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ORIGINAL ARTICLE

Neuropathies related to hepatitis E virus infection: A prospective, matched case–control study

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Abstract

Background: Acute hepatitis E virus (HEV) infection has recently emerged as a potential trigger for acute dysimmune neuropathies, but prospective controlled studies are lacking.

Aims: To compare the frequency of concomitant acute HEV infection in patients with neuralgic amyotrophy (NA), Guillain–Barré syndrome (GBS), and Bell's palsy with a matched control population.

Methods: Swiss multicenter, prospective, observational, matched case–control study over 3 years (September 2019–October 2022). Neurological cases with NA, GBS, or Bell's palsy were recruited within 1 month of disease onset. Healthy controls were matched

for age, sex, geographical location, and timing of blood collection. Diagnostic criteria for acute hepatitis E were reactive serum anti-HEV IgM and IgG assays (ELISA test) and/or HEV RNA detection in serum by real-time polymerase chain reaction (RT-PCR). RT-PCR was performed on sera to confirm IgM positivity.

Results: We included 180 patients (59 GBS, 51 NA, 70 Bell's palsy cases) and corresponding matched controls (blood donors) with median age 51 years for both groups and equal gender distribution. Six IgM+ cases were detected in the NA, two in the GBS, and none in the Bell's palsy group. Two controls were anti-HEV IgM-positive. At disease onset, most cases with acute HEV infection had increased liver enzymes. A moderate association ($p=0.027$, Fisher's exact test; Cramér's $V=-0.25$) was observed only between acute HEV infection and NA.

Conclusion: This prospective observational study suggests an association between concomitant acute HEV infection and NA, but not with GBS or Bell's palsy.

KEYWORDS
Bell's palsy, Guillain–Barré syndrome, hepatitis E, neuralgic amyotrophy, Parsonage–Turner syndrome

INTRODUCTION

Hepatitis E virus (HEV) is the most common cause of acute hepatitis worldwide. In developed countries, including European countries, awareness of HEV infection is constantly increasing [1, 2]. In Switzerland, the IgG seroprevalence of the disease is high (around 30%) [3], demanding increased awareness of the health authorities [4, 5]. HEV can cause not only life-threatening acute hepatitis, but also extrahepatic manifestations [6], notably neurological diseases [7–11] with a tropism for the peripheral nervous system.

In a retrospective and prospective Dutch–British cohort of 47 neuralgic amyotrophy (NA) cases, the seroprevalence of acute HEV infection was 10% [12], all cases exhibiting bilateral involvement [13]. In Guillain–Barré Syndrome (GBS), the reported prevalence of HEV as the preceding infection varies from 5% up to 11% [14–17], depending on the geographical location [18]. More recently, in the International Guillain–Barré Syndrome Outcome Study (IGOS), 16 of 768 GBS patients (2%) tested positive for HEV mono-infection [19]. Finally, three case reports of Bell's palsy with concomitant HEV infection have raised the suspicion of a possible association between HEV infection and this neurological condition [20–22].

However, the strength of the association between acute HEV infection and dysimmune neuropathies is still unclear because of the lack of prospective case–control studies [23]. We previously observed in Southern Switzerland a high number of neurological complications during acute HEV infection [10], therefore in the present study we further investigated the role of HEV as a possible trigger of NA, GBS, or Bell's palsy.

METHODS

Prospective, multicenter, observational, matched case–control study.

Participants

Neurological cases were enrolled within 1 month (30 days) of disease onset from September 2019 to October 2022 in 11 Swiss neuromuscular centers and consultations. Sex, age, alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT) levels at disease onset were obtained for each participant. Cerebrospinal fluid (CSF) samples were collected from all GBS patients. All NA and GBS patients underwent electrodiagnostic (EDX) studies for diagnostic purposes and had a follow-up visit at 3 months, when a second serum sample was collected.

Controls were healthy blood donors matched for sex, age, and canton (territorial district) of residence. The time of blood donation had to be in the range ± 6 months from the onset of HEV infection in the corresponding case. Blood donors were excluded from blood donation with a questionnaire if they had suffered from GBS in the last 2 years.

