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Neuralgic amyotrophy triggered by hepatitis E virus: a particular phenotype

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Abstract

Objective: The neuralgic amyotrophy may be of difficult diagnosis, due to phenotypic variability, with different initial presentations (upper plexus multiple mononeuropathy, lumbosacral involvement, distal reached, phrenic involvement). To date, there is little guidance on these patients' therapeutic management, especially those for which neuralgic amyotrophy is triggered by hepatitis E virus (HEV-NA). The study aims to identify specific features that characterize patients bearing the neuralgic amyotrophy triggered by HEV. **Methods:** We first describe a new case report of HEV-neuralgic amyotrophy, with delayed diaphragmatic reach. Then, the literature was searched for reports of HEV-NA (n=39), and neuralgic amyotrophy with phrenic paresis (n=42) from 1999 to June 2016. Relevant data were retrieved, analyzed and compared with the parameters of idiopathic neuralgic amyotrophy (n=199) of the largest cohort, described by Van Alfen and Van Engelen in 2006. **Results:** Compared to the published cohort, HEV-NA patients were more likely to be men (M/F 34/5 versus 136/ 63, p=0.017), with more frequent bilateral symptoms (86.8% cases versus 28.5%, p<0.0001) as well as phrenic paresis (18.0% versus 6.6%, p=0.028). The clinical improvement is poor, with 15.6% of cases with remission only. **Conclusions:** A particular phenotype characteristic of the HEV-induced neuralgic amyotrophy has arisen. Our findings call for action in validating the above mentioned features that illustrate the HEV-NA cases as an early diagnosis would prevent complications, especially the phrenic damage often associated with a worse functional outcome.

Manuscript

Introduction

The neuralgic amyotrophy syndrome (NA) is an acute multiple mononeuropathy predominantly affecting the brachial plexus described around 1880. An intensive neuropathic pain in the scapular area or upper arm, often exacerbated at night and when arm is at rest, is generally followed by multifocal paresis (stereotypically including the serratus or infrascapular muscles) and/or hypoesthesia, then an amyotrophy. However, several distinct subtypes can occur — as with phrenic nerves involvement — and generate the NA phenotypic variability [1].

In fact, there are 2 forms of NA: (i) the hereditary neuralgic amyotrophy (HNA) associated with a mutation in the SEPT9 gene, on chromosome 17q25, in 55% of families [2]; and (ii) the idiopathic form (INA), also known as brachial neuritis or Parsonage-Turner syndrome (the eponymous names of the authors of the first case series, 1948). A 1/1000/year incidence, previously underestimated, has recently been reported [3].

The exact etiopathogenesis is unknown, but post infectious immune reactions are frequent (HIV, Cytomegalovirus, Epstein-Barr virus, parvovirus B19, Campylobacter, Yersinia, Borrelia) [2]. Recurrences happen in 30-40% patients with INA [4,5] mostly athletic, therefore mechanical factors and an individual genetic susceptibility are assumed [1,6].

Hepatitis E virus (HEV) infection could trigger many NA. HEV has been found in 10% NA patients [7] and it is the leading cause of hepatitis worldwide (50%) [6]. It also accounts for an autochthonous emerging disease, spreading through industrialized countries (genotype 3, 4) [8]. Animals account for the primary reservoir, for instance 65% French pigs are HEV+ [9]. Although usually asymptomatic, genotype 3-HEV extrahepatic and neurological involvement has been reported more frequently since 2000 [8,10].

The study seeks to identify whether specific clinical features characterize patients bearing INA triggered by HEV, implying the arise of a specific phenotype.

Methods

The case of a man referred to the university hospital of Lille, France with INA induced by hepatitis E associated with a bilateral phrenic nerves involvement has been thoroughly described.

Additionally, a review of the literature was performed in June 2016, by searching the following combinations of keywords:

A] (((neuralgic amyotrophy) OR brachial neuritis) OR parsonage turner) AND ((hepatitis E) OR HEV).

B] (((neuralgic amyotrophy) OR brachial neuritis) OR parsonage turner) AND (phrenic OR diaphragmatic).

