Clinical phenotype and outcome of hepatitis E virus–associated neuralgic amyotrophy

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Supplemental data at Neurology.org

ABSTRACT

Objective: To determine the clinical phenotype and outcome in hepatitis E virus–associated neuralgic amyotrophy (HEV-NA).

Methods: Cases of NA were identified in 11 centers from 7 European countries, with retrospective analysis of demographics, clinical/laboratory findings, and treatment and outcome. Cases of HEV-NA were compared with NA cases without evidence of HEV infection.

Results: Fifty-seven cases of HEV-NA and 61 NA cases without HEV were studied. Fifty-six of 57 HEV-NA cases were anti-HEV IgM positive; 53/57 were IgG positive. In 38 cases, HEV RNA was recovered from the serum and in 1 from the CSF (all genotype 3). Fifty-one of 57 HEV-NA cases were anicteric; median alanine aminotransferase 259 IU/L (range 12–2,961 IU/L); in 6 cases, liver function tests were normal. HEV-NA cases were more likely to have bilateral involvement (80.0% vs 8.6%, $p < 0.001$), damage outside the brachial plexus (58.5% vs 10.5%, $p < 0.01$), including phrenic nerve and lumbosacral plexus injury (25.0% vs 3.5%, $p = 0.01$, and 26.4% vs 7.0%, $p = 0.001$), reduced reflexes ($p = 0.03$), sensory symptoms ($p = 0.04$) with more extensive damage to the brachial plexus. There was no difference in outcome between the 2 groups at 12 months.

Conclusions: Patients with HEV-NA are usually anicteric and have a distinct clinical phenotype, with predominately bilateral asymmetrical involvement of, and more extensive damage to, the brachial plexus. Involvement outside the brachial plexus is more common in HEV-NA. The relationship between HEV and NA is likely to be causal, but is easily overlooked. Patients presenting with NA should be tested for HEV, irrespective of liver function test results. Prospective treatment/outcome studies of HEV-NA are warranted. ***Neurology*® 2017;89:1–9**

GLOSSARY

ALT = alanine aminotransferase; **gt3** = genotype 3; **HEV** = hepatitis E virus; **LFT** = liver function test; **MRC** = Medical Research Council; **NA** = neuralgic amyotrophy.

The clinical syndrome of neuralgic amyotrophy (NA) has been recognized since the late 19th century[1] and defined by Parsonage and Turner in 1948.[2] Patients generally present with severe pain, usually in the shoulder, most often preceded by symptoms suggestive of an infection.[3] In 2006, a large cohort study[3] found a subgroup of patients with NA who were mostly middle-aged men with extensive peripheral nervous system damage and abnormal liver function tests (LFTs), for which no explanation could be found at the time. Recently, NA occurring in the context of hepatitis E virus (HEV-NA) infection has been reported.[4,5]

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HEV is a pathogen of global significance and is endemic in developed European nations[6] where hepatitis E is caused mainly by HEV genotype 3 (gt3), which is a porcine zoonosis.[7] In some developed countries, HEV infection is very common. In England, there are estimated to be 100,000 infections per annum,[8] but only a small minority of patients develop clinically apparent hepatitis, and most cases are either asymptomatic or unrecognized.[7] Several studies have described a range of neurologic injuries associated with HEV infection, including NA.[4,5,9] To date, 31 cases of hepatitis E–associated NA have been described in the literature, mostly European patients with gt3 infection.[5] We investigated whether such patients have a different clinical phenotype and outcome compared with patients with idiopathic NA.

METHODS

Patients. Cases of NA were eligible for inclusion if they had been tested for HEV. Cases of NA were identified in 11 different centers from 7 countries, including the Netherlands, United Kingdom, Switzerland, Germany, France, Belgium, and Italy. Sixteen patients have been reported before.[4,9–16] HEV-associated cases were detected through a combination of routine and sporadic HEV testing in patients with NA. In addition to these prospectively tested patients, we included 38 patients from an earlier Dutch study of antecedent infections and immunogenetic factors in NA.[4] HEV-negative patients came mainly from the latter study and 2 participating centers that increasingly test routinely for HEV in cases of NA. Data captured from the clinical records were a predefined list of variables and included demographics, clinical and laboratory findings, and treatment and outcome. We assessed neurologic outcomes by the Medical Research Council (MRC) sum-score of the 3 weakest muscles (ranging from 0 = full paralysis to 5 = normal strength) at 6 and 12 months and by the Functional Disability Score (ranging from 0 = no complaints to 5 = in need of continuous care) at final follow-up.[17] Most of our cases were tested for other infections, including hepatitis A, B, or C viruses, Epstein-Barr virus, Cytomegalovirus, Borrelia burgdorferi, or HIV when clinically indicated in the workup of liver function abnormalities or in the differential of NA by the local treating physicians. In a quarter of the patients with HEV-NA, all the above infections were excluded.