Diagnostic criteria

Acute hepatitis E

HEV infection was defined as positivity of both serum anti-HEV IgM and IgG assays and/or HEV RNA detected in serum by real-time polymerase chain reaction (RT-PCR) [24] (Figure 1). Cases with positive IgM, positive IgG, and increased liver enzymes, but negative HEV RNA test results, were screened for possible concomitant infection with Epstein–Barr virus (EBV) and cytomegalovirus (CMV). IgG were re-tested at 3 months to confirm seroconversion (true positivity).

NA

In addition to the routine clinical criteria [25] (subacute onset within hours; initial pain with visual analog scale score >7/10; multifocal

distribution of neurologic injury centered on the brachial plexus; monophasic course with slow recovery) each diagnosis was confirmed by EDX studies.

GBS

In addition to the clinical National Institute of Neurological Disorders and Stroke (NINDS) criteria [26] (progressive weakness in legs and arms; areflexia or decreased tendon reflexes in weak limbs; progressive phase lasting days to 4 weeks), each diagnosis was confirmed by EDX studies. We included all variants of GBS, such as acute motor axonal neuropathy (AMAN), acute inflammatory demyelinating polyneuropathy (AIDP), and Miller Fisher syndrome (MFS). Neurophysiological subtypes were defined according to the Hadden criteria [27].

Bell's palsy

Idiopathic acquired peripheral facial weakness [28] without signs of cranial polyneuritis (including GBS).

Laboratory testing

Serum samples from neurological cases were collected in the acute phase, before treatment start. All samples were obtained during routine diagnostic procedures and leftover material was stored at −80°C. Serological tests for cases and controls were performed on serum (patients) or plasma (controls) samples in a centralized laboratory (Interregional Blood Transfusion SRC, Bern, Switzerland) using the enzyme-linked immunosorbent assay (ELISA), the WANTAI HEV-IgG ELISA, and WANTAI HEV-IgM ELISA (Eurobio, Les Ulis, France) according to the manufacturer's instructions. ELISA results were presented as ratios of sample optical density (OD) divided by the cut-off OD. For both IgM and IgG antibodies OD ratios >1.1 indicated a positive result, whereas ratios <0.9 were classified as negative. Borderline OD ratios (0.9–1.1) were classified as positive if diagnosis was supported by positive anti-HEV IgG antibodies.

HEV RT-PCR was performed in serum samples of cases and controls with anti-HEV IgM+ results and/or with increased liver enzymes, using the RealStar kit (Altona Diagnostics, Hamburg, Germany) according to the manufacturer's instructions.

For CMV testing, a recent infection was defined as IgM positivity with negative IgG or IgG with low avidity. For EBV testing, recent infection was defined as viral capsid antigen (VCA) IgM and IgG positivity with negative EBV nuclear antigen (EBNA) IgG.

Statistical analysis

Cases were matched with controls on the basis of sex, age (±5 years), canton of residency, and time of blood collection (±6 months). Prior to analysis, data were checked for accuracy of matching. Continuous data (age, results of laboratory analyses) are presented descriptively as mean, standard deviation (SD), and median. Frequency data are presented as counts and percentages, and pairwise associations between variables were computed using contingency tables and carrying out chi-square or Fisher's exact tests, as appropriate, using Cramer's V as a measure of association. Stata Version 17 (StataCorp LCC) was used for all statistical analyses.

Ethical aspects

The study was approved by all concerned local ethics committees (File no. CE 2932). Written informed consent was obtained from all study participants. Blood donors signed the General Consent for research for blood donors of the Blood Transfusion Services of the SRC.

RESULTS

Overall, 184 neurological patients were asked to participate and 180 were enrolled; the 4 patients who refused to participate had Bell's palsy. Fifty-one suffered from NA, 59 from GBS, and 70 from Bell's palsy. Study population characteristics of neurological cases and controls were comparable, with equal gender distribution (males 48%) and a mean age of 51 years for cases and 50 years for controls (Table 1).

Acute HEV infection was detected in 8 (4.4%) cases (i.e., 6 NA and 2 GBS cases) and in 2 (1.1%) controls (Table 2). Positive IgM serological results were further confirmed by HEV RNA PCR

TABLE 1 Demographics of the study population.

