iv) pyomyositis 4 weeks after recovery from acute hepatitis E in a patient with recent history of type 2 diabetes [84], (v) inflammatory polyarthralgia revealing acute hepatitis E [85], and (vi) arthralgia associated with a diffuse maculopapular rash resolving with supportive measures [86] (Table 4). Further studies are needed to confirm the association of HEV infection with musculoskeletal manifestations.

### Hematological manifestations of HEV

#### Hemolytic anemia

**Hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency**

HEV is endemic in southern Asia, which is home to a significant proportion of glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals and instances of co-existence of both the conditions should not be rare; however, only seven case reports [31, 87–92] and three small case series [93–95], with a total of 17 cases, have been published of severe hemolysis occurring in patients with acute hepatitis E associated with G6PD deficiency (Table 5). All cases originated from southern Asia and were thought to be attributed to genotype 1. Patients presented with high-grade fever, chills, neutrophilic leukocytosis, severe hyperbilirubinemia, and renal failure—a combination that is seldom encountered in uncomplicated viral hepatitis. Their serum bilirubin ranged from 28–66 mg/dL. Acute renal failure was present in 10 patients and their serum creatinine ranged from 5.4–9.2 mg/dL, necessitating hemodialysis in seven of them. Death due to cerebral bleeding, sepsis, and hepatic failure was reported in three patients. Given the rarity of published cases, it is quite possible that more severe cases are reported, whereas less severe ones are under-diagnosed and under-reported. Wilson’s disease should be ruled out in this setting, along with other causes of hemolytic anemia. Tests for G6PD deficiency may be negative during and immediately after a hemolytic episode and should be performed 8–10 weeks after the disease subsides. Administration of vitamin K should be avoided in these patients because it may further aggravate hemolysis. Renal failure may be non-oliguric; therefore, kidney function should be assessed by regularly monitoring blood chemistry, urinary sodium and osmolarity. Preventive measures against acute renal failure—such as maintenance of high urinary output, correction of fluid and electrolyte imbalance and avoidance of nephrotoxic drugs—should be implemented early. All cases of acute viral hepatitis with marked hyperbilirubinemia should be observed carefully for impaired renal function and hemolysis. However hemolysis due to G6PD deficiency is not an extrahepatic manifestation in the strict sense. Rather, instigation of hemolysis in G6PD-deficient individuals may be associated with HEV infection, as with several other infections.

### Table 4. Musculoskeletal manifestations associated with acute HEV infection

| Authors/year | Country | Age/sex | HEV diagnosis/ genotype | Manifestations | Treatment | Outcome |
|--------------|---------|---------|-------------------------|----------------|-----------|---------|
| Kitazawa 2003 [82] | Japan | 59/M | IgM/NT | Elevated CK MM type | Supportive | Recovery |
| Serratrice 2007 [83] | France | 51/W | PCR/3 | Acute polyarthritis | Supportive | Recovery |
| Del Bello 2012 [53] | France | 65/M | PCR/3f | Necrotizing myositis, GBS | Ribavirin | Recovery |
| Annamalai 2013 [84] | India | 39/M | NM | Pyomyositis | Surgical drainage | Recovery |
| Bailé 2013 [85] | France | 40/F | IgM-PCR/NT | Inflammatory polyarthralgia | Supportive | Recovery |
| Al-Shukri 2013 [86] | UK | 52/F | IgM-PCR/3 | Arthralgia, maculopapular rash | Supportive | Recovery |

CK – creatine phosphokinase; GBS – Guillain-Barré syndrome; NM – not mentioned; NT – not tested
Auto-immune hemolytic anemia

Auto-immune hemolytic anemia (AIHA) is rarely associated with viral hepatitis. HCV infection has been the main reported association, but cases of HAV and HBV have been also described [96]. Three documented cases of AIHA associated with HEV infection have been published [97–99]. These cases revealed sudden and rapid drops in hemoglobin levels during the course of illness and were diagnosed after excluding other causes of anemia and hemolysis. Two patients were treated supportively with good outcomes [98, 99], and the treatment administered to the third patient was not mentioned [97].

Severe thrombocytopenia

A variety of hepatotropic viruses are known to cause severe thrombocytopenia. HEV infection associated with severe thrombocytopenia has been cited in six case reports [100–105] and one case series [106]—not necessarily in regions where the disease is endemic—with a total of nine cases (Table 6). The HEV genotype was not tested in all reports from southern Asia. Genotype 3 was found in patients originating from regions where HEV is not endemic. The diagnosis relies on the exclusion of other causes of thrombocytopenia. Patients’ platelet counts ranged from 1 x 10⁹/L to 21 x 10⁹/L. Most patients improved...

Table 6. Severe thrombocytopenia associated with acute HEV infection

| Authors/year | Age/sex | Country | HEV diagnosis / genotype | ALT (IU/L) | Purpura | Platelets (/mm³) | Anti-platelet antibodies | Co-morbidity | Bone marrow aspirate | Treatment | Outcome |
|--------------|---------|---------|--------------------------|------------|---------|-----------------|--------------------------|-------------|---------------------|-----------|---------|
| Bulang 2000 [100]ᵃ | 48/M | Germany | IgM/NP | 800 – | 18 000 | NT | Sinusitis | NT | Supportive | Recovery |
| Ali 2001 [101]ᵇ | 38/M | India | IgM/NP | 670 + | 10 000 | Negative | MGN | NT | IVIG, FFP, steroids | Recovery |
| Singh 2007 [102] | 34/M | India | IgM/NP | 783 + | 13 000 | Positive | – | Normal | IVIG, platelets | Recovery |
| Colson 2008 [103] | 72/F | France | PCR/3f | 1 520 – | 9 000 | NT | Normocellular | Transient neutropenia | Normocellular | Supportive | Recovery |
| Thapa 2009 [104] | 8/F | India | IgM/NP | 1 080 + | 21 000 | Positive | Normal | NT | IVIG | Recovery |
| Fourniquet 2010 [106] | 52/F | France | PCR/3f | 2 958 – | 13 000 | NT | – | NT | Supportive | Recovery |
| 20/M | France | PCR/3f | 461 + | 1 000 | Negative | – | NT | Steroids | Recovery |
| Massoud 2014 [105] | 25/M | Pakistan | IgM/NP | 1045 – | 9 000 | NT | normo-cellular | Supportive | Platelets | Recovery |

ᵃIndian patient living in Germany with recent travel to India
ᵇPatient with membranous glomerulonephritis
FFP – fresh frozen plasma; IVIG – intravenous immunoglobulin; MGN – membranous glomerulonephritis; NT – not mentioned; NM – not tested
spontaneously, while others received platelet transfusion, intravenous immunoglobulin (IVIG) and/or corticosteroids. Recovery was observed in all patients and no fatalities were recorded. The mechanism of severe thrombocytopenia is believed to be immune-mediated, and platelet-associated antibodies have been positive in two out of four tested patients. It may be appropriate to perform HEV testing in patients with severe thrombocytopenia associated with elevated liver enzymes, regardless of the patient’s travel history.

