Hepatitis E (HEV) is an under-diagnosed infection in developed countries, with significant morbidity and mortality potential. Like other viral hepatitides, extra-hepatic manifestations can occur; in particular, neurological disorders have been described. Here we report two cases of new neurological involvement in the shape of Parsonage Turner syndrome and encephalitis associated with cerebellitis, and conduct a literature review.

2. Cases description

2.1. First case

A 41-year-old man was admitted in August 2011 for walking difficulties, neuropathic pain of all four limbs, cerebellar ataxia, upper limb hypermetria, dysarthria, headache, and transient fever lasting 72 h. Reflexes were all present, without any pyramidal signs. No abnormalities were found on the medullar and cerebral magnetic resonance imaging. Electroencephalogram (EEG) and nerve conduction study was normal. The patient had no notable medical history.

At admission, alanine aminotransferase level was 479 IU/L (reference values 8–34 IU/L), aspartate aminotransferase level was 100 IU/L (reference 9–42), γ-glutamyl transferase level was 236 IU/L (reference 9–38 IU/L), alkaline phosphatase level was 112 IU/L (reference 42–98 IU/L), and bilirubin was 13 μmol/L (reference 2–17 μmol/L). Serum amylase level was 30 IU/L (reference 25–115 IU/L) and lipase was 133 IU/L (reference 73–393 IU/L). Cerebrospinal fluid (CSF) was clear; protein and glucose levels were 0.56 g/L (reference 0.15–0.45) and 3.6 mmol/L (reference 3.0–4.5 mmol/L) respectively; leukocyte count was 12 cells/mm³, including 80% of mononuclear cells. No antibiotics were given. CSF culture remained sterile at day 5. Several infectious diseases responsible for neurologic symptoms (HIV, syphilis, cytomegalovirus, Epstein–Barr virus, mycoplasma, HSV, VZV, measles, parvovirus B19, Lyme disease, HHV6, HHV8, toxoplasmosis, leishmaniasis, arboviruses) and acute hepatitides (hepatitis A, B, C, delta) were excluded by nucleic acid and serologic assays performed on serum and CSF.

In contrast, an HEV infection was diagnosed through the detection of anti-HEV immunoglobulin (Ig) M (index 12.00; threshold value 1 [ELISA test DIAPRO]) and HEV RNA in serum and CSF. Genotype 3f was identified through phylogenetic analysis, which is common in...
autochthonous cases in France. The contamination mode was the consumption of Corsican meat (figatelli).

Liver parameters returned to normal within 1 week, and the patient recovered fully 12 weeks after the neurological disorders’ onset. HEV RNA was cleared in serum 2 weeks after the first blood sample.

2.2. Second case

A 38 year-old man was hospitalized in December 2012 for Parsonage Turner syndrome with cytolytic hepatitis. He presented with a sudden onset of violent pains in the left shoulder girdle, associated with a painful paresis without esthetic impairment. Physical examination noted a winged scapula, amyotrophy in the supraspinatus and infraspinatus fossae (Fig. 1) and an abduction as well as external rotation impairment.

The patient had no notable medical history or treatment. At admission, alanine aminotransferase level was 1612 IU/L (normal levels 8–34 IU/L), aspartate aminotransferase level was 772 IU/L (reference 9–38 IU/L), Alkaline phosphatase, $\gamma$-glutamyl transferase, lipase level and bilirubin were in the normal range. Electromyogram found right long thoracic and suprascapular nerve damage with acute denervation criteria.

Infectious diseases responsible for neurologic symptoms were excluded by serologic assays performed on serum (borreliosis, toxoplasmosis, HIV, B and C hepatitis, arboviruses, EBV, CMV) and on CSF (HSV, VZV, borrelia). Auto immunity was ruled out (negative AAN, ANCA, and antigangliosides antibodies). CSF was clear; protein and glucose levels were at 0.68 g/L and 3.30 mmol/L respectively. It was a transudate, with moderate blood brain barrier damage (albumin quotient: $10.58 \times 10^{-3}$); IgG index was normal (0.49, normal levels inferior to 0.7) and isoelectrofocusing showed normal repartition of immunoglobulin. Leukocyte count was under 5 cells/mm$^3$.

However, HEV infection was diagnosed by detection of anti-HEV immunoglobulin M (index 3.00, ELISA test Wantai Bio-Pharm®); unfortunately no nucleic acid assay could be performed during hospitalization, HEV RT-PCR performed one month later was negative in serum and CSF.

Neurologic symptoms disappeared in four months, but a painful amyotrophy persisted. Liver parameters returned within normal range in 4 weeks, and HEV IgM were negative six months later with an increasing IgG count (index: 60.273).

3. Other similar and contrasting cases in the literature

These 2 cases establish some strong arguments in favor of an association between acute hepatitis E and neurological disorders. Temporal association, atypical neurological features, exclusion of other potential etiologies led to consider HEV as a possible cause of encephalitis or other neurological disorders.

Several cases have been described since the first patient was reported in 2000 [2]. A recent multicentric case series from Southwest England and Toulouse [3] found a high prevalence (5.5% – 7 out of 126 patients) of neurological complications associated with HEV infections. Only 19 cases were documented enough to report this association. Most (8 patients) of the cases concerned acute HEV infection associated with Guillain–Barre syndrome [2–9], 3 others were associated with brachial neuritis [3,10,11], 3 with polyradiculopathy [3,12], 3 with peripheral neuropathy [3,12,13], one with transverse myelitis [14], while acute encephalitis [3] or ataxia [3] was also reported.

HEV RNA in CSF was only detected in five of these patients [3,12] like our first case; acute encephalitis and cerebellitis associated with hepatitis E was only described once before. These two patients showed complete recovery in a few months, without any sequel.

4. Discussion and references

Several mechanisms for neurological symptoms associated with HEV have been suggested. For neuropathies such as Guillain–Barre syndrome, anti-ganglioside antibodies (GM1, GM2) may be triggered by HEV infection and play a pathogenic role [5–7,15]. In one case, Kamar et al. [3] showed different viral sequences within CSF and serum in the same patient; these could be caused by the emergence of neurotropic quasispecies which could directly affect the nervous system. However, this mechanism seems less probable in cases of acute infection resolving within days. Pathogenesis for peripheral neuropathy and other neurological disorders caused by HEV may involve multiple mechanisms, such as predisposing host immune factors, to account for the variety in manifestations, but the small number of cases and distribution in developing countries makes further investigations difficult. Moreover, both acute HE or chronic HE acquired in immunocompromised patient could lead to neurological disorders, which are often discontinued with HEV treatment by ribavirin [16]. Peg-IFN alpha 2a seems to be inefficient in chronic forms as reported in a liver transplant recipient [13].

Impact of HEV genotype seems to be important. All of the reported cases were genotype 3, which is found in developed countries. Autochthonous HE (genotype 3) has a distinctive clinical feature that separates it from epidemic forms due to genotypes 1 and 2 [16]. Genotype 3 HE infections are usually subclinical and mild, have highest rates among older adults and seem to be associated with neurological manifestations. No physiopathological explanation for this association could be found.

Previous and current observations suggest that HEV diagnostic testing should be performed in patients who have concurrent liver cytolysis and neurologic symptoms, after ruling out the most common etiologies.

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Competing interests

None declared.
Ethical approval

Not required.

References