Parameter	Cases ($n = 180$)	Controls ($n = 180$)	*P*-value
Male			
Frequency (%)	117 (48.15)	117 (48.15)	
Age (years)			
Mean (SD)	51 (15.91)	50.3 (15.18)	0.5742, NS
Median	51	50	
Female			
Frequency (%)	63 (51.85)	63 (51.85)	
Age (years)			
Mean (SD)	54.3 (17.22)	51.9 (15.35)	0.5653, NS
Median	58	56	
Total			
Age (years)			
Mean (SD)	52.2 (16.40)	50.8 (15.21)	0.4265, NS
Median	53	52	

Abbreviations: NS, not significant; SD, standard deviation.

TABLE 2 Results of hepatitis E virus serology in cases and controls.

	Acute HEV infection[a]		
Neuropathy	**Negative**	**Positive**	***P*-value**
NA			
Cases ($n=51$)	45	6	0.027
Controls ($n=51$)	51	0	
GBS			
Cases ($n=59$)	57	2	NS
Controls ($n=59$)	58	1	
Bell's palsy			
Cases ($n=70$)	70	0	NS
Controls ($n=70$)	69	1	NS

Abbreviations: GBS, Guillain–Barré syndrome; HEV, hepatitis E virus; NA, neuralgic amyotrophy; NS, not significant; RT-PCR, real-time polymerase chain reaction.

[a]Demonstrated by serum anti-HEV IgM+ and anti-HEV IgG+ and/or HEV RNA detected by RT-PCR (see also Figure 1).

testing, analysis of IgM and IgG kinetics on a 3-month follow-up serum sample, and exclusion of concomitant EBV or CMV infection (Figure 1).

Patients with positive HEV IgM serology had increased ALT and GGT levels, consistent with acute hepatitis (Table 3).

In the NA group, 6 of 51 cases (11%) had an acute HEV infection, compared with none of the 51 matched controls (Table 2); this resulted in a statistically significant association for NA ($p=0.027$, Fisher's exact test; Cramér's $V=-0.25$).

In the GBS group, 2 of 59 cases (3%) had an acute HEV infection (Table 2). When compared with the control group, the association was not statistically significant ($p=1.000$, Fisher's exact test; Cramér's $V=-0.0538$).

No cases in the Bell's palsy group were positive for HEV infection, in comparison with one in the matched control group (Table 2). The association for Bell's palsy ($p=1.000$, Fisher's exact test; Cramér's $V=-0.0848$) was also statistically not significant.

