Neuralgic amyotrophy and hepatitis E virus infection

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ABSTRACT

Objective: To determine whether there is an association between an acute preceding hepatitis E virus (HEV) infection and neuralgic amyotrophy (NA), and if so, whether patients with HEV-related NA differ from patients without an associated HEV infection.

Methods: HEV testing was conducted in a retrospective cohort of 28 Cornish patients with NA (2011–2013) and a prospective cohort of 38 consecutive Dutch patients with NA (2004–2007). Acute-phase serum samples were analyzed for the presence of anti-HEV immunoglobulin (Ig) M and IgG and HEV RNA (quantitative real-time PCR).

Results: Five cases (10.6%) of acute hepatitis E infection were identified in a total group of 47 patients with NA of whom serum samples were available. In 4 patients, HEV RNA was detected in serum samples taken at presentation. All patients with HEV-associated NA had clinical and electrophysiologic evidence of bilateral brachial plexus involvement. Anti-HEV IgM positivity was not related to age, sex, disease severity, disease course, or outcome.

Conclusions: Acute hepatitis E is found in 10% of patients with NA from the United Kingdom and the Netherlands. Further research is required to investigate the role of HEV in NA in other geographical locations and to determine pathophysiologic mechanisms. *Neurology*® 2014;82:498–503

GLOSSARY

GBS = Guillain-Barré syndrome; **HEV** = hepatitis E virus; **Ig** = immunoglobulin; **NA** = neuralgic amyotrophy.

Neuralgic amyotrophy (NA) is an acute monophasic brachial plexus disorder of unknown cause. The pathogenesis of NA is assumed to be multifactorial, with a significant proportion of the patients reporting a preceding infection that might have triggered symptoms.^{1–8}

Hepatitis E virus (HEV) is an emerging pathogen that has been reported in a number of acute monophasic neurologic disorders, including Bell palsy, Guillain-Barré syndrome, transverse myelitis, encephalitis, and NA.^{9–17} Patients with NA may show subclinical, mildly abnormal liver function tests for uncertain reasons, but HEV has not been systematically tested in these individuals.¹⁸ Herein, we present evidence of a recent HEV infection in a significant proportion of 2 cohorts of patients with NA from the United Kingdom and the Netherlands.

METHODS **Cornish patients.** A 37-year-old man presented with symptoms and signs suggestive of bilateral brachial neuritis to the Royal Cornwall Hospital, Truro, UK. He was found to have mildly deranged liver function tests, and subsequent investigation showed him to have acute hepatitis E infection. A 35-year-old man presented with bilateral brachial neuritis to the neurology clinic at our institution. He was also found to have had a recent hepatitis E infection (table). There was a possible epidemiologic link between these 2 cases because both were regular surfers and both had surfed the same beach in November and December 2012, which is 4 to 8 weeks before symptom onset in both patients.

Previous studies have shown that patients with hepatitis E in the United Kingdom are more likely to live near the coast.^{19,20} The reason for this observation is uncertain, but one possibility is that such patients become infected via recreational use of beach areas. This prompted us to perform a retrospective analysis of patients presenting to our institution with NA to determine whether there had been other cases of HEV-associated NA, and if so, whether these were epidemiologically linked to the 2 index cases. We retrospectively examined 1,100 nerve

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Table Demographic, clinical, biochemical, and virologic data of all patients with HEV-associated NA

	Case 1	Case 2	Case 3	Case 4	Case 5
Demographic features					
Age at onset, y	37	35	40	36	34
Sex	M	M	F	M	M
Geographical area	Cornwall	Cornwall	Netherlands	Netherlands	Netherlands
Hand dominance	Left	Right	Right	Left	Right
Immunocompetent	Yes	Yes	Yes	Yes	Yes
Clinical symptoms and course					
Antecedent events	URTI, surfing	Surfing	None	None	Diarrhea
Clinical phenotype	Bilateral, left > right	Bilateral, right > left	Bilateral, right > left	Bilateral, right > left	Bilateral, right > left
Predominant part of brachial plexus	Right upper trunk, left lower trunk	Right and left upper trunk	Right and left upper trunk	Right and left upper trunk	Right and left upper trunk
Clinical course and outcome at 6 mo	Slow recovery, residual weakness	Slow recovery, residual weakness	Slow recovery, residual weakness	Slow recovery, residual weakness	Slow recovery, residual weakness
3 weakest muscles at 6 mo	Right: D, SS, T; left: ID, EDC, FD	Right: SA, SS, IS; left: SA, SS, R	Right: SA, IS, R; left: SA, IS, R	Right: EDC; left: SA, IS, SS	Right: R, SA, IS; left: IS, R, TM
FDS score at onset (0-5) ^a	3	3	3	2	3
FDS score at 6 mo (0-5) ^a	2	2	2	1	2
Biochemical and virologic studies					
Timing (days after symptom onset)	1	90 ^b	4	15	7
ALT, U/L ^c	313	NT	183	34	76 ^d
ALP, U/L ^e	113	NT	177	64	86
Bilirubin, $\mu\text{mol/L}$ ^f	4	NT	3	4	8
Anti-HEV S/N ratio	IgM 6.49, IgG 17	IgM 2.8, ^g IgG 21.1	IgM 8.37, IgG 0.86 ^h	IgM 4.95, IgG 14.52 ⁱ	IgM 7.99, IgG 15.14
HEV viral load, log IU/mL	2.70		3.18	3.36	3.63
HEV genotype			3		