No date or language restriction was used for A] as opposed to B] where search was restricted to English articles on Pubmed from 1999 to 2016. After deletion of duplicates, we grouped all case-reports of INA induced by hepatitis E (A) and all cases reports of INA with phrenic paresis (B), including our patient.

The following features (i.e. gender ratio, mean age, prevalence of phrenic paresis, bilateralism and average transaminases in group A; prevalence of bilateral phrenic paresis in group B; and pain duration and clinical improvement (with the median of follow-up) in both groups) were analyzed with respect to those of the largest cohort of NA available, described by Van Alfen and Van Engelen in 2006 [4]. Quantitative variables are expressed as mean \pm standard deviation (SD). Qualitative variables are expressed as frequencies and percentages. Gender ratio and proportion of bilateral and asymmetric NA were compared using Chi-square test. Fisher Exact test was used to compare proportion of painless and proportion of phrenic paresis. The Student's *t*-test was used to compare mean age. In particular for the historic cohort, SD was estimated from the range (range/4) as such data was unavailable. Statistical testing was done at the two-tailed α level of 0.05 and data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC).

Results

Case report

A 42-year-old athletic (marathon, tennis) man rushed to emergency on October 1st, 2015 at night, stating a brutal, non-traumatic and very intense (numeric rating scale 10/10) para-spinal cervicothoracic, predominantly right back pain, associated with vagal symptoms (nausea, vomiting). His medical records revealed a 20-year-old malaria (*Plasmodium falciparum*) episode and a penicillin allergy (skin rash) without any relevant neurological family history.

Chest emergencies, including dissecting aorta were excluded. Neither pleural or parenchymal injury nor osteolytic or sclerotic foci were revealed. Intravenous morphine was administered to ease the pain. Soon after (<24h), the patient described transient paresthesiae in the right arm, hypoesthesiae of the right thenar eminence and inside of the left knee (territory of the saphenous nerve). Decreased deep tendon reflexes of the upper limbs and moderate high dysphagia were reported with neither amyotrophy nor pyramidal irritation. Brain MR-angiography and cerebrospinal fluid analysis excluded myelitis or subarachnoid hemorrhage. EMG did not reveal any signs of demyelination or neuropathy on any limb. However, the serratus anterior, infraspinatus, flexor pollicis longus and pronator quadratus (high-yield muscles for NA) had not been EMG-explored at that time.

Biological analysis depicted a sharp hepatic cytolysis and a moderate cholestasis, with no fulminant hepatitis. Lactate dehydrogenase (350 IU/L) and creatine kinase (260 IU/L) were also increased. Blood and PCR analyses excluded HBV, HCV, HIV, VZV, CMV, HSV, EBV, parvovirus B19, HHV6, HHV8, *Borrelia*, syphilis, ANCA, antinuclear antibodies, antibodies associated with autoimmune hepatitis as well as an inflammatory syndrome, thrombocytopenia (125,000/mm³), lymphopenia (500/mm³) with 10% mononucleosis-like cells. IgM were increased to 4.06g/L, along with a monoclonal IgM- λ spike on the blood protein electrophoresis.

Transferred to the internal medicine department, the patient narrated he had spent three weeks in Corsica in August. Further analyses were run to test for HAV, Hantavirus, Chikungunya, Leptospirosis, Enterovirus and HEV. HEV serology (IgM and IgG), confirmed by positive blood RT-PCR (32.100 replicas/mL) confirmed acute hepatitis E. Genotyping attested a subtype 3f. The infection was recognized via the Corsican sausage (Figatelli) consumption 5 to 8 weeks prior to the symptoms.

The intermittent spinal pain lasted for a week with a subsequent spontaneous, progressive improvement of the pain along with the liver parameters. The MRI revealed isolated T2 STIR hypersignal of the right infraspinatus, with no signs of muscular atrophy, suggesting myositis.

In November, the patient had no pain, no amyotrophy, no more paresthesia and biology revealed the normalization of lymphocytes, IgM, electrophoresis, the inversion IgM/IgG on HEV serology and the decrease of RT-PCR (1000 replicas/mm³).