Case definition of NA. We used the following case definition, adapted from van Alfen et al.,[18] to diagnose NA:

1. (Sub) acute onset (over hours or days)
2. Initial pain with numerical rating scale score ≥7
3. Multifocal distribution of neurologic injury centered on the brachial plexus
4. Monophasic course, with slow recovery
5. Preceding direct trauma, malignancy, and radiation excluded.

Confirmatory neurophysiology studies were not mandatory for defining a case, but were performed in most patients.

Definition of hepatitis E. We defined cases of hepatitis E by a combination of serologic and molecular assays at all centers. Acute or recent HEV infection was diagnosed when[19]:

1. serum anti-HEV IgM and anti-HEV IgG assays were both reactive and/or
2. HEV RNA was detected in the serum using RT-PCR.

Because of the retrospective and multicenter nature of the study differing, but validated, laboratory methods were used in participating centers.

Statistics. We compared the demographics, clinical/laboratory findings, and outcome of cases with evidence of HEV infection at the start of their neurologic illness to cases without evidence of HEV infection. We conducted linear, logistic, and ordered logistic regressions using R software (R Development Core Team, 2015). We considered a 2-sided p value <0.05 to be statistically significant. Missing at random was assumed, and complete case analysis was used to handle missing data.

Ethics. This was a descriptive retrospective study of anonymized previously documented data. Ethical approval was not required.

RESULTS

We documented 118 patients who fulfilled the case definition of NA and had been tested for HEV. Fifty-seven of these had evidence of current/recent HEV infection at the start of their neurologic illness. All but one were anti-HEV IgM positive; 54/57 were anti-HEV IgG positive. In 38 (66.6%) cases, HEV RNA was recovered from the serum and in 1 case from the CSF. In the 25 cases in which genotyping was successful, we identified HEV gt3. One patient was anti-HEV IgM negative but IgG and PCR positive. Sixty-one NA cases had no evidence of acute or recent HEV infection. Ten of these were anti-HEV IgG positive, consistent with previous infection. Tests for other causes of viral hepatitis were negative, excepting 1 patient with acute HEV infection who had pre-existing chronic hepatitis B virus infection. None of the patients who we serologically tested more extensively had evidence of an additional concomitant infection.

Clinical phenotype. We found the majority of NA cases to be middle-aged men (table e-1 at Neurology.org). HEV-NA cases were slightly older (median age 51 years) than cases not associated with HEV (median age 44 years, $p < 0.01$). There were no differences between the 2 groups in sex, history of autoimmune disease, antecedent events, or time from symptom onset to presentation (table e-1).

At presentation (table 1 and figure), HEV-NA cases were more likely to have bilateral involvement of the brachial plexus (80.0%) compared with cases not associated with HEV (8.6%, $p < 0.001$); neurologic involvement outside the brachial plexus ($p < 0.001$), including phrenic nerve and lumbosacral plexus involvement ($p < 0.01$); and diminished tendon reflexes in the affected limb(s) ($p = 0.03$). Some muscles were more often involved, including right supraspinatus ($p = 0.01$), right infraspinatus ($p = 0.01$), right deltoid ($p = 0.02$), and triceps bilaterally ($p = 0.01$ and 0.02). We found a higher proportion of muscles involved in the HEV-NA cases and with more frequent involvement of the upper trunk