Less-severe thrombocytopenia without significant consequences was noted in 12 out of 106 patients (11%) in a recent retrospective study of autochthonous acute and chronic hepatitis E in Cornwall, UK [41]. The lowest platelet count recorded at presentation in this study was 40 x 10^3/L.

**Hepatitis-associated aplastic anemia**

Hepatitis-associated aplastic anemia (HAAA) is a variant of the aplastic anemia syndrome, in which an acute attack of hepatitis leads to marrow failure and pancytopenia. It was first reported in 1955 and by 1975 more than 200 cases had been described [107–109]. HAV, HBV, HCV, hepatitis D virus (HDV), parvovirus B19, cytomegalovirus, and Epstein-Barr virus (EBV) have been associated with HAAA. Pancytopenia typically occurs 2–3 months after the hepatitis episode, which could be fulminating, acute, or chronic. The development of HAAA is always fatal if not managed promptly and the standard therapy is allogenic bone marrow transplantation from Human leukocyte antigen (HLA)-matched siblings, or immunosuppressive therapy if an appropriate donor is not available [110]. Two case reports of HAAA associated with HEV infection have been published, with a fatal outcome in one case and an absence of response to cyclosporine in the other [111, 112].

**Pure red cell asplasia**

Pure red cell asplasia (PRCA) is a syndrome characterized by anemia, reticulocytopeny, and markedly reduced or absent erythroid progenitor cells in the bone marrow with preservation of the other hematopoietic lineages. It may present as an isolated primary hematological disorder or secondary to parvovirus infection, collagen vascular disease, leukemia, lymphoma, thymoma, solid tumors, treatment with recombiant human erythropoietin or other drugs, and pregnancy: PRCA is acute and self-limiting. One case of PRCA has been published, of a 63-year-old Chinese man with acute liver failure associated with HEV infection, who improved with supportive care [113].

**Secondary hemophagocytic syndrome**

Secondary hemophagocytic syndrome (HPS), sometimes known as the macrophage activation syndrome, is a hyperinflammatory condition, characterized by excessive macrophage function. It is a rare, life-threatening complication of infection, hematological cancer, drug exposure, and autoimmune disease. The most common infectious trigger is EBV, but HIV is increasingly implicated, as well as other infections. There are no validated diagnostic criteria for HPS, but suggestive features include high temperatures, organomegaly, cytopenias and coagulopathy, markedly elevated ferritin levels, hypertriglyceridemia, and hypofibrinogenemia [114]. Four cases of HPS secondary to HEV infection have been published [115–118] (Table 7); high serum ferritin level was noted in all cases. Co-morbidities were observed in three cases (hepatitis A co-infection, splenic lymphoma, and rheumatoid arthritis treated with tocilizumab infusion; these could have played a role in the occurrence of hemophagocytic syndrome, due to known associations). Three patients recovered with supportive treatment, and the fourth died due to fulminant hepatitis.

**Other hematological manifestations**

Monoclonal gammapathy of undetermined significance (MGUS), without clinical or laboratory findings suggestive of myeloma or lymphoma, was noted in 17 out of 65 patients (26%) in a recent retrospective study of autochthonous acute and chronic hepatitis E in Cornwall, UK; however, bone marrow biopsy—which allows differentiation between MGUS and monoclonal gammapathy secondary to viral infections—was not performed in these patients [119]. Paraproteinemia disappeared in three out of six patients after a median of 44.5 months with follow-up serum electrophoresis.

One case of HEV-associated severe agranulocytosis was reported in a 70-year-old Spanish patient infected with genotype 3, with fatal outcome despite treatment with granulocyte-colony stimulating factor and a broad-spectrum antibiotic [120].

### Table 7. Hemophagocytic syndrome secondary to HEV infection

| Authors/year | Age /sex | Country | HEV diagnosis /genotype | Co-morbidity | Bone marrow aspirate | Hemoglobin (mg/dL) | Leucocytes (/mm³) | Platelets (/mm³) | Ferritin (mg/mL) | Treatment | Outcome |
|--------------|----------|---------|------------------------|--------------|---------------------|------------------|------------------|----------------|---------------|-----------|---------|
| Kamihira 2008 | 52/M | Japan | PCR/3 | – | – | 14.3 | 2 800 | 20 000 | 23 200 | Supportive | Recovery |
| Kaur 2011 | 6/F | India | IgM/NT | HAV co-infection, hepatic encephalopathy | HPC | 6.2 | – | 180 000 | 1 923 | Steroids | Death |
| Brun 2013 | 32/M | France | IgM/NT | Splenic lymphoma | Normal | Low | Low | 2 452 | Supportive | Recovery |
| Leroy 2005 | 33/M | France | IgM, PCR/NT | Rheumatoid arthritis, tocilizumab infusion | HPC | – | – | 63 000 | 8 856 | Supportive | Recovery |

