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CASE REPORT

REVISED Case Report: Severe bilateral amyotrophic neuralgia associated with major dysphagia secondary to acute hepatitis E [version 2; peer review: 4 approved]

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Abstract

Introduction: Several acute neurological syndromes can be triggered by immune events. Hepatitis E virus (HEV), an emerging infectious disease, can be one of these triggers.

Case report: We report the case of a 36-year-old man that presented nausea and a dull abdominal pain for a week and then felt an acute neuralgic pain involving both shoulders that lasted for 8 to 10 hours. Immediately after, the patient presented a severe bilateral muscular weakness of the proximal part of both upper limbs, corresponding to an amyotrophic neuralgia. Two days after the shoulder pain, the patient presented a dysphagia necessitating tube feeding. A blood sample confirmed hepatitis caused by hepatitis E virus (HEV; genotype 3F). Oral feeding resumed progressively after five months. The patient was fully independent for the activities of daily living but was still unable to work after six months.

Conclusion: Amyotrophic neuralgia and hepatitis E are both under-diagnosed. It is noteworthy that HEV can trigger amyotrophic neuralgia. Antiviral drugs, oral steroids and intravenous immunoglobulins can be proposed, but the optimal treatment has not yet been determined.

Keywords

Amyotrophic neuralgia , Hepatitis E , dysphagia

Open Peer Review

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4. **Michelle Cheung**, King's College Hospital, London, UK

Any reports and responses or comments on the

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article can be found at the end of the article.

Corresponding author: Xavier Moisset (xavier.moisset@gmail.com)

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REVISED Amendments from Version 1

We thank the reviewers for their comments. In addition to our detailed responses to reviewers at the bottom, the following is a summary of the changes made in response to reviewer's comments:

There is no validated treatment for neuralgic amyotrophy, with only one retrospective series reporting a benefit of corticosteroids. This point has been corrected in the text.

A sentence and a reference (Abbas and Afzal. 2013) have been added to justify the use of ribavirin.

Anti-HEV antibody testing of CSF was not performed and this is now clearly specified.

Concerning biological exams, it is now specified that the prothrombin time didn't increase, the immunological screening is detailed and PCR was not initially realized in stools.

The duration of the ribavirin therapy is now specified (35 days).

We now state in the discussion that this case concerned genotype 3f virus that is predominant in France (Luciano *et al.* 2012).

See referee responses**Introduction**

Neurological syndromes such as Guillain-Barré Syndrome, transverse myelitis, encephalitis or amyotrophic neuralgia can be triggered by immune events. Hepatitis E virus (HEV), discovered in the 1980s, can be one of these triggers. Epidemics of hepatitis E occur periodically throughout the developing world, but autochthonous HEV infections have also been reported in most developed countries during the last decade. Several HEV-associated neurological syndromes have been described but are probably under-diagnosed¹.

Case report

We report the case of a 36-year-old French man, Caucasian truck driver, without any significant medical history. The clinical symptoms started in May 2012 with nausea and a dull abdominal pain. No sign of chronic liver disease or of portal hypertension was noted. High liver enzymes were diagnosed after assay for: alanine aminotransferase (ALT) 1707 $\mu\text{mol/L}$ (normal range: $N < 78$), aspartate aminotransferase (AST) 554 $\mu\text{mol/L}$ ($N < 37$), gamma-glutamyltranspeptidase (GGT) 737 U/L ($N < 95$) and alkaline phosphatase at 311 U/L ($N < 136$). Total bilirubin level was at 54 $\mu\text{mol/L}$ ($N < 17$). There was no hepatitis A, B or C, no HIV and no sign of autoimmune disease. The immunological screening included antinuclear antibodies, anti-smooth muscles antibodies, anti-mitochondria antibodies, anti LKM antibodies, anti-hepatic cytosol antibodies, complement (C3, C4, CH50), rheumatoid factor, antineutrophil cytoplasmic antibody (ANCA), antiganglioside antibodies (GM1, GM2, GD1a, GD1b, GQ1b) and onconeural antibodies (Hu, Ri, Yo, PNMA2, CV2, Amphiphysine). Liver ultrasound was normal. The prothrombin time stayed within the normal range throughout the monitoring period.