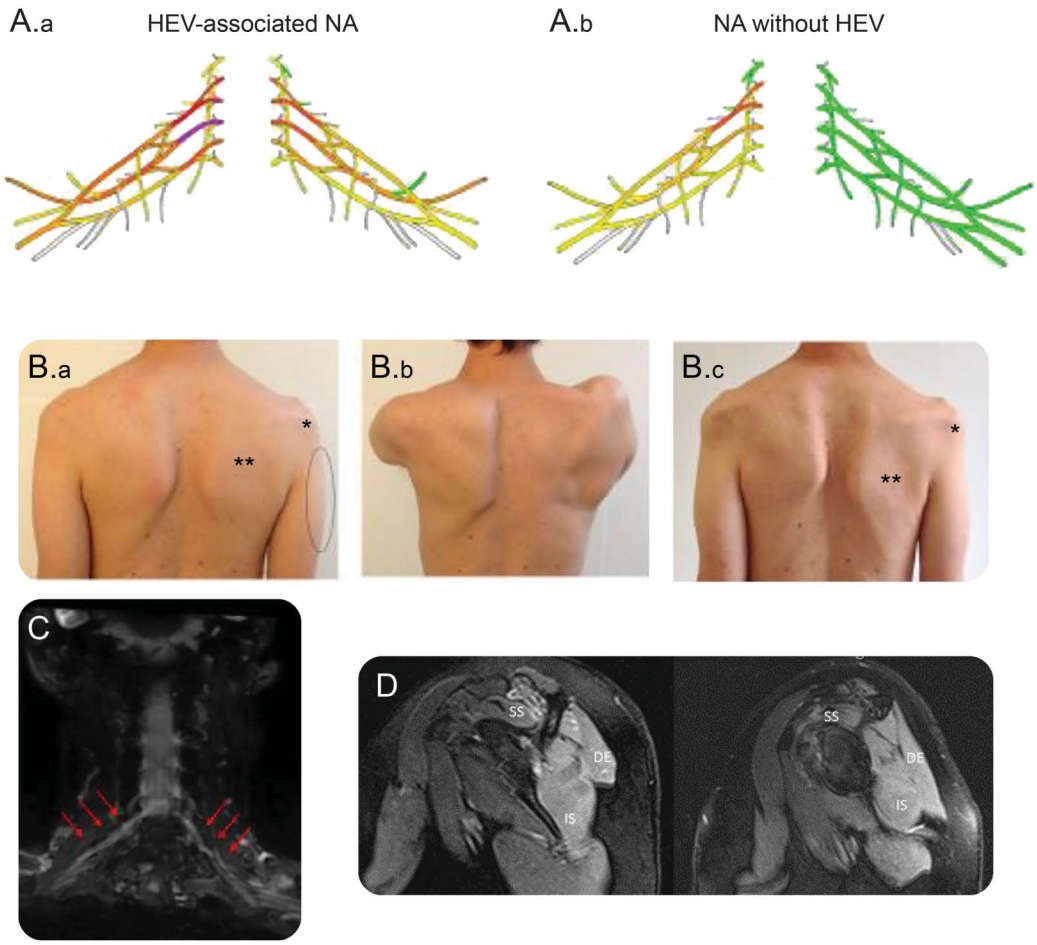
Table 1 Neurologic features at presentation