HPC = hemophagocytosis; NT = not tested
(eGFR, -5 mL/min) has been described in France in 51 transplant patients during the acute phase of HEV infection genotype 3 [121]. The decrease appeared to be related to HEV, since other causes were ruled out (e.g., acute rejection, infection, modification in immunosuppression regimen). One case of HEV-related acute tubular necrosis has been reported in an immunocompetent patient who was successfully treated with steroids [122]. Two cases of acute renal failure of unknown cause, in association with HEV infection, were reported, one case in a kidney transplant patient who recovered with supportive treatment [123], and a second case in an Indian patient with severe hyperbilirubinemia that responded to hemodialysis [124]. Renal biopsy was not done in either of these cases. Finally, at least eight cases of glomerulonephritis, associated with nephrotic syndrome and/or mixed cryoglobulinemia, have been described [101, 121–126] (Table 8). Types of renal injury included membranoproliferative glomerulonephritis, membranous nephropathy, relapsing IgA nephropathy, and nephroangiosclerosis; seven of these cases occurred in immunosuppressed patients. Immunosuppressant dose reduction or antiviral administration led to complete recovery in three patients and stabilization in one, whereas end-stage renal disease occurred in three patients. It is noteworthy that six out of eight cases of glomerulonephritis were published by the Toulouse group [121, 124, 125] which raises the possibility that other cases may have gone undetected elsewhere. The mechanism of HEV-induced kidney disease could be immune-driven in a manner similar to that with HCV. HEV should be screened for in cases of glomerulonephritis, especially if it is associated with transaminase elevation. Ribavirin can then be used to obtain a rapid viral clearance.

### Mixed cryoglobulinemia

Mixed cryoglobulinemia has been associated with several viral infections; at least nine viruses have been implicated [127]. HCV chronic infection is recognized as the major cause of mixed cryoglobulinemia, reported in 90% of Italian patients in one series [128], although later studies found wide geographical variations [129]. Some cases of mixed cryoglobulinemia are related to HIV [130], HBV [131] and, less frequently, to HAV [132], as well as other viruses.

Four reports of HEV-related mixed cryoglobulinemia, associated with glomerulonephritis and/or nephrotic syndrome, have been published, with a total of 11 patients [121, 126, 133, 134] (Table 9). In one of these cases, HCV-HEV co-infection was present, and HEV RNA was not tested, which makes this case a probable HEV-related mixed cryoglobulinemia [133]. In the other 10 cases, HEV-related mixed cryoglobulinemia was well documented. In all cases published thus far, the presence of HEV RNA in the cryoprecipitate was not evaluated.

HEV-related mixed cryoglobulinemia occurred during active infection in 9 cases or after viral clearance in one case [134]. The occurrence of mixed cryoglobulinemia after viral clearance is similar to what has been observed in other extra-hepatic manifestations related to HEV infection. As with other viral infections, HEV could trigger autoimmunity, which could explain the development of extra-hepatic manifestations after viral clearance [135]. All reported patients with mixed cryoglobulinemia (i) were immunosuppressed because of solid organ transplantation, (ii) had chronic hepatitis E with persistent HEV replication for more than 3 months, and (iii) originated from western Europe, where genotype 3 is prevalent, with confirmation of this genotype in nine patients. All patients had type II or III...

### Table 8. Renal manifestations associated with HEV infection

| Authors/year | Age/sex | Country                  | HEV diagnosis/genotype | Associated disease   | Renal manifestations | Treatment | Outcome               |
|--------------|---------|--------------------------|------------------------|----------------------|----------------------|-----------|-----------------------|
| Verschuuren  | 34/F    | Netherlands             | IgM/NT                | None                 | ATN (unknown cause) | Steroids  | Recovery              |
| Ali 2001     | 38/M    | India                   | IgM/NT                | Renal transplant     | MGN                  | Steroids  | Recovery              |
| Kamar 2005   | 28/M    | France                  | PCR/NT                | Renal transplant     | MPGN, NS             | TAC reduction | Recovery     |
| Kamar 2012   | 33/M    | France                  | PCR/3f                | Renal transplant     | IGAN relapse, MC II, NS | Ribavirin | Recovery              |
| Kamar 2015   | 46/M    | France                  | PCR/3f                | Renal transplant     | IGAN relapse, MC II, NS | Ribavirin | Recovery              |
| Taton 2013   | 60/M    | France                  | PCR/3c                | Renal transplant     | MPGN, MC III, NS     | Rituximab | End stage renal disease |
| Vikrant 2013 | 58/M    | France                  | PCRC/3c               | Liver transplant     | NAS, MC III, NS      | PegIFN    | Hemodialysis          |
| Kamar 2015   | 46/M    | France                  | PCR/3f                | Renal transplant     | MN, NS               | Ribavirin | TAC reduction, ribavirin |
| Del Bello    | 46/M    | France                  | PCR/3f                | Renal transplant     | MPGN                 | TAC reduction | Recovery   |

ATN – acute tubular necrosis; CV – cardiovascular; IGAN – IgA nephropathy; MGN – membranous glomerulonephritis; MC – mixed cryoglobulinemia, MN – membranous nephropathy; MPGN – membranoproliferative glomerulonephritis; NAS – nephroangiosclerosis; NS – nephrotic syndrome; NT – not tested; PegIFN – pegylated interferon; TAC – tacrolimus
Mixed cryoglobulinemia. Antiviral treatment (peginterferon or ribavirin) was given in nine cases. Viral clearance and negativity of cryoglobulinemia were obtained in all patients 3 months after the beginning of antiviral treatment. Similarly, rheumatoid factor, when present, disappeared and the C3 complement component was slightly decreased during antiviral therapy.

Immunosuppressive treatment was given in one case (steroids and increase of immunosuppressants) with rapid symptomatic improvement; however, two relapses occurred after reduction of corticosteroids. During the second relapse, the patient developed an acute, fatal episode of severe intestinal mucositis.

**HEV infection** should be added to the other viral infections causing mixed cryoglobulinemia [136]. Further studies are needed to delineate the frequency of HEV-related mixed cryoglobulinemia, its pathophysiology, and to confirm in a larger cohort of patients the excellent—albeit preliminary—data on antiviral treatment.

