Acute hepatitis E complicated by Guillain-Barré syndrome in Portugal, December 2012 – a case report

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Autochthonous hepatitis E virus (HEV) infection has been increasingly reported in Europe and the United States, mostly arising from genotype 3 and less frequently genotype 4. We report here on a patient with HEV genotype 3a infection complicated by Guillain-Barré syndrome in Portugal in December 2012. We draw attention to the diagnosis of autochthonous HEV infection and to its rare, but important, neurological complications.

Case report

We report on a patient in Portugal with autochthonous acute hepatitis E complicated by Guillain-Barré syndrome (GBS).

Clinical description

At the end of November 2012, a man in his late 50s was hospitalised, having presented with signs and symptoms of acute hepatitis. He had not travelled outside Portugal and had no history of risky sexual behaviour or drug addiction. Two weeks before hospitalisation, he complained of malaise, nausea, vomiting and right upper quadrant abdominal pain: these symptoms were followed by onset of jaundice some days after. At admission (day 1), besides jaundice, he had right upper quadrant tenderness and an enlarged liver.

During the three days after admission, he began to complain of muscle weakness and was then admitted to an intermediate care unit (three days after admission). After being observed by a neurologist on day 4, the patient was treated with intravenous immune globulin (0.4g per kg of body weight per day for five days) and ceftriaxone (4g/day for 10 days). During that day and the following day, a rapid ascending weakness and sensitivity loss with a non-impaired mental status was observed. At this point, the presumed diagnosis was GBS. This worsening of neurological symptoms led to the patient being transferred to our hospital on day

5, where he was admitted to the intensive-care unit (ICU). Due to hypoventilation, decreased reflex cough and hoarseness, the patient needed intubation, ventilation support and sedation. Besides the tetraparesis and areflexia, the patient also had autonomic instability with bradycardia and hypertension.

The day before admission to the ICU, magnetic resonance imaging of the spinal cord was normal. Electromyography nerve conduction studies of peripheral motor and sensory nerves in upper and lower limbs the day following ICU admission revealed a severe acquired demyelinating sensory and motor polyneuropathy.

A tracheostomy was performed five days after ICU admission and sedation was stopped. The patient began a rehabilitation programme; he was fully able to breathe spontaneously at day 26. His clinical evolution was favourable: he had progressive recovery of muscle strength, with efficacious cough and no need for oxygen supplementation. He was discharged 34 days after admission to the ICU. Two months later, he continued to have a favourable outcome and was already able to walk if assisted.

Laboratory analysis

The results of blood tests taken at various time points are shown in Table 1.

Analysis of the patient's cerebrospinal fluid (CSF) taken on day 2 after ICU admission showed normal cell count (4 cells/ μ L; norm: $<5/\mu$ L) and level of proteins (181 mg/dL; norm: 15–45 mg/dL) and glucose (77 mg/dL; norm: >60 mg/dL). The CSF and blood cultures were negative for bacteria.

Serum samples (taken on admission to the referring hospital and on admission to the ICU) and CSF (taken

TABLE 1

Blood test results, case of acute hepatitis E, Portugal, November–December 2012

Item tested (units)	Laboratory results			Reference values
	Admission to referring hospital	Transfer to ICU	ICU discharge (34 days after admission)	
Haemoglobin (g/dL)	14.3	12.8	11.4	13–18
Platelets (x 10 ⁹ /L)	328	308	286	150–400
AST (U/L)	–	79	72	<37
ALT (U/L)	2,320	101	156	<37
G-GT (U/L)	566	367	69	<49
AF (U/L)	336	274	155	<155
Total bilirubin (mg/dL)	6.71	1.13	0.4	<1.2
Conjugated bilirubin (mg/dL)	5.5	0.8	0.18	<0.4
Albumin (g/L)	–	27.9	–	38–51
CRP (mg/L)	60.5	50.3	8.1	<3
aPTT (seconds)	41	35.1	–	–
PT (seconds)	12.4	12.3	–	–

AF: alkaline phosphatase; ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; CRP: C-reactive protein; G-GT: gamma-glutamyl transpeptidase; ICU: intensive-care unit; PT: prothrombin time; U: units.

The dashes indicate that the test was not done.

on admission to the ICU) were tested by serology and polymerase chain reaction to detect the presence of various pathogens (Table 2). Although *Toxoplasma* and *Mycoplasma* infections were initially suspected, based on the presence of specific IgM in the patient's serum, polymerase chain reaction (PCR) of CSF and blood samples did not confirm the presence of these agents.

Serological analysis to detect hepatitis viruses was negative for all except HEV, being positive for anti-HEV IgM and negative for anti-HEV IgG, suggesting an acute infection with HEV. Serological markers for Epstein–Barr virus (EBV) – EBV nuclear antigen and viral capsid antigen IgG – were positive, but EBV IgM was negative. The diagnosis of HEV infection was confirmed by the presence of HEV RNA in the serum sample taken the day the patient was admitted to the referring hospital. CSF and stool samples were not available at that time for testing. HEV RNA in serum was detected using a nested broad-spectrum reverse transcription PCR with amplification within the open reading frame (ORF) 1 region of HEV genome [1].

The amplicon obtained (330 bp) was sequenced and compared with reference HEV strains, using a neighbor-joining method based on the Jukes-Cantor model [1] for ORF 1 nucleotide sequences of selected HEV isolates representing genotypes 1–4. This phylogenetic analysis revealed that the amplicon clustered with HEV genotype 3, specifically subgenotype 3a (Figure).

In a routine visit to the hospital two months after being discharged, analysis of a blood sample collected at

that time showed that HEV RNA was undetectable, anti-HEV IgM was negative and anti-HEV IgG was positive.