	HEV+	HEV−	*p* Value (CI)
Hand dominance			
Left:right	4/37 (10.8%)	7/50 (14%)	0.7 (0.19 to 2.75)
Median NRS pain score (range)	9 (6–10)	9 (5–10)	0.57 (−0.75 to 0.41)
Median duration in days of initial pain (range)	15 (0.25–365)	20 (1–80)	0.6 (−13.81 to 23.62)
Side affected			
Dominant	2/10 (20%)	21/53 (39.6%)	0.25 (0.05 to 1.70)
Nondominant	4/10 (40%)	28/53 (52.8%)	0.46 (0.14 to 2.32)
Bilateral	44/55 (80%)	5/58 (8.62%)	<0.001 (14.82 to 146.21)
Median MRC sum-score; 3 weakest muscles (range)	10 (1–15)	10 (2–13)	0.84 (0.53 to 2.21)
Pattern of weakness			
Upper trunk: right	39/45 (86.7%)	34/59 (57.6%)	<0.001 (1.85 to 14.12)
Middle trunk: right	23/45 (51.1%)	12/59 (20.3%)	<0.001 (1.76 to 9.96)
Lower trunk: right	12/45 (26.7%)	5/59 (8.5%)	0.02 (1.33 to 13.28)
Upper trunk: left	37/45 (82.2%)	30/59 (50.8%)	<0.001 (1.40 to 5.46)
Middle trunk: left	22/45 (48.9%)	20/58 (34.5%)	0.14 (0.82 to 4.07)
Lower trunk: left	6/45 (13.3%)	7/59 (11.9%)	0.82 (0.34 to 3.7)
Muscle involvement			
Supraspinatus: right	24/35 (68.6%)	19/48 (39.6%)	0.01 (1.35 to 8.59)
Infraspinatus: right	26/39 (66.7%)	19/48 (39.6%)	0.01 (1.28 to 7.55)
Deltoid: right	27/43 (62.7%)	20/52 (38.4%)	0.02 (1.19 to 6.32)
Triceps: right	21/43 (48.8%)	12/51 (23.5%)	0.01 (1.30 to 7.67)
Triceps: left	18/45 (40.0%)	9/50 (18%)	0.02 (1.22 to 8.03)
Median proportion of muscles involved[a] (range)	0.36 (0.06–0.93)	0.19 (0.03–0.63)	<0.001 (1.31 to 2.98)
Scapula dyskinesia	31/56 (55.4%)	41/60 (68.3)	00.15 (0.27 to 1.22)
Glenohumeral complications	9/53 (17%)	8/59 (13.6%)	0.61 (0.46 to 3.75)
Sensory symptoms	41/51 (80.4%)	38/61 (62.3%)	0.04 (1.07 to 6.09)
Myalgia	9/48 (18.8%)	1/60 (1.7%)	0.02 (2.42 to 256.09)
Involvement outside brachial plexus			
Lumbosacral	14/53 (26.4%)	4/57 (7%)	0.01 (1.57 to 17.79)
Phrenic	13/53 (24.5%)	2/57 (3.5%)	0.01 (2.30 to 59.22)
Facial	1/53 (1.9%)	Nil	NA
Other	5/53 (7.5%)[b]	1/57 (1.8%)[c]	0.18 (0.65 to 91.04)
Any	32/53 (60.3%)	6/57 (10.5%)	0.00 (4.64 to 35.65)
Tendon reflexes			
Diminished/absent	22/55 (40%)	12/58 (20.7%)	0.03 (1.13 to 6.02)
Normal	30/55 (54.5%)	42/58 (72.4%)	0.05 (0.21 to 0.99)

Abbreviations: CI = confidence interval; HEV = hepatitis E virus; MRC = Medical Research Council; NA = not available; NRS = numerical rating scale.
[a] Number of paretic muscles/total number of muscles tested (Kruskal-Wallis test).
[b] Cerebral (n = 1), trigeminal (n = 1), and recurrent laryngeal (n = 3) nerve involvement.
[c] Cervical.

(either side) and right middle and lower trunk (table 1), suggesting more extensive/severe nerve injury in this group. At presentation, patients with HEV-NA were more likely to have (had) myalgia in the upper and lower limbs ($p = 0.02$). Hoarseness (recurrent laryngeal nerve involvement), peripheral facial nerve palsy, and trigeminal neuropathy were also reported in the HEV-NA group (table 1).

Figure Hepatitis E virus–associated imaging



(A) Typical plexplots from (a) hepatitis E virus (HEV)-associated case; (b) non–HEV-associated case of neuralgic amyotrophy. Normal neurologic tissues of the brachial plexus are shown in green, mildly affected in yellow, moderately affected in orange, and severely affected in red. HEV-associated cases of neuralgic amyotrophy are characterized by bilateral, patchy, asymmetrical damage to the brachial plexus. These figures were derived from clinical and electrophysiologic data of patients included in the study. (B) Typical clinical phenotype of HEV-associated neuralgic amyotrophy. HEV-associated bilateral neuralgic amyotrophy at presentation (a, b) and after 6 months (c). Bilateral winged scapula, caused by long thoracic neuropathy, is already evident at rest (a) but is accentuated when the patient raises his arms forward (b). The dotted black ovoid indicates the area of hypoesthesia (axillary nerve). Mild atrophy of right deltoid (*) and infraspinatus (**) muscles can be appreciated 12 days after paresis onset (a) but becomes more prominent after 6 months (c). (C and D) MRI in HEV-associated neuralgic amyotrophy. (C) Brachial plexus MRI at presentation of HEV-associated bilateral neuralgic amyotrophy. Reformatted coronal maximum intensity projection T2 SPACE with fat suppression shows thickening and hyperintensity (red arrows) of the postganglionic C6 root. NA = neuralgic amyotrophy.