Around one week after the first digestive symptoms, the patient felt an acute neuralgic pain involving both shoulders that lasted for 8 to

10 hours. Immediately after, the patient presented a severe bilateral muscular weakness of the proximal part of both upper limbs. Two days after the shoulder pain, the patient presented with hypophonia and dysphagia. The MRI did not show any brain abnormality. The spinal cord and the brachial plexus were unharmed. The cerebrospinal fluid (CSF) was normal (2 white blood cells/ mm^3 ; CSF Protein = 0.37 g/L) and there was no intrathecal antibody synthesis, although it was not tested for the synthesis of specific anti-HEV antibodies. Electromyography (EMG) and nerve conduction studies (NCS) showed normal amplitudes and conduction velocity but bilateral denervation in the supraspinatus, infraspinatus, subscapularis and deltoid muscles. An acute hepatitis E infection was suspected due to the presence of IgM and confirmed by PCR (genotype 3f). The initial serum HEV RNA count was 5.2 log-copies/ml. The PCR was negative in the CSF and was not initially performed in stools.

A treatment with intravenous immunoglobulins (Tegeline®, LFB laboratory, France; 0.4 g/kg/day) was given for 5 days. Ribavirin (600 mg/day) was also introduced. Nine days after ribavirin initiation, the PCR showed 2.02 log-copies/ml and was negative after 18 days in both blood and stools. Ribavirin treatment was discontinued after 35 days. After three weeks, the patient still required nasogastric tube-feeding and a gastric feeding tube was placed endoscopically. There was no contraction of the shoulder girdle muscles. Oral feeding resumed progressively after five months. After six months follow-up and intensive rehabilitation, there was a 3/5 muscular strength in the affected muscles, corresponding to a movement possible against gravity, but not against resistance by the examiner. The patient was fully independent for the activities of daily living but still unable to work.

Discussion

This is the first report of both severe bilateral amyotrophic neuralgia and dysphagia caused by an acute hepatitis E infection. Amyotrophic neuralgia (AN) is a peripheral neuropathy consisting of multiple symptoms including abrupt onset of shoulder pain, usually unilaterally, followed by motor weakness, with an annual incidence above 2 per 100,000 inhabitants². Concomitant involvement of other peripheral nervous system structures (such as the lumbosacral plexus or phrenic nerve) is described. AN can be triggered by immune events but also by trauma or surgery. Many patients are left with residual disabilities that affect their ability to work and their everyday life. It is noteworthy that a particularly severely affected subgroup presents sign of liver dysfunction, as seen in HEV infections². The only proposed treatment (with a low level of evidence) is corticosteroids but this may have been dangerous in this case of acute hepatitis E³. Some authors have also reported a positive effect of intravenous immunoglobulins and this was the option we selected⁴⁻⁶.

HEV-associated neurological syndromes include both central and peripheral nervous system involvement⁷. Such cases have been described in the Asian sub-continent (probably due to HEV1) but also in Western Europe with acute and chronic HEV3 infection. The present case concerned genotype 3f virus that is predominant

in France⁸. For patients with chronic HEV infections, neurological symptoms completely resolved or significantly improved when viral clearance was achieved¹. Moreover, several authors suggest treating severe acute HEV infections in order to preclude the development of acute liver failure⁹. This is the reason why we tried antiviral treatment. Unfortunately, although viral clearance was achieved quickly, this did not lead to fast clinical improvements.

An alternative diagnosis of pharyngeal-cervical-brachial variant of Guillain-Barré syndrome could have been made. This pathology is characterized by oropharyngeal, neck, and upper limb muscle involvement. However, in the present case, this diagnosis was excluded (no neck involvement, atypical EMG, no albuminocytologic dissociation of the cerebrospinal fluid and negative GQ1b antibody).

Conclusion

Post-infectious neurological diseases following HEV infection must be recognized to avoid unnecessary and potentially invasive procedures such as liver biopsy. Further studies are needed in order to determine the optimal treatment. In the meantime, antiviral drugs, steroids and IV-immunoglobulins are all possibilities.

Consent

Written informed consent for publication of clinical details was obtained from the patient.