### Table 9. Mixed cryoglobulinemia associated with HEV infection

| Authors/year | Country | Age/sex | Co-morbidity | Cryoglobulinemia Type | Manifestation | HEV infection Diagnosis/ genotype | Treatment | Outcome |
|--------------|---------|---------|--------------|-----------------------|---------------|-----------------------------------|-----------|---------|
| Marson 1995  | Italy   | 62/F    | HCV co-infection | II                   | Peripheral neuropathy | IgG/NM PCR/3 PegIFN or ribavirin | Negative PCR 3 month after beginning of treatment, but SVR not reported |
| Kamar 2012   | France  | NM      | Solid organ transplantation | II-III | Glomerulonephritis, nephrotic syndrome | PegIFN or ribavirin | Negative PCR 3 month after beginning of treatment, but SVR not reported |
| Pischke 2014 | Germany | 35/M    | Liver transplant | III                  | Arthralgia, myalgia, thrombocytopenia | PCR/NM Steroids | Death (mucositis) |
| Del Bello 2015 | France | 46/M    | Renal transplant | III                  | MPGN | PCR/3f TAC reduction then ribavirin | SVR, recovery |

MPGN = membranoproliferative glomerulonephritis; NM = not mentioned; PegIFN = pegylated interferon; TAC = Tacrolimus; SVR = sustained virological response

### Table 10. Other possibly autoimmune extra-hepatic manifestations associated with acute HEV infection

| Authors/year | Country | Age/sex | HEV diagnosis/ genotype | Manifestations | Treatment | Outcome |
|--------------|---------|---------|--------------------------|-----------------|-----------|---------|
| Thyroid diseases |
| Hui 2003 [139] | Hong Kong, China | 38/M | IgG-IgM/NT | Inactive HBsAg carrier, Grave’s disease, fulminant hepatitis | Lithium, methimazole | Recovery |
| Kong 2006 [138] | South Korea | 34/F | IgG-IgM/NT | Subclinical hyperthyroidism | PTU | Recovery |
| Dumoulin 2012 [137] | South Korea, Germany | 42/M | IgG-IgM/NT | Grave’s disease | intractable to PTU | Recovery |
| Martinez-Artola 2015 [140] | Argentina | 45/M | IgG-IgM/3a | Subacute thyroiditis | Carbimazol, radiiodine | Recovery |
| Inagaki 2015 [141] | Japan | 65/F | Painless thyroiditis, severe hepatitis | Steroid | Recovery |

**Myocarditis**

| Goyal 2009 [142] | India | 21/M | IgM/NT | Dyspnea, hypotension, acidosis | Ventilation, steroids inotropic support, Indomethacin | Recovery |
| Dougherty 2012 [143] | USA | 50/F | IgM/NT | Chest pain, palpitations, dyspnea | | Recovery |
| Premkumar 2015 [144] | India | 26/M | IgM/NT | Acute kidney injury | Supportive, SLED | Recovery |

**Other manifestations**

| Thapa 2010 [145] | India | 6/F | IgM/NT | Schöenlein, Henoch purpura | Supportive | Recovery |
| Belbezier 2014 [146] | France | 33/W | RNA/3f | Myasthenia gravis, anti musk+ | prostigmine, IVIG, ribavirin | Recovery |

IVIG: intravenous immunoglobulin; MuSK: muscle specific kinase; NT: not tested; PTU: propylthiouracil; SLED: slow low efficiency dialysis
spontaneously or following treatment with indometacin or steroids [142–144]. One case of Schöenlein-Henoch purpura, which resolved itself spontaneously after clearance of the virus [145], and another case of myasthenia gravis, which resolved itself after treatment with ribavirin and intravenous immunoglobulin [146], have also been reported (Table 10). Further studies are needed to confirm these associations.

**Conclusion**

Numerous extra-hepatic manifestations have been described in patients with HEV infection, mostly as case reports or small case series. Most of these reports were published during the last 5 years, which reflects increased awareness of HEV infection in regions where the disease is not endemic, as well as increased awareness of the extra-hepatic manifestations associated with this infection in general. Acute pancreatitis, neurological disorders with predominantly peripheral nerve involvement, hemolytic anemia due to G6PD deficiency, severe thrombocytopenia, glomerulonephritis, and mixed cryoglobulinemia are the most frequent. For several manifestations, there is a possibility that the association was conjectural. One needs to distinguish between anti-HEV IgM positivity and actual clinical illness resembling hepatitis. Such critical evaluation was not feasible. The other extra-hepatic manifestations are uncommonly reported. They may develop either in acute or chronic infection, and during active infection or after clearance of HEV infection. Unless a diagnosis of HEV infection is specifically sought, the diagnosis will be missed because the clinical presentations overlap with many other disorders. We anticipate that more extra-hepatic manifestations of HEV will be reported in the future and that a greater understanding of their immuno-pathogenesis and treatment will evolve.

**Acknowledgment**

We are grateful to Dr. Sudhamshu for providing us with supplementary information regarding his prospective study of acute pancreatitis associated with HEV infection.