In patients presenting with HEV infection, the biochemical evidence of hepatitis was modest: the median serum bilirubin level at presentation (table 2) was 13 μmol/L and alanine aminotransferase (ALT) 259.5 IU/L. Six of the 57 (10.5%) patients with hepatitis E had clinically detectable jaundice. In 5 patients, this was mild (bilirubin 50–100 μmol/L). In 1 patient, the bilirubin level was 346 μmol/L; however, this was in the context of pre-existing decompensated chronic hepatitis B. In 6 HEV-associated cases, the LFTs were normal.

Twenty-four HEV-associated cases underwent lumbar puncture, 6 of whom had a CSF pleocytosis with white cell counts >10/mm^3 and protein >0.42 g/L. HEV RNA was detected in the abnormal CSF of 1 patient infected by HEV gt3.[15] Five (83%) patients with CSF pleocytosis had involvement of nerves outside the brachial plexus, i.e., phrenic nerve (n = 3), lumbosacral plexus (n = 3), and trigeminal neuropathy (n = 1). The median Functional Disability Score was not different to that in patients without CSF pleocytosis. CSF samples from 7 patients in the HEV negative group were all normal.

Outcome and response to treatment. Functional Disability Scores at final follow-up were no different between the 2 groups (table 3). The MRC sum-scores of the 3 weakest muscles were lower in the

Table 2 Investigations

	[a]HEV+	HEV−	*p* Value (CI)
Median ALT at presentation (range)	259.5 (12–2961)	23 (7–396)	<0.001 (426.81–853.96)
Median bilirubin at presentation (range)	13 (0.7–346)	6 (1–27)	<0.001 (8.32–41.49)
Median ALKP at presentation (range)	149 (4–659)	68 (31–155)	<0.001 (55.95–126.10)
CSF WBC ≥10/mm^3	6/24 (25%)	0/7 (0%)	NA
CSF protein >0.42 g/L	15/22 (68.18%)	2/6 (33.33%)	0.14 (0.67–36.75)
CSF HEV PCR+	1/11	0/1	NA
Cervical spine MRI			
Root compression	2/30 (6.7%)	1/11 (9.1%)	0.79 (0.06–16.35)
Myelopathy	Nil	Nil	NA
Degenerative	8/30 (26.7%)	2/11 (18.2%)	0.58 (0.33–12.26)
Normal	20/30 (66.7%)	8/11 (72.7%)	0.71 (0.14–3.27)
Brachial plexus MRI			
GD enhancement	3/17 (17.6%)	Nil	NA
Plexus swelling	2/17 (11.7%)	1/5 (20%)	0.32 (0.01–7.18)
Normal	12/17 (70.6%)	4/5 (80%)	0.82 (0.03–8.32)

Abbreviations: ALKP = alkaline phosphatase; ALT = alanine aminotransferase; CI = confidence interval; GD = gadolinium; HEV = hepatitis E virus; NA = not available; WBC = white blood count.
Normal range: bilirubin = 3–17 μmol/L; ALT = <41 IU/L; ALKP = 40–160 IU/L; CSF = WBC <10/mm^3, protein 0.12–0.42 g/L.
Electrophysiologic examination was not different between the 2 groups with regard to the presence of findings suggestive of axonal loss (30/39 [77%] vs 49/56 [87%], not significant [NS]) and demyelinating pathology (3/39 [7%] vs 2/48 [4%], NS). Because of the retrospective nature of the study and institutional differences in daily practice, the timing of the electrophysiologic studies was very heterogeneous (HEV positives: median time to electrophysiologic examination 90, range 3–850 days; HEV negatives: median 40, 5–330 days) and should be interpreted with caution.
[a] Thirty-six patients were HEV PCR positive in the serum and were HEV gt3 when sequencing was possible (n = 24).