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; D = deltoid; EDC = extensor digitorum communis, FD = flexor digitorum; FDS = functional disability scale; HEV = hepatitis E virus; ID = interosseus dorsalis I; Ig = immunoglobulin; IS = infraspinatus; NA = neuralgic amyotrophy; NT = not tested; R = rhomboid; SA = serratus anterior; S/N ratio = signal-to-noise ratio; SS = supraspinatus; T = triceps; TM = teres major; URTI = upper respiratory tract infection.

^aFDS scale: 0 = no complaints; 1 = complaints, no restriction; 2 = restrictions, no help in daily life; 3 = needs help in daily life, is independent; 4 = not independent, requires help regularly; 5 = in need of continuous care.

^bThis patient presented late. His initial symptoms were thought to be musculoskeletal in origin, and he was referred for physiotherapy. After several weeks, winging of the scapula was noted, prompting neurologic referral.

^cALT upper limit of normal = 34 (F) 45 (M) U/L.

^dALT at symptom onset 224, day 7 HEV IgG S/N ratio 18.41.

^eALP upper limit of normal = 98 (F) 115 (M) U/L.

^fBilirubin upper limit of normal = 17 $\mu\text{mol/L}$.

^gResampled 4 wk after presentation IgM S/N ratio 1.42.

^hResampled at 2 wk IgG S/N ratio 18.41.

ⁱResampled at 2 wk IgG S/N ratio 18.41.

conduction study and EMG reports (January 2011 to April 2013). Twenty-six additional cases of NA were identified, and of these patients, sera for HEV testing were available in 7.

Dutch patients. All patients attended the Department of Neurology of the Radboud University Nijmegen Medical Centre between October 2004 and June 2007 to take part in a prednisone treatment trial for NA. Patients were seen in the acute phase (within 4 weeks from onset of neurologic symptoms) with a well-documented attack of acute, severe shoulder and/or arm pain followed by paresis, in whom diagnoses other than NA were excluded. For the NA diagnoses, we used the criteria of Hannibal et al. for hereditary NA, although we did not consider family history.²¹ Nerve conduction and EMG studies supported the clinical diagnosis, and an MRI of the cervical spine was performed to exclude degenerative pathology as a cause of symptoms when necessary. None of the patients had a history of autoimmune disease or Guillain-Barré syndrome (GBS), or had been treated with immune-modulating medication at the time of presentation to the outpatient clinic. In addition to history-taking, a standard (pretreatment) questionnaire was completed by the patients to assess recent antecedent events and patients were clinically evaluated in a standardized manner at 3 and 6 months. Serum samples were obtained at first presentation (within 4 weeks of onset of pain and neurologic symptoms) and 2 weeks later. Sera were stored aliquoted at -80°C until use.

Standard protocol approvals, registrations, and patient consents. Ethical committee approval for the work in the United Kingdom was not appropriate, because it was considered by the clinicians and virologists involved as an investigation of a possible outbreak. However, the patients whose clinical details are described gave informed consent.

The local ethics committee (CMO Nijmegen/Arnhem) approved the Dutch study, and patients were included in this study after providing written informed consent.

Virologic testing. All available serum samples were tested for the presence of anti-HEV immunoglobulin (Ig) M and IgG using commercially available HEV ELISAs (Wantai, Beijing, PR China), according to the manufacturer's instructions. Samples with a signal-to-noise ratio <1.1 were considered negative. All anti-HEV IgM-positive samples were screened for the presence of HEV RNA (figure 1), using a previously described, internally controlled, quantitative real-time reverse transcription PCR.^{22,23} The reverse transcription PCR had a lower limit of detection (95% hit rate) of 143 (2.16 log) IU/mL as determined by the first World Health Organization standard for HEV RNA nucleic acid amplification technique-based assays (code 6329/10, Paul Ehrlich Institute, Langen, Germany).²⁴ Phylogenetic analysis of HEV-ORF1b was performed as described previously to determine genotype and to exclude a common source of infection.^{22,23} The sequences of all isolates

Figure 1 Flowchart of all Dutch and Cornish patients with NA

HEV = hepatitis E virus; Ig = immunoglobulin; NA = neuralgic amyotrophy; neg = negative; pos = positive.

were deposited into GenBank under accession number KF219921.