**Conflict of interest statement:** none declared.

**References**

1. WHO. Hepatitis E [cited 14 October 2014]. Available from: http://www.who.int/mediacentre/factsheets/fs280/en/.
2. Dalton HR, Bendall R, Ijaz S et al. Hepatitis E: an emerging infection in developed countries. Lancet Infect Dis 2008;8: 698–709.
3. Ditah I, Ditah F, Devaki P et al. Current epidemiology of hepatitis E virus infection in the United States: low seroprevalence in the National Health and Nutrition Evaluation Survey. Hepatology 2014;60:815–22.
4. Beale MA, Tettmar K, Szypula R et al. Is there evidence of recent hepatitis E virus infection in English and North Welsh blood donors? Vox Sang 2011;100:340–2.
5. Mansuy JM, Bendall R, Legrand-Abravanel F et al. Hepatitis E virus antibodies in blood donors, France. Emerg Infect Dis 2011;17:2309–12.
6. Bazerbachi F and Haffar S. Acute fulminant vs. acute-on-chronic liver failure in hepatitis E: diagnostic implications. Infect Dis (Lond) 2015;47:112.
7. Kamar N, Selves J, Mansuy JM et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. N Engl J Med 2008;358:811–17.
8. Kamar N, Izopet J, Dalton HR. Chronic hepatitis E virus infection and treatment. J Clin Exp Hepatol 2013;3:134–40.
9. Wedemeyer H, Pischke S, Manns MP. Pathogenesis and treatment of hepatitis e virus infection. Gastroenterology 2012;142:1388–97, e1.
10. Drobeniuc J, Meng J, Reuter G et al. Serological assays specific to immunoglobulin M antibodies against hepatitis E virus: pangentotypic evaluation of performances. Clin Infect Dis 2010;51:e24–7.
11. Kamar N, Bendall R, Legrand-Abravanel F et al. Hepatitis E. Lancet 2012;379:2477–88.
12. Kamar N, Rostaing L, Legrand-Abravanel F et al. How should hepatitis E virus infection be defined in organ-transplant recipients? Am J Transplant 2013;13:1935–6.
13. Aggarwal R and Jameel S. Hepatitis E. Hepatology 2011;54:2218–26.
14. Hill AB. The environment and disease: association or causation? J R Soc Med 2015;108:32–7.
15. Ede NJ, Moore KP, Marshall WJ et al. Frequency of pancreatitis in fulminant hepatic failure using isoenzyme markers. Gut 1988;29:778–81.
16. Haffar S, Bazerbachi F, Lake JR et al. Frequency and prognosis of acute pancreatitis associated with acute hepatitis E: a systematic review. Pancreatology 2015;15:321–6.
17. Alvarez-Da-Silva MR, Franciisoni CF, Waechter FL. Acute hepatitis C complicated by pancreatitis: another extrahepatic manifestation of hepatitis C virus? J Viral Hepat 2000;7:84–6.
18. Mishra A, Saigal S, Gupta R et al. Acute pancreatitis associated with viral hepatitis: a report of six cases with review of literature. Am J Gastroenterol 1999;94:2292–5.
19. Boroghain SA, Dudjea RK, Singla S et al. Acute pancreatitis associated with acute hepatitis E virus infection. Indian Acad Clin Med 2000;1:282–4.
20. Deniel C, Coton T, Brardjianian S et al. Acute pancreatitis: a rare complication of acute hepatitis E. J Clin Virol 2011;51:202–4.
21. Jaroszewicz J, Flisiak R, Kalinowska A et al. Acute hepatitis E complicated by acute pancreatitis: a case report and literature review. Pancreas 2005;30:382–4.
22. Javid GS, Shoukat A, Iqbal A et al. Pancreatic involvement in non fulminant acute viral hepatitis. J Med Sci 2012;15: 44–6.
23. Karanth SS, Khan Z, Rau NR et al. (4 Jun 2014) Acute hepatitis E complicated by acute pancreatitis and multiorgan dys-function. BMJ Case Rep, 10.1136/bcr-2014–203875.
24. Maity SG and Ray G. Severe acute pancreatitis in acute hepatis E. Indian J Gastroenterol 2002;21:37–8.
25. Majumder AK, Halder A, Talapatra DS et al. Hepatitis E associated with acute pancreatitis with pseudocyst. J Assoc Physicians India 1999;47:1207–8.
26. Makhrinja GK, Garg PK, Tandon RK. Acute pancreatitis associated with acute hepatitis E infection. Trop Gastroenterol 2003;24:200–1.
27. Nayak HK, Kamble NL, Raizada N et al. Acute pancreatitis complicating acute hepatitis E virus infection: a case report and review. Case Reports Hepatol 2013;2013:5311235.
28. Rudrajit PS, Sourav P, Partha SC et al. A case of acute hepatitis E complicated by acute pancreatitis in Eastern India. Int Med J Malaysia 2013;12:71.
29. Sinha S, Jha R, Lakhtakia S et al. Acute pancreatitis following kidney transplantation - role of viral infections. Clin Transplant 2003;17:32–6.
30. Somani S, Ghosh A, Awasthi G. Severe acute pancreatitis with pseudocyst bleeding due to hepatitis E virus infection. Clin J Gastroenterol 2009;2:39–42.
31. Thapa R, Biswas B, Mallick D et al. Acute pancreatitis: complicating hepatitis E virus infection in a 7-year-old boy with glucose 6 phosphate dehydrogenase deficiency. Clin Pediatr (Phila) 2009;48:199–201.
32. Bhagat S, Wadhawan M, Sud R et al. Hepatitis viruses causing pancreatitis and hepatitis: a case series and review of literature. Pancreas 2008;36:424–7.
33. Jain P, Nijhawan S, Rai RR et al. Acute pancreatitis in acute viral hepatitis. World J Gastroenterol 2007;13:5741–4.
34. Mohindra S, Ghoshal UC, Saraswat VA et al. Acute Pancreatitis Associated With Acute Hepatitis E: A Series of 16 Patients. Gastroenterology 2014;144:5–272.
35. Sudhamshu KC, Khadka S, Sharma D et al. Acute pancreatitis in acute viral hepatitis. JNMA J Nepal Med Assoc 2011;51:7–10.
36. Lee WM, Stravititz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology 2012;55:965–7.
37. Tenner S, Baillie J, DeWitt J et al; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400–16.
38. Banks PA, Bollen TL, Dervenis C et al. Classification of acute pancreatitis: 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
39. Sood A, Midha V, Sood N. Guillain-Barre syndrome with acute hepatitis E. Am J Gastroenterol 2000;95:3667–8.
40. Kamar N, Bendall RP, Peron JM et al. Hepatitis E virus and neurological disorders. Emerg Infect Dis 2011;17:173–9.