patients with HEV-NA at 6 months ($p = 0.02$), but there was no difference at 12 months. There was no difference in the median time from onset to resolution of symptoms. HEV-NA cases were more likely to have received immunomodulatory therapy (58.3%) than non–HEV-associated cases (37.5%, $p = 0.04$). Twenty-two HEV-NA cases (38.6%) were given oral corticosteroids and 11 (19.3%) IV immunoglobulin (Ig). Of the HEV-negative cases, 21 (34.4%) patients received oral prednisolone and 1 received methylprednisolone. There were no differences in outcomes between cases with and without HEV infection treated with prednisolone or methylprednisolone, as determined by the MRC sum-scores at 6 and 12 months and Functional Disability Score at final follow-up. No adverse events leading to discontinuation of corticosteroids were observed in either group. HEV-NA cases used opioid and neuropathic analgesics more frequently, and pain control was better ($p = 0.04$) than in the HEV-negative cases.

In the HEV-NA group, 4 patients were treated with ribavirin within a few days of symptom onset (table e-2). Of these patients, 2 also received IVIg, and the other 2 patients received oral corticosteroid therapy. The outcome was variable. Of the 11 HEV-NA cases that received treatment with IVIg, 4 patients were cotreated with oral corticosteroids and 2 with ribavirin. There were no differences in the final Functional Disability Score in these eleven patients compared with the HEV-NA group as a whole ($p = 0.12$). However, compared with patients within the group who received any immunomodulatory therapy (n = 28), patients treated with IVIg had an improved mean Functional Disability Score at final follow-up ($p = 0.039$), confirmed by the ordered logistic regression analysis of individual scores ($p = 0.041$). Most (7/11) patients treated with IVIg were from 1 center (Lugano, Switzerland) and received a 5-day course of treatment at a dose of 0.4 g/kg/d. IVIg treatment was well tolerated, and in most cases, pain improved or disappeared within 10 days of starting therapy.

DISCUSSION HEV-NA appears to have a distinctive clinical phenotype. Patients are older, have bilateral and more extensive involvement of the brachial plexus, and are more likely to have nerve injury outside the brachial plexus (phrenic nerve and lumbosacral plexus) compared with NA cases without HEV infection. The clinical phenotype of HEV-NA may indicate the

Table 3 Treatment and outcomes

	HEV+	HEV−	*p* Value (CI)
Median time (range) from presentation to final follow-up, mo	11.5 (1–179)	12 (3–110)	0.94 (−7.95 to 8.62)
Median NRS pain score at follow-up (range)	3 (0–6)	3 (0–10)	0.54 (−1.14 to 0.60)
Median MRC sum-score (range)[a]			
At 6 mo[a]	11 (5–15)	13 (6–15)	0.02 (0.10 to 0.83)
At 12 mo[a]	13 (11–15)	14 (8–15)	0.64 (0.18 to 2.13)
Immunomodulatory treatment			
Treated[b]	28/48 (58.3%)	21/56 (37.5%)	0.04 (1.07 to 5.20)
Oral corticosteroids	22/48 (45.8%)	21/56 (37.5%)	1.00 (0.45 to 2.22)
IV methylprednisolone	0/48 (0%)	1/56 (1.79%)	NA
IVIg	11/48 (22.9%)	Nil	NA
Antiviral treatment			
Ribavirin	4/50 (8%)	Nil	NA
Analgesics			
Paracetamol	35/52 (67.31)	46/56 (82.14%)	0.08 (0.18 to 1.08)
Nonsteroidal anti-inflammatory drugs	33/51 (64.71%)	47/57 (82.46%)	0.04 (0.16 to 0.94)
Opioids	29/48 (60.42%)	23/56 (41.07%)	0.05 (1.01 to 4.87)
neuropathic analgesia (tricyclic antidepressant, duloxetine, gabapentin)	26/49 (53.06%)	16/58 (27.59%)	0.01 (1.34 to 6.75)
Successful pain relief	27/46 (58.7%)	21/55 (38.18%)	0.04 (1.04 to 5.19)
Functional Disability Score at final follow-up			
0 = no complaints	12/51 (23.53%)	8/58 (13.79%)	0.19 (0.72 to 5.35)
1 = complaints but no restrictions	10/51 (19.61%)	20/58 (34.48%)	0.09 (0.19 to 1.10)
2 = restrictions but no help in daily life	26/51 (50.98%)	29/58 (50%)	0.92 (0.49 to 2.21)
3 = needs help in daily life but independent	2/51 (3.92%)	0/58 (0%)	NA
4 = not independent, requires help regularly	1/51 (1.96%)	1/58 (1.72%)	0.93 (0.04 to 29.33)
5 = in need of continuous care	0/51 (0%)	0/58 (0%)	NA
Comparison of mean scores	1.41	1.41	0.99 (−0.34 to 0.33)
Comparison of outcomes (0–5) as a whole[a]			0.86 (0.52 to 2.19)
Median time (range) from onset to complete resolution of symptoms, mo	3 (1–120)	12 (3–26)	0.85 (−25.15 to 30.39)