In January, the patient referred orthopnea, paradoxical breathing and dyspnea on exertion with a gradual appearance since he had been dismissed in November. Respiratory function tests revealed forced vital capacity, 5.15L (i.e. 92% predicted), with 50% decrease in the supine position; total lung capacity, 7.42L (94% predicted); forced expiratory volume in 1 second, 4.3L (83% predicted). The global inspiratory muscle strength was low in voluntary moves, with a P_{Imax} (maximum inspiratory pressure) of 63 cmH₂O (predicted=105 cmH₂O). His sniff nasal pressure was underperforming. The phrenic EMG confirmed the left paralysis (no motor potential after stimulation) and the very severe right paresis.

A final diagnosis of HEV-induced INA with severe bilateral phrenic paresis was established. The patient was offered physiotherapy and respiratory rehabilitation, with no treatment for hepatitis as RT-PCR was negative at that time.

At the 12-month-follow up visit, there were no motor deficits, no amyotrophy, and full recovery of the tendon reflexes. Nonetheless, hypoesthesia persisted, and the phrenic paresis had clinically moderately

improved. Supine fall of forced vital capacity improved at 25% and maximal inspiratory pressure was normalized at 123 cmH₂O. The left phrenic paralysis decreased.

Review of the relevant literature

Thirty-eight cases (group A) relating HEV-induced INA and 41 cases (group B) reporting INA with phrenic paresis were found in the literature. Sources and characteristics are detailed in the table 1 [6,7,11-32] and appendix table e-1, respectively. The features of each group are described in table 2.

The patients with HEV-INA were 46 years old (46±9.8), with statistically more males (87.2%) than INA of all etiologies (68.3%) and the syndrome is more frequently bilateral and asymmetric (86.8% vs 27.7%). A phrenic paresis is more frequently reported: 18.0% (7/39), vs 6.6%. The clinical improvement is poor: remission only occurs in 15.6% cases over a 10 month follow-up. The cytolysis predominates on the ALT with a 2/1 ratio.

The patients affected by INA with phrenic paresis were 53 years old (52.9±13.0). The absence of initial pain (23.8%) emerges as a peculiar feature of this group.

Discussion

Our case report illustrates the phenotypic variability of NA and underlines the difficulty of a prompt diagnosis. The two essential criteria are: a typical pain (acute onset of very severe and analgesic-resistant pain in the shoulder area) and a multifocal sensory and/or motor neuropathy [1]. Other signs are optional. Amyotrophy depends on motor neuropathic impairment. Electrophysiological support findings are not fundamental because negative results are often due to sampling error [1]: it is essentially a clinical diagnosis. In our case, the NA initial presentation combines several subtypes: a pure sensory form (patient did not show motor weakness or amyotrophy of limbs); a lumbosacral involvement (8.2% of cases, and only <6.7% for sensory signs [4]) with anesthesia of the territory of the left saphenous nerve; a distal reached (thenar hypoesthesia); an involvement of the cranial nerves (<2.6% of cases [4]) with a brief high dysphagia. In addition, when the phrenic involvement occurs, it exacerbates the severity of the syndrome.

The analysis of the literature review has yielded to a particular phenotype for the HEV-induced INA that is described by: a prevalence of men, moderately older, a bilateral and very asymmetric form, and a frequent phrenic nerve involvement.

Our findings are in agreement with a previous suggestion reported by Van Alfen et al. derived from their large cohort: "...there were the grossly elevated liver enzymes for which no cause could be identified in 10, usually male, patients, most of whom seemed to have a clinical subtype of NA with extensive bilateral brachial

plexus and phrenic nerve involvement. This subtype may be triggered by a specific but unknown antecedent infection that also causes a transient hepatitis” [4].

At that time, HEV had not yet been identified (and the HEV-INA prevalence was unknown.) In the past decade, HEV has been reported to (i) trigger neurological disorders including Guillain-Barre syndrome, meningoencephalitis and INA and (ii) to be implicated in extra hepatic manifestations [10,28]. In fact, research on HEV has recently evidenced the HEV neurotropism by proving its capability of replicating, assembling and entering specific nervous system-derived cells [33]. Another hypothesis is that HEV may promote INA in predisposed people [6]. Recent guidelines recommend to systematically search HEV for all INA [10].