Case definition. A case of hepatitis E was defined as:

- HEV PCR-positive and/or
- IgM- and IgG-positive or
- IgM-positive, IgG-negative at presentation, but IgG-positive on a second serum sample.

Statistical analysis. Differences in proportions were tested using the χ^2 test, Fisher exact test, or the Kruskal-Wallis test, and differences in continuous variables were tested using the Mann-Whitney *U* test. A *p* value <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS version 20 (IBM Corp., Armonk, NY).

RESULTS Five cases (10.6%) of hepatitis E infection were identified from a total of 47 patients with NA who were tested for HEV. Anti-HEV IgM was detected in 2 of 9 Cornish and 3 of the 38 Dutch patients with NA (table, figure 1). All 5 patients were anti-HEV IgG-positive, or became positive in the follow-up sample after 2 weeks. HEV RNA was detected in serum in all 4 patients who were tested early (days 1, 4, 7, and 15) after the onset of NA symptoms. Further characterization classified one strain within genotype 3 (case 3, figure e-1 on the *Neurology*[®] Web site at www.neurology.org); the viral loads of the other HEV RNA-positive samples were too low for Sanger sequencing. One patient (case 2) presented 3 months after symptom onset; anti-HEV IgG and IgM serology was positive (table), but no HEV RNA could be detected in his serum at this stage.

Of the 47 patients with NA tested in total, 13 had anti-HEV IgG (figure 1). In patients without confirmed recent hepatitis E infection (*n* = 42), anti-HEV IgG was found in 8. This included 7 of the Dutch cohort, so in total 10 (26%) of 38 Dutch patients with NA had anti-HEV IgG. One patient from the Dutch cohort had a modestly elevated anti-HEV IgM signal-to-noise ratio (2.28) with negative PCR and negative anti-HEV IgG. The anti-HEV IgM result was therefore considered to be false-positive.

Twenty-eight patients with NA were identified in the Cornish cohort, but only 5 of these patients had their liver function tests checked within 1 month of symptom onset. Two of these patients (including case 1) had mildly abnormal liver function with an alanine aminotransferase of 66 and 313 IU/L, respectively, and a normal bilirubin. In the Dutch cohort, 9 of 38 patients (24%) had mildly abnormal liver function (alanine aminotransferase median 98 U/L, range 48–396; bilirubin 27 μ mol/L in 1 patient), including cases 3 and 5 (table, figure 1).

The patients with HEV-associated NA were aged between 34 and 40 years, compared with a median

age of 40 years (range 23–72) in the patients without hepatitis E infection; 4 were male and 1 female (table). Before onset of neurologic symptoms, one patient developed symptoms of an upper respiratory tract infection, and another patient had diarrhea. None of the patients reported traveling to areas traditionally considered hyperendemic for HEV in the 3 months before symptom onset. All had clinical evidence of patchy bilateral involvement of the brachial plexus. EMG confirmed bilateral patchy axonal involvement predominantly of the upper trunk of the brachial plexus in all patients (figure e-2). In 4 of the patients with HEV-associated NA, the neurologic injury was worse in the dominant arm. All patients showed some symptomatic improvement, but all had significant residual neurologic impairment at 6 months (table).

All of the patients with HEV-associated NA had bilateral brachial plexus involvement, compared with 15 of 35 (43%) of the Dutch cohort without recent evidence of hepatitis E infection. In the Dutch cohort, the presence of anti-HEV IgM was not related to age, sex, disease severity (functional disability scale), presence of sensory deficits, prednisone use, and outcome at 6 months (functional disability scale), or any specific preceding symptoms of an infection. Both groups showed a slow recovery over 6 months, with significant residual deficits.