Abbreviations: CI = confidence interval; HEV = hepatitis E virus; MRC = Medical Research Council; NA = not available; NRS = numerical rating scale (1–10).
There was no relationship between CSF pleocytosis and involvement outside the brachial plexus ($p = 0.15$; CI 0.7–120.4).
There was no relationship between CSF pleocytosis and Functional Disability Score at final follow-up ($p = 0.15$; CI 0.66–40.6).
[a] Ordered logistic regression was used to compare the ordered outcomes.
[b] Some patients received more than one modality of immunomodulatory treatment.

involvement of nerve roots as well. These observations extend previous findings of bilateral involvement published in case reports and small case series of HEV-associated NA in developed countries.[4,5,9–11,15,16] Among the HEV-NA cases we describe, neurologic illnesses dominated the clinical picture. Most patients were anicteric with mostly only mildly abnormal LFTs, which quickly returned to the normal range (data not shown). The diagnosis of HEV in such cases is easily overlooked.

The exact pathophysiologic mechanism of NA is unknown. Indirect evidence points to a multifactorial disorder with an innate susceptibility to the disease and one or more external trigger(s) such as antecedent infections and/or a mechanical factor such as strenuous exercise.[3,20] Our data support the suggested relationship between an antecedent HEV infection and NA. Most patients with HEV-NA were viremic when tested within 2 weeks after symptom onset, but a subgroup of HEV-IgM–positive patients was RNA negative

(6/31, 19.4%) when tested within this period. These findings suggest that HEV could be neurotropic and might directly infect the brachial plexus and the cervical roots. Alternatively, or in addition, HEV may induce an immunologic response that causes nerve damage or aggravates the neural injury primarily caused by direct infection. The absence of HEV RNA in the CSF suggests that only neural structures outside the intrathecal space were infected or that the HEV had already cleared at the onset of nerve injury. To date, there is insufficient evidence to prove these mechanisms, although there is some evidence from laboratory and animal studies that supports the concept of HEV as a neurotropic virus.[21–23]

We found no differences in outcomes between groups, although we expected that the HEV-associated NA group would have a worse prognosis because of the more extensive nerve damage seen. Both groups recovered over the course of months to years, but half of all the patients were still in need of some form of help after 1 year. Whether the differences in the use of immunomodulatory therapy influenced this outcome (HEV cases received were more commonly given immunomodulatory treatment than non-HEV cases) is a matter of debate, but in view of the putative immune-mediated etiology of NA, its efficacy should be prospectively tested. Equally important is that we did not encounter serious treatment-related adverse events in any of the patients, and in particular, we did not see worsening of HEV infection in viremic patients treated with corticosteroids or IVIg. Nonetheless, our treatment and outcome data need to be interpreted with caution, as this study was not designed to define treatments of HEV-NA. Furthermore, the outcome measures have not been specifically validated for NA. For example, the MRC sum-score used relies on weakness in just 3 muscles and may not be able to reliably distinguish between HEV-NA cases with more extensive neurologic injury and HEV-negative cases.