41. Woolson KL, Forbes A, Vine L et al. Extra-hepatic manifestations of autochthonous hepatitis E infection. Aliment Pharmacol Ther 2014;40:1282–91.
42. van den Berg B, van der Eijk AA, Pas SD et al. Guillain-Barre syndrome associated with preceding hepatitis E virus infection. Neurology 2014;82:491–7.
43. van Eijk JJ, Madden RG, van der Eijk AA et al. Neuralgic amyotrophy and hepatitis E virus infection. Neurology 2014;82:498–503.
44. Kamar N, Izopet J, Cintas P et al. Hepatitis E virus-induced neurological symptoms in a kidney-transplant patient with chronic hepatitis. Am J Transplant 2010;10:1321–4.
45. Kumar RBS, Kumar M, Sharma B et al. Guillain-Barré syndrome and acute hepatitis E: a rare association. JIACM 2002;3:389–91.
46. Kamani P, Baijal R, Amarapurkar D et al. Guillain-Barre syndrome associated with acute hepatitis E. Indian J Gastroenterol 2005;24:216.
47. Khanam RA, Faruq MO, Basunia RA et al. Guillain-Barré Syndrome Associated with Acute HEV Hepatitis. 2009.
48. Loly JP, Rikir E, Seivert M et al. Guillain-Barre syndrome following hepatitis E. World J Gastroenterol 2009;15:1645–7.
49. Chalupa P and Holub M. Jaundice complicated by an atypical form of Guillain-Barre syndrome. J Clin Virol 2010;49:229–30.
50. New PK, Nichols S, Kavanagh E et al. Anti-glycolipid GM2-positive Guillain-Barre syndrome due to hepatitis E infection. J Intern Med 2011;180:255–7.
51. Maurissen I, Jeurissen A, Strauven T et al. First case of anti-ganglioside GM1-positive Guillain-Barre syndrome due to hepatitis E virus infection. J Hepatol 2012;56:323–6.
52. Tse AC, Cheung RT, Ho SL et al. Guillain-Barre syndrome associated with acute hepatitis E virus infection. J Clin Neurosci 2012;19:607–8.
53. Del Bello A, Arne-Bes MC, Lavayssiere L et al. Hepatitis E virus-induced severe myositis. J Hepatol 2012;57:1152–3.
54. Santos L, Mesquita JR, Rocha Pereira N et al. Acute hepatitis E complicated by Guillain-Barre syndrome in Portugal, December 2012: a case report. Euro Surveill 2013;18(34), pii:20563.
55. Sharma B, Nagpal K, Bakki Sanegowda R et al. Hepatitis E with Guillain-Barre syndrome: still a rare association. J Neurovirol 2013;19:186–7.
56. Geurtsvankessel CH, Islam Z, Mohammad QD et al. Hepatitis E and Guillain-Barre syndrome. Clin Infect Dis 2012;57:1369–70.
57. Scharn N, Ganzenmueller T, Wenzel JJ et al. Guillain-Barre syndrome associated with autochthonous infection by hepatitis E virus subgenotype 3c. Infection 2014;42:171–3.
58. Chen XD, Zhou YT, Zhou JJ et al. Guillain-Barre syndrome and encephalitis/encephalopathy of a rare case of Northern China acute severe hepatitis E infection. Neurol Sci 2014;35:1461–3.
59. Comont T, Bonnet D, Sigur N et al. Acute hepatitis E infection associated with Guillain-Barre syndrome in an immunocompetent patient. Rev Med Interne 2014;35:333–5.
60. Fong F and Illahi M. Neuralgic amyotrophy associated with hepatitis E virus. Clin Neurol Neurosurg 2009;111:193–5.
61. Rianthavorn P, Thongmee C, Limpaphayom N et al. The entire genome sequence of hepatitis E virus genotype 3 isolated from a patient with neuralgic amyotrophy. Scand J Infect Dis 2010;42:395–400.
62. Carli P, Landais C, Poineel E et al. Shoulder pain in a 30-year-old man. Rev Med Interne 2012;33:111–14.
63. Inghilleri ML, Grini Mazouzi M, Juntas Morales R. Neuralgic amyotrophy as a manifestation of hepatitis E infection. Rev Neurol (Paris) 2012;168:383–4.
64. Cheung MC, Maguire J, Carey I et al. Hepatitis E: an unexpected problem at home. Scand J Gastroenterol 2012;47:253.
65. Motte A, Franques J, Weitten T et al. Hepatitis E-associated Parsonage-Turner syndrome, France. Clin Res Hepat Gastroenterol 2014;38:e11–14.
66. Moisset X, Vitello N, Bicilli E et al. Severe bilateral amyotrophic neuralgic paralysis with major palate paralysis secondary to acute hepatitis E. F1000Res. 2013;2:259.
67. Deroux A, Brion JP, Hyerle L et al. Association between hepatitis E and neurological disorders: two case studies and literature review. J Clin Virol 2014;60:60–2.
68. Theochari E, Vincent-Smith L, Ellis C. (4 Mar 2015) Neuralgic amyotrophy complicating acute hepatitis E infection: a rare association. BMJ Case Rep. 10.1136/bcr-2014-207669.
69. Decard BF, Grimm A, Andelova M et al. Neuralgic amyotrophy associated with sustained plexus brachialis swelling visualized by high-resolution ultrasound. J Neurol Sci 2015;35:208–10.
70. Despierres LA, Kaphan E, Attarian S et al. Neurological disorders and hepatitis E, France. 2010. Emerg Infect Dis 2011;17:1510–12.
71. Peri AM, Milazzo L, Meroni L et al. Radiculoneuropathy associated with acute hepatitis E. Dig Liver Dis 2013;45:963–4.
72. Yadav KK, Rohatgi A, Sharma SK et al. Oculomotor palsy associated with hepatitis E infection. J Assoc Physicians India 2002;50:737.
73. Dixit VK, Abhilash VB, Kate MP et al. Hepatitis E infection with Bell’s palsy. J Assoc Physicians India 2006;54:418.
74. Jha AK, Nijhawan S, Nepalia S et al. Association of Bell’s Palsy with Hepatitis E Virus Infection: A Rare Entity. J Clin Exp Hepatol 2012;2:88–90.
75. Bennett S, Li K, Gunson RN. Hepatitis E virus infection presenting with paraesthesia. Scott Med J 2015;60:e27–9.
76. Kejariwal D, Roy S, Sarkar N. Seizure associated with acute hepatitis E. Neurology 2001;57:1935.
77. Naha K, Karanth S, Prabhu M et al. Dual infection with hepatitis A and E virus presenting with aseptic meningitis: a case report. Asian Pac J Trop Med 2012;5:578–8.
78. Muralidharan K and Chopra N. Acute transverse myelitis following hepatitis E virus infection. Indian Pediatr 2006;43:365–6.
79. Thapa R, Mallick D, Biswas B. Pseudotumor cerebri in childhood hepatitis E virus infection. Headache 2009;49:610–11.