DISCUSSION The current study suggests that approximately 10% of patients with NA have acute hepatitis E infection at the start of their neurologic illness. The patients with HEV-associated NA were aged between 34 and 40 years and had modestly elevated serum transaminases with bilateral brachial plexus involvement and residual functional impairment at 6-month follow-up. The evidence suggests that hepatitis E infections documented in the patients with NA were locally acquired, because none had traveled to an HEV-endemic area and HEV genotype 3 was found in the single patient in whom viral sequencing was possible. HEV genotype 3 is the dominant genotype in Europe in both human and pig populations.^{10,11,22}

It is not possible to be certain what proportion of patients with NA have an associated hepatitis E infection, because some of the Cornish patients were studied in retrospect. This may have led to case ascertainment bias. However, the Dutch cohort, although small, was prospectively studied and rigorously defined. Analysis of the data from our Dutch cohort suggests that 8% of patients with NA have an associated infection with HEV. Our data should be interpreted in light of a recent large Dutch study: 49 of 5,239 (0.9%) healthy blood donors tested positive for anti-HEV IgM and 4 (0.0008%) were HEV

RNA-positive.²⁵ Although previous studies show a large proportion of patients with NA report clinical symptoms of a preceding infection, extensive serologic studies on the type of infections in NA have not been conducted.¹⁸ Many case reports of NA related to a range of microorganisms have been published. So far, case series have been published in relation to a recent infection with *Bartonella* and coxsackie virus type A2, but controlled studies in larger groups are required to define whether or not they are associated with NA.^{7,26}

The abnormalities in liver function are transient and mild, and none of the patients with NA were clinically jaundiced. The Cornish data demonstrate that in standard clinical practice, liver function tests are rarely checked in patients with NA. These observations mean that there are often either no (or very subtle) clinical or biochemical prompts for the physician to consider viral hepatitis as a diagnostic possibility. Patients with NA often present late, because they are initially thought to have musculoskeletal problems (as illustrated by case 2) and may take a rather circuitous route to a neurologist.¹⁸ “Late presenters” are usually HEV PCR-negative when tested, because viremia in hepatitis E infections is often brief in immunocompetent patients.^{10,11}

The mechanism by which HEV triggers NA is uncertain. Direct infection of the brachial plexus cannot be excluded because HEV RNA was demonstrated in all HEV-associated patients at the start of their illness. Alternatively, HEV may trigger an immune response that damages the peripheral nervous system, similar to the pathogenesis of GBS. Both are monophasic disorders and more frequent in men, in contrast to many classic autoimmune diseases. In the current 2 studies, we identified a new link between these 2 disorders that both may be preceded by a recent hepatitis E infection. Interestingly, the frequency of HEV infections preceding NA and GBS are similar: 8%–10% and 5%, respectively. The cases of HEV-associated NA we have documented all had bilateral peripheral nervous system involvement as seen in GBS. The phenotype of (asymmetric) bilateral NA is generally seen in 25% to 30% of the patients with NA.¹⁸ In all previous case reports of HEV-associated NA, there was bilateral involvement of the brachial plexus.^{9,12–17} Given the similarities between GBS and NA, these disorders may represent 2 clinical syndromes in the same spectrum of immune-mediated peripheral nerve disorders, related to HEV infection.

At present, there is no evidence that HEV-related NA should be treated differently than any other forms of NA. Further studies are required to confirm our findings and to demonstrate whether patients are viremic at presentation. If this proves to be the case, one

could consider treatment with antiviral therapy, but at present this is speculative.

The results of our study suggest that an acute hepatitis E infection is found in approximately 10% of patients with NA from the United Kingdom and the Netherlands. The pathophysiologic relationship remains to be established, as does the role of HEV in patients with NA in other geographical settings. The finding that hepatitis E is associated with both NA and GBS adds weight to the notion that these syndromes reflect differing parts of the same spectrum of neurologic immune-mediated diseases.

AUTHOR CONTRIBUTIONS

Jeroen J.J. van Eijk: coinstigated the study, analyzed and interpreted the data, wrote the paper, reviewed the drafts. Richie G. Madden: collected and interpreted patient data and reviewed the drafts. Annemiek A. van der Eijk: performed the virologic analysis, interpreted the data, and reviewed the drafts. Jeremy G. Hunter: collected and interpreted patient data and reviewed the drafts. Johan H.J. Reimerink, Richard P. Bendall, and Suzan D. Pas: performed the virologic analysis, interpreted the data, and reviewed the drafts. Vic Ellis: performed the virologic analysis and reviewed the drafts. Nens van Alfen, Laura Beynon, and Lucy Southwell: collected patient data and reviewed the drafts. Brendan McLean: collected and interpreted patient data and reviewed the drafts. Bart C. Jacobs: coinstigated the study, interpreted the data, and reviewed the drafts. Baziel G.M. van Engelen: coinstigated the study and reviewed the drafts. Harry R. Dalton: coinstigated the study, interpreted the data, wrote the paper, reviewed the drafts, and is the guarantor.

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