During the course of our studies of HEV-NA, we observed cases that did not fulfill our case definition of NA, but are worthy of discussion. An example of such a case is as follows. A 55-year-old man from Cornwall developed severe, progressive pain in the right shoulder while working. Clinical assessment in the emergency department showed no abnormal neurologic signs, and he was not jaundiced. However, his serum ALT level was found to be 572 IU/L. After 12 hours, his pain completely abated, and he developed no further neurologic symptoms or signs. He was found to have HEV infection, as he was anti-HEV IgM and IgG positive, and gt3 HEV was recovered from his serum. This case is compatible with a self-limiting, "forme fruste" of NA. Several such cases were seen at more than one center during our studies, but have not been included in our data analysis. How frequently these kinds of cases occur is not known, as the diagnosis and underlying infectious trigger are easily overlooked. NA has previously been considered a rare condition, but a recent detailed analysis in primary care in the Netherlands showed that the true incidence may be 1:1,000 cases per year,[18] forme fruste cases (such as the one described above) excluded. In our experience, the triad of severe bilateral shoulder pain in a middle-aged man with abnormal LFTs is highly predictive of the diagnosis of HEV infection.

The main limitation of our study is its retrospective nature. In common with all retrospective studies, there was an issue with missing data that were not recoverable. This may have led to us to miss important observations regarding the phenotype and outcome in HEV-NA. Also, although our study shows that approximately 50% of the 118 cases of NA were associated with HEV, this may not be a true reflection of the proportion of cases associated with HEV in the community due to case-ascertainment bias. For example, in the past 2 years, 41 patients with NA have been seen in 's-Hertogenbosch, the Netherlands, and all prospectively tested for HEV, but only 11/41 (26.8%) had HEV infection. The opposite is true for patients included from Southern Switzerland, where 11/13 (84.6%) had acute HEV infection. Therefore, the proportion of NA cases associated with HEV infection may reflect the amount of circulating virus in a community and may vary considerably, as the incidence and prevalence of HEV varies significantly between and within countries and over time.[7]

To date, all cases of HEV-NA have been from developed countries and, where viral sequencing data were available, caused by HEV gt3.[5] HEV is an ancient virus, and biological time clock studies suggest that it diverged into the 4 main genotypes (HEV gt1-4) that cause human disease several hundred years ago.[24,25] It is interesting to go back to Parsonage and Turner's[2] original description of NA, the data for which were collected during and just after the 2nd World War. Approximately 50% of the cases were found in military personnel serving in South Asia, mainly India and Burma, where HEV gt1 was circulating at around the same time.[26] Around 30% had bilateral neurologic involvement, consistent with what we now know to be the predominant HEV-associated phenotype. It is tempting to speculate, but quite impossible to prove, whether such cases were also associated with HEV, possibly gt1. It is also interesting to note that nearly half of Parsonage and

Turner's cases described were in individuals who were already hospitalized, many of whom were recovering from preceding infections including suspected typhoid and cholera and other infections of uncertain etiology.[2] The role of infectious agents other than HEV in NA remains to be determined.

HEV-associated NA results in a distinct clinical phenotype with predominantly bilateral, asymmetrical involvement of the brachial plexus often with the involvement of the phrenic nerve in older men and may be part of a spectrum of HEV-associated (sub)acute nerve injury, including mononeuritis multiplex and Guillain-Barré syndrome.[5,27] The relationship between HEV and NA is likely to be causal. Prospective studies are required to determine optimal treatment and outcome. The diagnosis of HEV in patients with NA is easily overlooked, as the LFTs are sometimes normal, and the typical phenotype described above is not universal in patients with HEV-associated NA. We recommend that all patients with NA be tested for HEV at presentation. This will further improve our understanding of the prevalence, phenotypic spectrum, and disease mechanisms of HEV-NA cases.

AUTHOR CONTRIBUTIONS

H.R.D., J.J.J.v.E., and P.R. coconceived the study, established the collaborations, and cowrote the manuscript. R.G.M., C.J., M.F., C.G., G.M., J. Herrod, R.F.L., H.H.A., M.A., O.A.B.A.L.M., M.F., D.B., T.K., H.B.-P., S.A., M.T.G., J. Hartl, S.P., and B.N.M. identified/cared for patients and provided comments on the manuscript. E.P., V.A., R.S., P.C., R.P.B., M.P., and J.I. performed the virologic studies and commented on the drafts. N.X.L. performed the statistical analysis and commented on the drafts. D.M., R.G., J.-M.P., and N.K. oversaw and coordinated data collection and reviewed the drafts. B.C.J. cowrote the manuscript. N.v.A. and B.G.M.v.E. contributed cases to the Dutch study site and revised the manuscript for intellectual content.

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