Background

In recent years, an increasing number of autochthonous infections with HEV have been reported in Europe and in United States [2]. Most of these autochthonous cases have been caused by HEV genotype 3 (HEV3) and less frequently by genotype 4 [2]. Seroprevalence studies also show that HEV infection in the population of industrialised countries is higher than previously thought [3]. HEV3 infections have been associated with the consumption of raw or insufficiently cooked pork, deer and wild boar [2,4] and to direct contact with infected swine [5].

Autochthonous HEV infection is usually subclinical or runs a mild course and is self-limiting, but chronic autochthonous infection has been identified among immunocompromised persons, including organ transplant recipients, patients receiving cancer chemotherapy and persons infected with human immunodeficiency virus (HIV) [6].

A broad set of symptoms of autochthonous HEV disease has been seen as well as increasing recognition of its extra-hepatic manifestations [7]. Both acute and chronic HEV infections have been reported to be associated with muscular weakness, neurological disorders including polyradiculopathy, GBS, bilateral brachial neuritis, encephalitis or proximal myopathy [8]. Although neurological disorders associated with HEV3 are rare, some data are emerging in literature [8]. In

TABLE 2

Serological and PCR analysis to detect various pathogens, case of acute hepatitis E, Portugal, December 2012

Pathogen	Serology results	PCR results	
		Serum ^a	CSF ^b
HEV	IgM positive	Positive	–
HAV	Negative	–	–
HBV	Negative	–	–
HCV	Negative	–	–
HIV	Negative	–	–
HSV-1	IgG positive	–	–
HSV-2	Negative	–	–
CMV	Negative	Negative	Negative
EBV	IgG positive,	–	Negative
	IgM negative		
<i>Toxoplasma</i>	IgM positive	Negative	Negative
<i>Mycoplasma</i>	IgG positive	–	Negative
	IgM positive		
<i>Bartonella</i>	–	–	Negative
<i>Borrelia</i>	Negative	Negative	Negative
<i>Leptospira</i>	–	–	Negative
<i>Coxiella</i>	Negative	Negative	–

CMV: cytomegalovirus; CSF: cerebrospinal fluid; EBV, Epstein–Barr virus; HAV, hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus; HIV: human immunodeficiency virus; HSV-1, herpes simplex virus 1; HSV-2, herpes simplex virus 2; ICU: intensive-care unit; PCR, polymerase chain reaction.

The dashes indicate that the test was not done.

^a Taken on admission to the referring hospital and on admission to the ICU.

^b Taken on admission to the ICU.

FIGURE

Phylogenetic analysis of a hepatitis E virus amplicon from a case of acute hepatitis E, Portugal, December 2012

HEV: hepatitis E virus.

Neighbor-joining method based on the Jukes-Cantor model for open reading frame (ORF) 1 nucleotide sequences of selected HEV isolates representing genotypes 1–4. An avian HEV sequence was used as an outlier. The sequence of the case (HSJ GB) is shown in bold. Sequences are denoted by the GenBank accession number followed by genotype (G) and subgenotype for G3. Numbers at the nodes indicate bootstrap values. The tree was constructed by using a 334 base pair (bp) region. Evolutionary analyses were conducted in MEGA5.

recent years, a number of GBS cases associated with HEV infections have been described [8,9]. GBS is an acute, acquired, autoimmune disorder of peripheral nerves that develops in susceptible individuals after infection and, in rare cases, after vaccination [10]. In about 60% of cases, GBS is preceded by an infection, most frequently by *Campylobacter jejuni*, but other pathogens, such as viruses from Herpesviridae family (cytomegalovirus, varicella zoster virus, Epstein–Barr virus) or bacterial agents (*Haemophilus influenzae*, *Mycoplasma pneumoniae*) can be responsible [10].

Discussion

Exhaustive tests to detect the agents mostly frequently associated with GBS, other than *Campylobacter*, gave negative results in samples from our patient. *Campylobacter* was not tested for because of the patient's symptoms. Although rare, the increasing number of reports of neurological disorders associated with autochthonous HEV infections in Europe drew our attention to a possible HEV diagnosis. Given the serological results, EBV was not considered likely as the causative agent. Detection of both IgM anti-HEV and HEV RNA in the patient's serum confirmed acute hepatitis E.

The actual incidence of GBS associated with HEV infection is unknown because autochthonous hepatitis E is still underdiagnosed in many industrialised countries [11]. This is in part due to the fact that frequently HEV infection is subclinical and because the neurological findings surpass the liver injuries and hepatitis is not suspected. Hence, HEV infection should be considered in neurological diseases associated with abnormal levels of liver enzymes [7,12].

Since the patient reported no travel history, it seems likely that the HEV infection was locally acquired. We consider it most probably resulted from consumption of pork or pork products, as there is a strong tradition of pork consumption among Portuguese people and HEV3 has been detected in domestic pigs from several farms in Portugal [13].

Interestingly, the patient was in his late 50s. It is known that middle-aged and elderly men are more vulnerable to severe HEV3 infection, which can ultimately lead to hospitalisation and possibly death [6].

To our knowledge, this is the first report of a neurological disorder associated with an autochthonous HEV3 infection in a Portuguese patient. Considering the GBS-HEV cases reported, we recommend that testing for HEV should be included routinely in the diagnostic algorithm of GBS when liver function is altered.

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Conflict of interest

None declared.

Authors' contributions

LS, NRP took part in the clinical management of the patient and wrote the manuscript. CLA, RS, PF, JR, AS took part in the clinical management of the patient and reviewed the manuscript. JS collaborated in molecular biology techniques. MSJN and JRM did the molecular diagnosis tests and the sequence of the HEV and wrote the lab section. All authors read and approved the final manuscript.

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