Author contributions

XM: wrote the manuscript. NV: revised the first draft. EB, RC and CL: managed the patient in the rheumatology and neurology departments. AF: suggested HEV diagnosis. FT: did the EMG. AAH: managed the patient in the intensive care unit. FT, CG and PC: decided on the treatment plan. All authors were involved in the revision of the manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

Grant information

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Michelle Cheung

King's College Hospital, London, UK

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 06 March 2014

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Bruce Brew

Department of Neurology, St Vincent's Hospital, Sydney, NSW, Australia

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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Thierry Coton

Service de Pathologie Digestive, Hôpital d'instruction des Armées Laveran, Marseille, France

This is a very interesting article fitted for a 'letter to the editors' concerning emerging complications of HEV infection previously unknown to neurologists and gastroenterologists.

The title is appropriate for the content of the article and the abstract is a suitable summary of the text. The Bibliography is good quality, conclusions are clear and useful, all data are correct and missing ones are justified by the authors in the discussion.

This version can be accepted without corrections.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 23 December 2013

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Michelle Cheung

King's College Hospital, London, UK

This is a report of an emerging viral infection with well-documented but still uncommon neurological symptoms, and adds to the knowledge of the natural history and potential treatment of this clinical syndrome. It is clearly written and the case is described well.

I have the following minor comments:

1. The referenced Cochrane review found no evidence from randomised trials to support any form of treatment for neuralgic amyotrophy, with only one retrospective series reporting a benefit. Therefore it seems an over-statement to say that corticosteroids are a validated treatment for the condition.
2. Are there any cases of prednisolone use specifically for HEV-induced neuralgic amyotrophy?

What is the evidence of using ribavirin to treat acute (rather than chronic) HEV, which is a self-limiting infection?

3. The authors state that '*a severely affected subgroup present with signs of liver dysfunction, as seen in HEV*' - do you mean that cases associated with HEV infection (and therefore presenting with liver dysfunction) have a more severe clinical course compared to neuralgic amyotrophy associated with other causes?
4. Please justify the conclusion that recognition of HEV infection avoids invasive procedures?

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response () 31 Dec 2013

Xavier Moisset, CHU Gabriel Montpied, Clermont-Ferrand, France

We want to thank Dr Cheung for the comments she made that have helped us to improve the quality of our text.

1. Dr Cheung is right; the Cochrane review identified one open label retrospective series suggesting that prednisone can shorten the duration of the initial pain and leads to earlier recovery in some patients. Thus, the expression "validated treatment" has been replaced by "*proposed treatment (with a low level of evidence)*".
2. To our knowledge, there is no description of prednisone use in the specific case of HEV-induced neuralgic amyotrophy. Concerning the use of ribavirin to treat acute HEV, there is a low level of evidence but several authors suggest treating severe acute form in order to preclude the development of acute liver failure (Abbas Z and Afzal R. 2013 [Epub ahead of print] [Hepatitis E: when to treat and how to treat](#)). A sentence and this reference are now included in the discussion section.
3. We cannot know if neuralgic amyotrophy secondary to HEV infections are more severe compared with neuralgic amyotrophy associated with other causes. But among the patients with amyotrophic neuralgia, it has been described that a subgroup of patients had a particularly severe clinical course and that these patients had liver dysfunction. Thus, we hypothesized that some of these patients were possibly affected by HEV.
4. Unexplained severe hepatic cytolysis can lead to liver biopsy. HEV infection recognition can avoid this invasive procedure.

Competing Interests: No competing interests were disclosed.

Reviewer Report 20 December 2013

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José Manuel Echevarría

Department of Virology, National Centre of Microbiology, Carlos III Health Institute Majadahonda, Madrid, Spain

The manuscript describes the association of a convincingly diagnosed case of acute hepatitis E due to HEV genotype 3 infection with the development of severe amyotrophic neuralgia and major dysphagia in the patient. Reports of neurological complications among otherwise healthy patients after acute HEV-3 infection are scarce (I found just six cases from three reports since 2009, five of them reported in 2011), and the manuscript adds significant knowledge to the background.