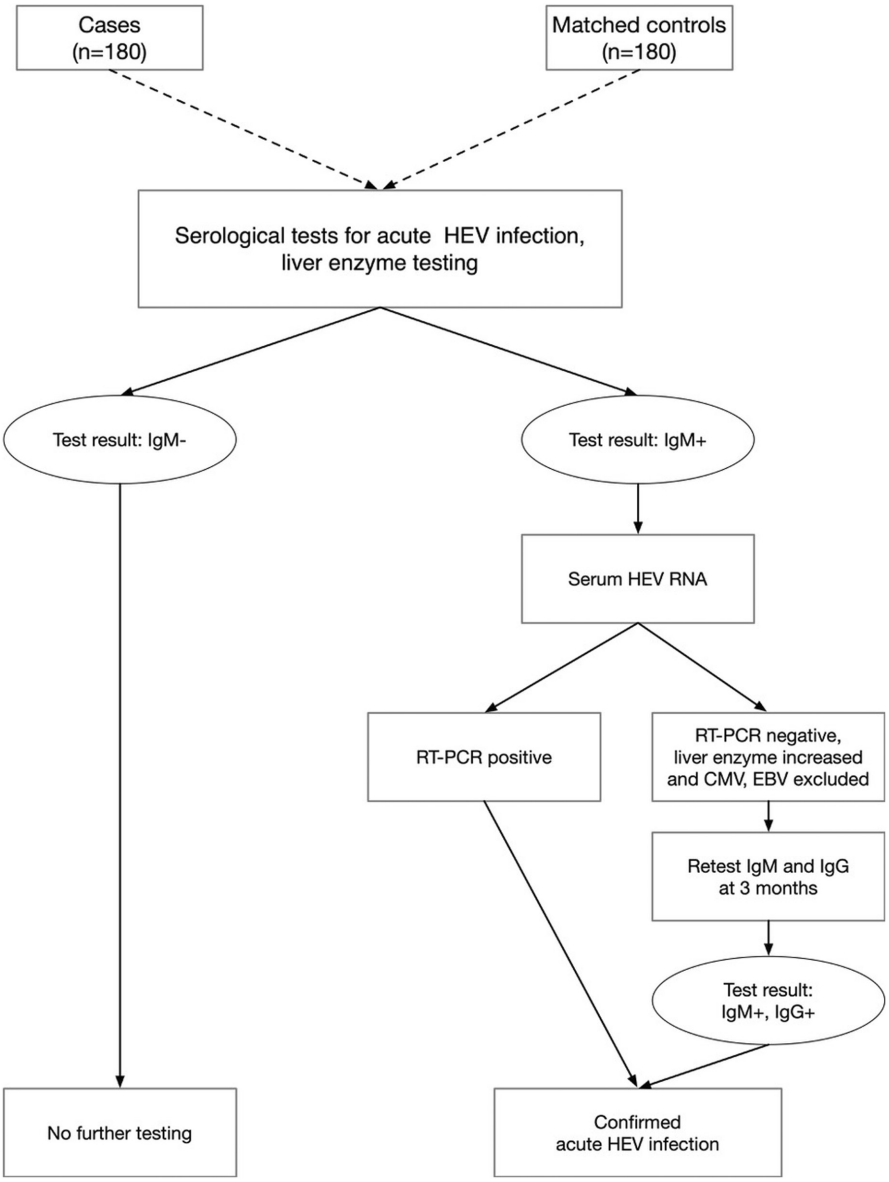

FIGURE 1 Criteria used for the diagnosis of an acute hepatitis E virus infection in the neurological patients and the controls included in the study. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HEV, hepatitis E virus; RT-PCR, real-time polymerase chain reaction.

TABLE 3 Liver function tests in hepatitis E virus-positive (HEV+) and HEV-negative patients.

	Acute HEV (IgM+)		
Liver enzyme values[a]	Negative	Positive	*P*-value
Mean ALT (IU/L) (SD)	39.1 (37.51)	274.14 (319.92)	0.000
Mean GGT (IU/L) (SD)	48.45 (64.65)	117.17 (101.53)	0.015

Abbreviations: ALT, alanine aminotransferase (normal value <50 IU/L); GGT, gamma glutamyl transferase (normal value<70 IU/L); HEV, hepatitis E virus; IU, international units; SD, standard deviation.

[a]Level at disease presentation (first blood sample available).

Clinical details of HEV+ NA and HEV+ GBS cases

Four of six (66%) HEV+ NA cases, all in the age range 31–50 years, had bilateral involvement of the brachial plexus, and showed increased ALT and GGT levels, consistent with concomitant acute hepatitis. RT-PCR results were positive for HEV RNA in 3 of 6 (50%) HEV+ NA cases. HEV+ NA patients were all treated in the acute phase with oral prednisone 60 mg/day for 7 days with tapering 10 mg/day, and one patient also received intravenous immunoglobulin (IVIg) at a dose of 2 g/kg for 5 days. At the 3-month follow-up, all these HEV + NA patients reported complete pain regression and improvement of upper limb muscle strength.

Of the two HEV+ GBS patients, one reported diarrhea in the preceding 4 weeks and developed subacute tetraparesis, areflexia, and stocking-glove hypoesthesia (GBS disability score = 3), and was classified as AIDP. Anti-ganglioside antibodies were all negative. This patient was treated with two subsequent courses of IVIg, but at 3 months had persistent difficulties in walking (GBS disability score = 3).

The second patient suffered from subacute ophthalmoparesis with diplopia and areflexia; anti-GQ1b IgG antibodies were positive at high concentrations in the serum (172 IV, reference interval 0–50 IV) and the protein level in the CSF was high (1.3 g/L) without pleocytosis. The patient was diagnosed with Miller Fisher syndrome and had a full recovery within 1 month.

None of the HEV+ GBS cases, despite being tested within the first week from symptom onset, were positive for HEV RNA by RT-PCR, and none had elevated liver enzymes on admission.