Overall, this literature review suggests that the phrenic paresis is an important symptom in the phenotype HEV-INA. This preponderance may be underestimated because some cases with phrenic paresis within the historic cohort could have been triggered by HEV. Ten patients were described with hepatitis [4] but HEV like etiology was unknown in 2006. In contrast, the increased prevalence of phrenic involvement in this subgroup must be moderated. Now Van Eijk et al. estimate 10% of phrenic reached in their current cohort (>1,200 patients), but they don't precise the proportion of HEV or HNA [1]. This impairment not uncommon in HNA family (14%) [4], could overestimate the prevalence of our group A (cases 30 and 33 suggest a possible HNA, but no mutation of the SEPT9 gene were found [6]). The neuralgic amyotrophy physiopathology associates biomechanical factors (on the plexus brachial) to an immune trigger [1,2]. The authors hypothesize that the strong neurotropism of HEV may induce a more diffuse form of neurologic disorders. The phrenic involvement is likely the most symptomatic, therefore the most often diagnosed and mentioned, but not the only one (like the transient high dysphagia of our patient).

Furthermore, NA is a disease of young adults (35-40 years on average) [4,34] although those with INA triggered by HEV tend to be on the older side of such young adulthood. On the other hand, hepatitis E more frequently affects older patients (median age 64 years for Woolson et al. [24]) however, those patients with neurological manifestations tend to be among the younger ones. This curious overlap seems to correspond to a population that interestingly matches most of the reported HEV-INA cases.

The general characteristics of HEV-INA phenotype appear independent of phrenic involvement. When all INA with phrenic involvement are considered, the hereby reviewed cases are older subjects, as previously reported in two small series [35,36] of 19 patients (mean age 59.5 and 61 years, respectively). As described in our case, a symptomatic phrenic involvement may appear much later than the hepatitis E. Moreover, pain was

not reported in many cases of group B. We can suggest that some asymptomatic hepatitis E has gone misdiagnosed.

A better understanding of this NA phenotype seems crucial to early diagnose HEV-INA. In fact, in our case the clinical picture has been confused with HEV-induced myositis, as it has previously been described [37].

Recovery of strength is rather slow (several years) and often incomplete as pain, disabilities, little residual paresis or intolerance to effort are still present in 3 patients out of 5 [2,5]. A worse prognosis is linked to phrenic involvement [1,35,38], which accounts for a severity factor affecting sport and work abilities and leading to a worse quality of life and sleep. It is therefore necessary to be aware of and search for phrenic involvement, especially in cases of hepatitis E.

There is no current treatment for NA. A combination of nonsteroidal anti-inflammatory drugs and opiate is the best symptomatic option to treat initial neuropathic pain [4]. It is uncertain whether a short corticotherapy at NA onset decrease the symptom duration [39] and it has been reported as non-effective on phrenic damage [38].

Acute hepatitis E doesn't usually require a specific treatment. In general, immunocompromised patients are to be treated because of the risk of chronic hepatitis. In particular, ribavirin is effective on acute or chronic HEV [40]. However, we are still debating whether patients with extra-hepatic manifestations should be treated for HEV. Strong arguments in favor of treating male patients are poor clinical improvement of INA and rather great proportion of phrenic nerve damage. As a continuous effort to (i) decrease neurological symptoms, (ii) improve quality of life and (iii) decrease overall sick leave, we feel that stronger therapeutic studies for INA triggered by HEV and guidelines are required. In fact, only empirical treatments are currently available in the literature.

The multiple limitations of a retrospective analysis of cases of independent publications must be considered (missing information and misclassification, publication bias and risk of non-representability and evaluation bias). We suggest that our observational findings be supported by prospective studies with multivariate analysis.

At this time, it seems that a particular phenotype for the INA induced by HEV has emerged: male with bilateral and asymmetric type, and a frequent phrenic nerve involvement. The excess risk of phrenic paresis supports the HEV earlier and curative treatment in addition to the symptomatic therapy.