Pathogenic mechanisms underlying neurological complications of hepatitis E are still unclear. Such diseases after viral infection may involve the invasion of the nervous system or may be of a pure, post-infectious, immune-mediated nature. Reports involving immunocompromised patients ([Kamar et al., 2011](#); four patients) found HEV genome in CSF from all of them and detected anti-HEV IgM in one, which confirmed CNS invasion at the time of the onset of the neurological symptoms.

Among the six healthy patients mentioned above ([Loly et al., 2009](#); [Kamar et al., 2011](#); [Despierre et al., 2011](#)), CSF testing for HEV markers was performed in three cases. One tested positive for both HEV RNA and anti-HEV IgM, and one tested negative for both markers ([Despierre et al., 2011](#)). CSF from the remaining patient was tested for viral RNA only and was found negative. It seems likely therefore, that both mechanisms may be involved, in absence of immune impairment.

The patient mentioned in the present report tested negative for HEV RNA in CSF, but I understand from the text that anti-HEV testing of CSF was not performed (if the sentence "*there was no intrathecal antibody synthesis*" refers to immunoglobulins and not to HEV-specific antibody, which should be stated more clearly). It would have provided useful information if the patient's CSF had been tested for anti-HEV IgG and IgM. The lack of a viral genome at the time of sampling does not exclude CNS invasion, and demonstration of intrathecal synthesis of a specific antibody provides the diagnosis once viral particles are no longer present. As far as I know, nobody has yet communicated results from the evaluation of the intrathecal synthesis of a specific antibody to HEV in these cases (only the presence of anti-HEV IgM has been documented), so I would suggest performing such an evaluation if anti-HEV was detected. From my former experience with the diagnosis of neurological infections caused by varicella-zoster virus, testing for specific IgG antibody optimizes the yield, and the most useful criteria of evaluation is the antibody to albumin index, though several others can be used (see [Echevarría et al. 1997](#)).

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response () 31 Dec 2013

Xavier Moisset, CHU Gabriel Montpied, Clermont-Ferrand, France

Dr Echevarría is right; anti-HEV antibody testing of CSF was not performed and this is now clearly specified in our version 2. Indeed, it would be of interest in future cases to test CSF for both RNA and intrathecal synthesis of specific anti-HEV antibodies.

Competing Interests: No competing interests were disclosed.

Reviewer Report 20 December 2013

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Thierry Coton

Service de Pathologie Digestive, Hôpital d'instruction des Armées Laveran, Marseille, France

This is a very interesting article about an emerging complication of acute hepatitis E.

The following information is missing however:

1. the gender of the patient.
2. if prothrombin time increased during hepatitis.
3. which auto antibodies were screened for.
4. if PCR was realised in stools.
5. the duration of the ribavirine therapy.

Additionally in the discussion, the authors must highlight that this case concerned a genotype 3f virus which is predominant in France ([Luciano et al. 2012](#)).

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response () 31 Dec 2013

Xavier Moisset, CHU Gabriel Montpied, Clermont-Ferrand, France

We want to thank Dr Coton for the comments and suggestions he made that have helped

us to improve the quality of our case report.

1. The gender of the patient (male) was specified in the abstract but not in the core text. It is now corrected.
2. The prothrombin time stayed stable within the normal range throughout the monitoring period.
3. The immunological screening included: antinuclear antibodies, anti-smooth muscles antibodies, anti-mitochondria antibodies, anti LKM antibodies, anti-hepatic cytosol antibodies, complement (C3, C4, CH50), rheumatoid factor, antineutrophil cytoplasmic antibody (ANCA), anti ganglioside antibodies and onconeural antibodies (Hu, Ri, Yo, PNMA2, CV2, Amphiphysine).
4. PCR was not initially realized in stools. The only PCR in stools was realized after 3 weeks of Ribavirin treatment and was negative.
5. The ribavirin therapy lasted for 35 days. The treatment was stopped on the basis of negative PCR results in both blood and stools.
6. We now specify in the discussion that this case concerned a genotype 3f virus which is predominant in France.

Competing Interests: No competing interests were disclosed.

Reviewer Report 04 December 2013

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Bruce Brew

Department of Neurology, St Vincent's Hospital, Sydney, NSW, Australia

This is an important case report highlighting HEV as a cause for brachial neuritis. Recognition of this association is clinically important as treatment with corticosteroids should be avoided.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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