DISCUSSION

Our data confirm for the first time in a prospective, matched case–control study that acute HEV infection can be present in up to 11% of NA cases, suggesting a potential role of the virus in the pathogenesis of this neuropathy [10] in a subset of patients. Our results are similar to those from another population (a mixed Dutch–British cohort), in which 5 of 47 (10.6%) NA cases had concomitant acute hepatitis E [12]. We also identified HEV in the bloodstream in the very acute phase, and observed that a bilateral involvement occurs frequently in middle-aged patients with HEV infection [13].

We did not see any association between GBS and Bell's palsy and HEV infection. Previous reports have suggested a potential role of HEV as disease trigger of both conditions [7, 8, 14, 18], but the estimated prevalence of acute HEV infection in GBS cases in Europe was overall low, that is, 1% in Germany [29], 5% in the Netherlands [14], and 6% in Belgium [16]. In a recent international prospective cohort of 768 GBS cases [19], only 2.1% had serological evidence of an acute HEV infection (confirmed by PCR in 2 of 23 cases) after exclusion of concomitant infections.

For Bell's palsy, our results confirm the negative findings of Fritz-Weltin et al. [30] in a different population. Based on this, and the fact that the theoretical association between HEV and Bell's palsy was raised only in three case reports (one in Japan and two in India) [20–22], we would not recommend routine testing of HEV in Bell's palsy for clinical purposes.

The prevalence of HEV infection can vary consistently not only among different regions, but also over time in the same geographical area, as previously reported in Switzerland [3]. This is not only caused by regional eating habits but also differences in food production, age, and sex of the tested population. It is important to match controls for age because the IgG seroprevalence of HEV infection increases with age, reaching in Switzerland 30%–35% in healthy blood donors aged over 60 years [3]. Therefore, the strength of our study is not only its prospective design in comparison with other retrospective studies [29, 30], but also the collection of biological samples in a short time period (3 years) in a homogeneous population, with accurate matching of controls (gender, age, canton of residence, timing of blood collection). To date, published studies have been completely lacking in controls [12, 16, 19] or did not match for gender and age [30].

We tested for acute hepatitis E according to European guidelines [24], using the same kit used in previous studies [14, 29], and centralized the tests in the same laboratory for both cases and controls. HEV IgM cases and controls were tested for infections associated with potential cross-reactivity, such as CMV or EBV [31, 32]. This is relevant especially for GBS, as previously reported in other studies [16, 19]. In addition, we tested the serum samples by RT-PCR for the presence of HEV RNA, and repeated the serological tests at 3 months to confirm changes in the kinetics of IgM and IgG antibodies to confirm true seroconversion (Figure 1). Since HEV RNA persists in the bloodstream for only a couple of weeks, whereas IgM+ serology is detectable for up to 3–6 months [1], it is not surprising that we could identify viral RNA in only three of the HEV IgM+ NA cases, whereas IgM positivity was confirmed at 3 months in all cases positive at first screening. The finding that liver enzymes were increased in the HEV IgM+ group further supports the notion of an ongoing hepatitis, and not of an isolated serological positivity (Table 3).

The main limitation of our study is represented by the limited sample size.

In conclusion, this study suggests an association between acute HEV infection and NA (11% of cases) but does not show an association with GBS or Bells' palsy. We suggest routinely testing all NA patients for acute HEV infection, especially those with increased

liver enzymes and bilateral involvement of the brachial plexus. The increased awareness among neurologists and hepatologists of this association may help to diagnose NA in the acute phase.

AUTHOR CONTRIBUTIONS

PR conceived the study, established the collaborations, visited the patients, collected and analyzed the data, and wrote the original manuscript. CG established the collaborations, analyzed the data, and revised the manuscript for intellectual content. AML, OS, LSH, BS, PT, AV, AKP, TH, AD, HJ, TK, EWS, AMH, and BFD identified/cared for patients and provided comments on the manuscript. EP, GZ, GLM, and DS performed biological assays, contributed to data collection, and revised the manuscript for intellectual content. OP performed the statistical analysis and revised the manuscript for intellectual content. SF, PG, and CN identified controls and collected their samples, and revised the manuscript for intellectual content.

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CONFLICT OF INTEREST STATEMENT

All authors report no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

Anonymized data from this study that are not published in this article will be shared on request with any qualified investigator.

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