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Table 1: Cases of neuralgic amyotrophy presumed triggered by hepatitis E virus

No.	First authors year	Age (y)	Sex	Associated medical condition	H E V g.	Transmission	Hepatic biology (at the onset) IU/L	Pain location	Pain duration	Associated neurologic features	P P	Follow-up and clinical improvement
1	Fong 2009 [11]	53	M	None		Travel in Equator (faecal-oral transmission)	ALT 2547, bilirubin 20 µmol/L, ALP 247	Shoulder, radiating to the chest	6wk	Amyotrophy, proximal paresis, sensory loss, abnormal reflexes in the upper limbs.	N	2y / remission
2	Rianthavorn 2010 [12]	49	M		3f	Travel in India	ALT 795, AST 155, bilirubin 32 µmol/L, ALP 284,	Shoulders	5wk	Amyotrophy, paresis, sensory loss, abnormal reflexes in the upper limbs	N	10mo / partial improvement
3	Kamar 2011 [13]	38	M	Diabetes type 1	3e	–	ALT 1160, bilirubin 70µmol/L	Upper arms	–	Amyotrophy, paresis, sensory loss, abnormal reflexes in the upper limbs. Left vocal cord paralysis, normal functions of the other cranial nerves	N	18mo / partial improvement
4	Carli 2012 [14]	30	M	None		–	ALT 1518, AST 517, γ-GT 59	L shoulder	–	Amyotrophy, paresis in the upper limbs. No sensory loss, normal reflexes. Serpiginous choroiditis in the L eye.	N	–, treatment by bolus of corticosteroids / partial improvement
5	Inghilleri 2012 [15]	28	M			Pork sausage and ingestion of raw meat	ALT 1007, AST 147, ALP 162	Shoulders and upper arms	15d	Amyotrophy, paresis, abnormal reflexes in the upper limbs.	N	–
6	Cheung 2012 [16]	56	M			Pork sausage	AST 234, bilirubin 30 µmol/L	Upper limb	10mo	Paresis in a upper limb	N	10mo / no improvement
7	Peri 2013 [17]	53	M		3	Unknown ^a	ALT 1768, AST 696, bilirubin 129µmol/L, g-GT 404	Shoulders	6 wk	Proximal paresis, sensory loss, abnormal reflexes in the upper limbs.	N	3mo / remission
8	Deroux 2013 [18]	38	M			–	ALT 1288, AST 988	–	–	–	N	6mo / remission
9	Valence 2014 [19]	62	M			Travel in Africa	Cytolysis and cholestasis 2xNV	Shoulders	–	Paresis in the upper limbs. Dysphonia	Y	–
10	Chirio 2014 [20]	32	M		3	–	ALT 10xNV	Shoulders	–	Amyotrophy, proximal paresis, sensory loss, in the upper limbs.	N	2mo / partial improvement
11	Chirio 2014 [20]	34	M		3	–	ALT 10xNV	Shoulders	–	Amyotrophy, proximal paresis, sensory loss, in the upper limbs.	N	2mo / partial improvement
12	Motte 2014 [21]	52	M	Prostatic adenoma	3f	Unknown ^a	ALT 590, AST 179, LDH 262, ALP 48, g-GT 212	Cervicodynia to the upper limbs	2mo	Amyotrophy, proximal paresis, in the upper limbs. Paresis and abnormal reflexes in the lower limbs. No sensory loss	Y	–
13	Moisset 2014 [22]	36	M	None	3f	–	ALT 1707, AST 554, bilirubin 54 µmol/L, ALP 311, g-GT 737	Shoulders	–	Proximal paresis in the upper limbs. Hypophonia, dysphagia	N	6mo, treatment by IVIg 5d and ribavirin 35d / partial improvement
14	Deroux 2014 [23]	38	M	None		–	ALT 1612, AST 772, (bilirubin, ALP, g-GT : normal)	L shoulder	–	Amyotrophy, proximal paresis in the upper limbs.	N	4mo / partial improvement
15	Van Eijk 2014 [7]	37	M			–	ALT 313, bilirubin 4 µmol/L, ALP 113	–	–	Patchy bilateral brachial plexus involvement	N	6mo / partial improvement
16	Van Eijk 2014 [7]	35	M			–	–	–	–	Patchy bilateral brachial plexus involvement	N	6mo / partial improvement
17	Van Eijk 2014 [7]	40	F		3	–	ALT 183, bilirubin 3 µmol/L, ALP 177	–	–	Patchy bilateral brachial plexus involvement	N	6mo / partial improvement
18	Van Eijk 2014 [7]	36	M			–	–	–	–	Patchy bilateral brachial plexus involvement	N	6mo / partial improvement
19	Van Eijk 2014 [7]	34	M			–	ALT 224	–	–	Patchy bilateral brachial plexus involvement	N	6mo / partial improvement
20	Woolson 2014 [24]	late 30th	M		3	–	ALT 1160, bilirubin 70 µmol/L	–	–	Bilateral NA	N	12mo / partial improvement
21	Woolson 2014 [24]	late 30th	M		3	–	ALT 319, bilirubin 4 µmol/L	–	–	Bilateral NA	N	12mo / partial improvement
22	Woolson 2014 [24]	late 30th	M			–	–	–	–	Bilateral NA	N	12mo / partial improvement
23	Theochari 2015 [25]	65	M			–	ALT 1368, ALP 167	–	–	Bilateral NA	N	10mo, treatment by corticosteroid / remission
24	Décad 2015 [26]	47	M	Hypertension, type 2 non-insulin requiring diabetes		–	ALT 106, AST 221, g-GT 239	Shoulders and upper arms	Several days	Amyotrophy, proximal paresis in the upper limbs. No sensory loss, normal reflexes.	N	12mo, treatment by corticosteroids / partial improvement