80. Maddukuri VC, Russo MW, Ahrens WA et al. Chronic hepatitis E with neurological manifestations and rapid progression of liver fibrosis in a liver transplant recipient. Dig Dis Sci 2013;58:2413–16.
81. de Vries MA, Samijn JP, de Man R et al. (30 Apr 2014) Hepatitis E-associated encephalopathy in a renal transplant recipient. BMJ Case Rep, 10.1136/bcr-2014-204244.
82. Kitazawa T, Ota Y, Suzuki M et al. Acute hepatitis E with elevated creatine phosphokinase. Intern Med 2003;42:899–902.
83. Serratrice J, Didier P, Colson P et al. Acute polyarthritis revealing hepatitis E. Clin Rheumatol 2007;26:1973–5.
84. Annamalai AK, Gopalakrishnan C, Jesuraj M et al. Pyomyositis. J Assoc Physicians India 2010;58:241–3.
85. Serratrice J, Disdier P, Colson P et al. Acute polyarthritis revealing hepatitis E. Clin Rheumatol 2007;26:1973–5.
86. Al-Shukri I, Davidson E, Tan A et al. Rash and arthralgia caused by hepatitis E. Lancet 2013;382:1856.
87. Monga A, Makkar RP, Arora A et al. Case report: Acute hepatitis E infection with coexistent glucose-6-phosphate dehydrogenase deficiency. Can J Infect Dis 2003;14:230–1.
88. Zamvar V, McClean P, Odea E et al. Hepatitis E virus infection with nonimmune hemolytic anemia. J Pediatr Gastroenterol Nutr 2005;40:223–5.
89. Thapa R, Pramanik S, Biswas B et al. Hepatitis E virus infection in a 7-year-old boy with glucose 6-phosphate dehydrogenase deficiency. J Pediatr Hematol Oncol 2009;31:223–4.
90. Au WY and Chan SC. Association between glucose 6-phosphate dehydrogenase (G6PD) deficiency and fatal outcome of hepatitis E infection in middle-aged men. Singapore Med J 2012;53:148–9.
91. Somani SK, Srivastava AP, Ahmad M et al. Hepatitis E Virus Infection Leads To Severe Hemolysis In Glucose-6-phosphate Dehydrogenase Deficiency Patients. Webmed Central Gastroenterology 2011;2(2):WMC001537.
92. Tomar LR, Aggarwal A, Jain P et al. Acute viral hepatitis E presenting with haemolytic anaemia and acute renal failure in a patient with glucose-6-phosphate dehydrogenase deficiency. Trop Doc 2014 Dec 12. [Epub ahead of print]
93. Abid S and Khan AH. Severe hemolysis and renal failure in glucose-6-phosphate dehydrogenase deficient patients with hepatitis E. Am J Gastroenterol 2002;97:1544–7.
94. Au WY, Ngai CW, Chan WM et al. Hemolysis and methemoglobinemia due to hepatitis E virus infection in patient with G6PD deficiency. Ann Hematol 2011;90:1237–8.
95. Jain AK, SIRCAR S, Jain M et al. Increased morbidity in acute viral hepatitis with glucose-6-phosphate dehydrogenase deficiency. Indian J Gastroenterol 2013;32:133–4.
96. Ikram HK and Tufail S. Hepatitis associated autoimmune haemolytic anaemia. Int J Pathol 2004;2:24–6.
97. Jin SQ, Chen XR, Wu XL et al. A report of acute hepatitis E with immunological hemolysis. Zhonghua Gan Zang Bing Za Zhi 2005;13:120.
98. Mishra P, Mahapatra M, Kumar R et al. Autoimmune hemolytic anemia and erythroid hypoplasia associated with hepatitis E. Indian J Gastroenterol 2007;26:195–6.
99. Thapa R and Ghosh A. Childhood autoimmune hemolytic anemia following hepatitis E virus infection. J Paediatr Child Health 2009;45:71–2.
100. Bulang T and Forst H. Hepatitis E after travel to India: 2 case reports. Z Gastroenterol 2000;38:249–53.
101. Ali G, Kumar M, Bali SK et al. Hepatitis E associated immune thrombocytopenia and membranous glomerulonephritis. Indian J Nephrol 2001;11:70–2.
102. Singh NK and Gangappa M. Acute immune thrombocytopenia associated with hepatitis E in an adult. Am J Hematol 2007;82:942–3.
103. Colson P, Payraudeau E, Leonnet C et al. Severe thrombocytopenia associated with acute hepatitis E virus infection. J Clin Microbiol 2008;46:2450–2.
104. Thapa R, Mallick D, Ghosh A. Childhood hepatitis E infection complicated by acute immune thrombocytopenia. J Pediatr Hematol Oncol 2009;31:151.
105. Masood I, Raqif A, Majid Z. Hepatitis E presenting with thrombocytopenia. Trop Doc 2014;44:219–20.
106. Fourquet E, Mansuy JM, Bureau C et al. Severe thrombocytopenia associated with acute autochthonous hepatitis E. J Clin Virol 2010;48:73–4.
107. Lorenz E and Quaiser K. Panmyelopathy following epidemic hepatitis. Wien Med Wochenschr 1955;105:19–22.
108. Fomina LG. Modifications of hemopoiesis in liver diseases. Sov Med 1955;19:28–31.
109. Hagler L, Pastore RA, Bergin JJ et al. Aplastic anemia following viral hepatitis: report of two fatal cases and literature review. Medicine (Baltimore) 1975;54:139–64.
110. Raff B, Idrees M, Shah SA et al. Hepatitis associated aplastic anemia: a review. Virol J 2011;8:87.
111. Amarapurkar DN and Amarapurkar AD. Extrahepatic manifestations of viral hepatitis. Ann Hepatol 2012;1:192–5.
112. Shah SA, Lal A, Idrees M et al. Hepatitis E virus-associated aplastic anaemia: the first case of its kind. J Clin Virol 2012;54:96–7.
113. Li C and Wang HF. Hepatitis E virus-related acute liver failure associated with pure red cell aplasia. Hepatobiliary Pancreat Dis Int 2011;10:557–8.
114. George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. J Blood Med 2014;5:69–86.
115. Kamihira T, Yano K, Tamada Y et al. Case of domestically infected hepatitis E with marked thrombocytopenia. Nihon Shokakibyo Gakkai Zasshi 2008;105:841–6.
116. Brun MK, Farnault L, Harle JR et al. Premier cas de syncope d’activation macrophagique secondaire à une hépatite virale E (VHE) chez un patient atteint d’un lymphome splénique. LA REVUE DE MEDECINE INTERNE 2013;34(S1):A91–2.
117. Kaur S, Kulkarni KP, Mahajan A et al. Hemophagocytosis associated with hepatitis A and E coinfection in a young child. Indian J Hematol Blood Transfus 2011;27:117–18.
118. Leroy M, Coiffier G, Pronier C et al. Macrophage activation syndrome with acute hepatitis E during tocilizumab treatment for rheumatoid arthritis. Joint Bone Spine 2015;82:278–9.