25	Frezel 2015 [27]	50	M						L shoulder		Amyotrophy, paresis, sensory anomalies in L upper limb.	N			
26	Blasco-Perrin 2015 [28]	51	M						Shoulder		Amyotrophy, paresis a upper limb.	N	100wk, treatment by ribavirin nad IVIg / remission		
27	Blasco-Perrin 2015 [28]	55	F						Shoulder		Amyotrophy, paresis in the upper limbs.	N	126wk / partial improvement		
28	Blasco-Perrin 2015 [28]	56	M						Shoulder		Amyotrophy, paresis, abnormal reflexes in the upper limbs.	N	42wk / partial improvement		
29	Blasco-Perrin 2015 [28]	56	M	3f					Shoulder		Amyotrophy, paresis, abnormal reflexes in the upper limbs.	N	16wk, treatment by ribavirin and IVIg / partial improvement		
30	Dartevell 2015 [6]	54	M	Familial history : NA in his son and suspected in his daughter	3f	Unknown ^a			ALT 1036, AST 259, ALP 180, g-GT 334		Cervicodynia to the upper limbs		Amyotrophy, proximal paresis, sensory anomalies, abnormal reflexes in the upper limbs.	Y	10mo, treatment by corticosteroids / partial improvement, persistence of orthopnea
31	Dartevell 2015 [6]	54	M	Chronic alcoholic (10g/d)	3f	Unknown ^a			ALT 812, AST 332, bilirubin 8 µmol/L, ALP 89, g-GT 66		Upper L limb, scapular muscles and lower limbs		Amyotrophy, paresis, sensory loss, in the L upper limb and lower limbs. Normal reflexes	N	1y / partial improvement
32	Dartevell 2015 [6]	40	F	Hashimoto's thyroiditis	3f	Unknown ^a			ALT 1305, AST 438, ALP 208, g-GT 170,		Shoulders irradiating in the upper limbs		Proximal paresis, sensory loss, in the upper limbs.	N	1y, (treated by IVIg 3d) / partial improvement
33	Dartevell 2015 [6]	51	F	Crohn's disease, NA 6y before (with phrenic paralysis), daughter had developed NA		Unknown ^a			normal (1wk after onset symptoms)		Cervicodynia, R shoulder		Paresis in R upper limb.	Y	10mo, treatment by IVIg / good improvement of the R shoulder, but persisted dyspnea
34	Dartevell 2015 [6]	59	M	Type-2 diabetes		Unknown ^a			ALT 88, AST 32, g-GT 365		Cervicodynia, shoulders		Amyotrophy, distal paresis in the upper limbs. Normal reflexes. No sensory loss	Y	
35	Avila 2015 [29]	52	M						Increased transaminases		Shoulders		Paresis, abnormal reflexes, in the upper limbs.	Y	5mo, treatment by corticosteroids / partial improvement, with persisted orthopnea
36	Martinez Rodriguez 2015 [30]	41	M	not significant		Unknown ^a			ALT 1270, AST 481, bilirubin 68 µmol/L, ALP 241, g-GT 1189		R shoulder		Paresis of R upper limb. No sensory loss, normal reflexes.	N	
37	Silva 2016 [31]	51	M		3				ALT 2579, AST 1234, normal bilirubin, ALP 167, g-GT 308		Proximal L leg, L hemithorax and L arm	2wk	Paresis, distal sensory loss, in the upper limbs.	N	12 mo, treatment by IVIg / partial improvement
38	Bisciglia 2016 [32]	50	F		3	Unknown ^a			ALT 2086, AST 812, ALP 152, g-GT 98		L upper limb		Distal paresis, distal sensory loss, in L upper limb. Normal reflexes	N	9mo, treatment by corticosteroids 3mo (3mo after onset of symptoms) / partial improvement
39	Our case	42	M	Malaria 20y ago	3f	Pork sausage			ALT 1658, AST 642, bilirubin 34 µmol/l, ALP 181, g-GT 285		Cervico-thoracic para spinal	10d	Cf. case report	Y	9mo / partial improvement, dyspnea persisted

ALT=alanine aminotransferase; ; ALP=alkaline phosphatase; AST=aspartate aminotransferase; CSF=cerebrospinal fluid; g-GT=gamma glutamyl transferase; HEV g.=hepatitis E virus genotype; L=left; LDH=lactate dehydrogenase; Nv=normal value; PP=phrenic paresis; R=right; Y/N=yes/no;

^a Unknown=No source for HEV transmission, including travel, cases in the family, eating undercooked pork or drinking unsafe water

Table 2: Parameters of neuralgic amyotrophy induced by hepatitis E (A) and neuralgic amyotrophy with phrenic paresis (B) in the review of the literature, compared with the largest cohort of NA, described by Van Alfen and Van Engelen, 2006

	Group A (INA+HEV)	Cohort	p-value
Age , mean±SD [n]	46.0 ±9.8 [36]	41.3 [194]	0.12
Gender M/F	34/5	136/63	0.017
Phrenic paresis , % (Y/N)	18.0% (7/32)	6.6% (13/186)	0.028
Bilateral and asymmetric NA , % (Y/N)	86.8% (33/5)	27.7% (67/175) ^a	<0.0001
Pain characteristics			
Pain less, % (Y/N)	0% (0/29)	3.7% (9/237) ^a	
Duration of pain if it was precised, [n] or %			
<24h	[0]	4.9%	
1-7days	[0]	22.7%	
7-60days	[6]	62.4%	
>60days	[2]	10%	
Clinical improvement			
% [n] (median of the follow-up)			
No improvement	3.1% [1] (10mo)		
Partial improvement	81.3% [26] (9mo)		
Remission	15.6% [5] (10mo)		
Average transaminases , IU/L [n]			
ALT	1093 [32]		
AST	510 [23]		

	Group B (INA+phrenic paresis)	Cohort	p-value
Age , mean±SD [n]	52.9 ±13.0 [42]	41.3 [199]	<0.0001
Gender M/F	33/9	136/63	0.19
Phrenic paresis lateralisation , % [n]			
Bilateral	51.3% (20)		
Unilateral	48.7% (19)		
Pain characteristics			
Pain less, % (Y/N)	23.8% (5/16)	3.7% (9/237) ^a	0.002
Duration if pain occurs, % [n]			
<24h	6.25% [1]	4.9%	
1-7days	18.75% [3]	22.7%	
7-60days	56.25% [9]	62.4%	
>60days	18.75% [3]	10%	
Clinical improvement			
% [n] (median of the follow-up)			
No improvement	33.3% [12] (12mo)		
Partial improvement	47.2% [17] (12mo)		
Remission	19.4% [7] (16mo)		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ; HEV=hepatitis E virus; INA=idiopathic neuralgic amyotrophy; mo=month; Y/N=yes/no; ^a on 246 cases including hereditary NA