119. Ozturk E and Baran B. Letter: Monoclonal gammopathy of HEV infection. When is it significant? Aliment Pharmacol Ther 2015;41:1027–8.

120. Lens S, Mensa L, Gambato M et al. HEV infection in two referral centers in Spain: epidemiology and clinical outcomes. J Clin Virol 2015;63:76–80.

121. Kamar N, Mansuy JM, Esposito L et al. Acute hepatitis and renal function impairment related to infection by hepatitis E virus in a renal allograft recipient. Am J Kidney Dis 2005;45:193–6.

122. Vers chu ren EA, Haagsma EB, Zijlstra JG et al. Non-oliguric acute renal failure associated with hepatitis E. Nephrol Dial Transplant 1997;12:799–801.

123. Kamar N, Weclawiak H, Guilleau-Frugier C et al. Hepatitis E virus and the kidney in solid-organ transplant patients. Transplantation 2012;93:617–23.

124. Vikrant S and Kumar S. Severe hyperbilirubinemia and acute renal failure associated with hepatitis E in a patient whose glucose-6-phosphate dehydrogenase levels were normal. Clin Exp Nephrol 2013;17:596–7.

125. Taton B, Moreau K, Lepreux S et al. Hepatitis E virus infection as a new probable cause of de novo membranous nephropathy after kidney transplantation. Transpl Infect Dis 2013;15:E211–215.

126. Del Bello A, Guilleau-Frugier C, Josse AG et al. Successful treatment of hepatitis E virus-associated cryoglobulinemic membranoproliferative glomerulonephritis with ribavirin. Transpl Infect Dis 2015;17:279–83.

127. Ramos-Casala M, Stone JH, Cid MC et al. The cryoglobulinaemias. Lancet 2012;379:448–60.

128. Ferri C, Greco F, Longobardo G et al. Association between hepatitis C virus and mixed cryoglobulinemia [see comment]. Clin Exp Rheumatol 1991;9:621–4.

129. Sansonno D, Carbone A, De Re V et al. Hepatitis C virus infection, cryoglobulinemia, and beyond. Rheumatology (Oxford) 2007;46:572–8.

130. Dimitrakopoulos AN, Kordossis T, Hatzakis A et al. Mixed cryoglobulinemia in HIV-1 infection: the role of HIV-1. Ann Intern Med 1999;130:226–30.

131. Yadav YK, Aggarwal R, Gupta O et al. Hepatitis-B associated cryoglobulinemia presenting as pseudoleucocytosis. J Lab Physicians 2011;3:133–5.

132. Murat G, Bernon H, Zenone T et al. A case of hepatitis A-associated cryoglobulinemia. Ann Biol Clin (Paris) 1999;57:218–20.

133. Marson P, Donadel C, Vicario M et al. Low prevalence of hepatitis E virus in type II mixed cryoglobulinemia. Haematologica 1995;80:574–5.

134. Pischke S, Behrendt P, Manss MP et al. HEV-associated cryoglobulinaemia and extrahepatic manifestations of hepatitis E. Lancet Infect Dis 2014;14:678–9.

135. Wedemeyer H, Rybczynska J, Pischke S et al. Immunopathogenesis of hepatitis E virus infection. Semin Liver Dis 2013;33:71–8.

136. Haffar S, Bazerbachi F, Lake JR. HEV-associated cryoglobulinaemia and extrahepatic manifestations of hepatitis E. Lancet Infect Dis 2015;15:268.

137. Dumoulin FL and Liese H. (23 Apr 2012) Acute hepatitis E virus infection and autoimmune thyroiditis: yet another trigger? BMJ Case Rep, 10.1136/bcr.12.2011.5441.

138. Kong SJ, Min SK, Kim IK et al. Two cases of acute hepatitis E in patients with hyperthyroidism. Korean J Gastroenterol 2006;47:65–71.

139. Hui AY, Chan HL, Chan FK et al. Fulminant hepatic failure in a patient with inactive HBsAg carrier state, acute hepatitis E and thyrotoxicosis. Hepatol Res 2003;27:248–51.

140. Martínez-Artola Y, Poncino D, García ML et al. Acute hepatitis E virus infection and association with a subacute thyroiditis. Ann Hepatol 2015;14:141–2.

141. Inagaki Y, Oshiro Y, Hasegawa N et al. Clinical features of hepatitis E virus infection in Ibaraki, Japan: autochthonous hepatitis E and acute-on-chronic liver failure. Tohoku J Exp Med 2015;235:275–82.

142. Goyal B, Mishra DK, Kawar R et al. Hepatitis E associated myocarditis: an unusual entity. Bombay Hospital Journal 2009;51:361.

143. Dougherty TS and Borum M. Acute myopericarditis due to hepatitis E virus infection: a case report. American College of Gastroenterology; Las Vegas, NV2012, P847.

144. Premkumar M, Rangegowda D, Vashishtha C et al. Acute viral hepatitis E is associated with the development of myocarditis. Case Reports Hepatol 2015;2015:458056.

145. Thapa R, Biswas B, Mallick D. Henoch-Schonlein purpura triggered by acute hepatitis E virus infection. J Emerg Med 2010;39:218–19.

146. Belghezir A, Deroux A, Sarrot-Reynaud F et al. Myasthenia gravis associated with acute hepatitis E infection in immunocompetent woman. Emerg Infect Dis 2014;20:908–10.