Heliyon 6 (2020) e04247

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Case report

Third time's a charm: diagnosis of herpes simplex encephalitis after two negative polymerase chain reaction results

Mahbobeh Niksefat [a], Daniel Guillen [a], Pouria Moshayedi [b,*], Charles R. Rinaldo [c], Ajitesh Ojha [b]

[a] UPMC Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[b] Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[c] Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

ARTICLE INFO

Keywords:
Neuroscience
Nervous system
Viral disease
Neurology
Diagnostics
Neurovirology
MRI
Infectious disease
EEG

ABSTRACT

Introduction: Polymerase chain reaction (PCR) testing of cerebrospinal fluid (CSF) is a sensitive and specific method in diagnosing herpes simplex virus (HSV) encephalitis. However there are increasing reports of false negative HSV PCR.

Case description: We present a patient in the 9th decade of life with abnormal behavior and focal seizures with MRI showing a right temporal T2 hyperintense non-enhancing lesion with electrographic evidence of right lateralized periodic discharges. CSF analysis and PCR for HSV-1 and 2 yielded negative results twice, and therefore acyclovir was discontinued. Patient initially improved following correction of hyponatremia. Patient however deteriorated and imaging revealed a new right parietal lesion. Third CSF sample showed lymphocytic pleocytosis with positive HSV-1 PCR. Patient improved following antiviral treatment.

Discussion: Acyclovir treatment should continue in high clinical suspicion scenarios despite negative HSV PCR. We further discuss causes of PCR false negatives and challenges it poses for patient care.

1. Introduction

Herpes simplex virus (HSV) is the most common cause of infectious encephalitis that if untreated has a 70% mortality rate [1]. Clinical presentation including altered mental status, headache, seizure and behavioral changes is nonspecific and therefore laboratory analysis of CSF is the primary means of diagnosis. The initial CSF cell count is normal in 22% of patients with acute HSV encephalitis [2]. However, the HSV polymerase chain reaction (PCR) is known to be a very sensitive (98%) and specific (94%) test [3] and therefore it has become "gold standard" in diagnosis of HSV encephalitis.

We present an intriguing case of HSV encephalitis who presented with altered mental status and two negative HSV PCR results of CSF, but had PCR positive for HSV the third time. We will then discuss the challenges PCR-negative HSV encephalitis poses to patient care.

2. Clinical description

In order to obviate the need for an informed consent, the patient presented in this case has been de-identified by removing gender and exact age. A patient in the 9th decade of life with past medical history of hypertension, hyperlipidemia and right corneal transplant secondary to Fuchs' corneal dystrophy presented with new onset bizarre behavior followed by left gaze deviation, left head turn, and left beating nystagmus with extension of left arm concerning for left focal seizure. Patient's vital signs, including temperature, were unremarkable. Patient's seizure aborted following intravenous (IV) lorazepam but patient remained confused with a mild left side weakness. Initial labs were notable for serum sodium of 121 mMol/lit. Brain MRI showed foci of non-enhancing T2 signal hyperintensity in the inferior right temporal lobe (arrow in Figure 1A) and the left cerebellar peduncle (arrow in Figure 1B) in addition to extensive small vessel disease in periventricular white matter and basis pontis. Electroencephalogram revealed right side temporal lateral periodic discharges, therefore patient was started on empiric treatment of IV acyclovir and levetiracetam continued. CSF analysis was notable for 0 WBC, 3 RBCs/mm^3, protein 55 mg/dl and glucose 60 mg/dl (serum glucose 101 mg/dl). CSF examination for HSV-1 and HSV-2 was performed by real-time polymerase chain reaction (RT-PCR) using primers specific for HSV-1 and HSV-2 genomes and Taqman probes. PCR did not detect any segment of HSV-1 or HSV-2 DNA. Due to high clinical suspicion of HSV encephalitis CSF analysis was repeated three days after admission and revealed 3

* Corresponding author.
E-mail address: pouria@cantab.net (P. Moshayedi).

https://doi.org/10.1016/j.heliyon.2020.e04247
Received 13 January 2020; Received in revised form 13 June 2020; Accepted 15 June 2020

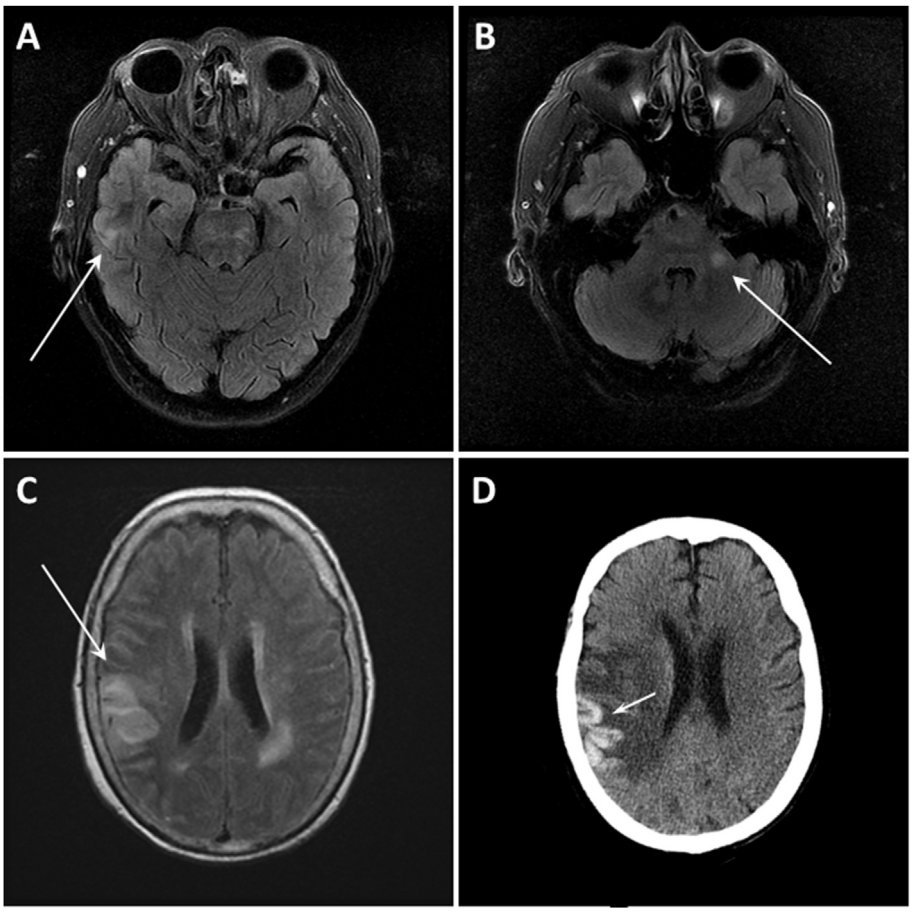

Figure 1. Brain imaging in a case of HSV encephalitis. (A) and (B) demonstrate T2 weighted brain MRI 1 day after presentation with arrows showing signal abnormalities in right temporal (A) and left middle cerebellar peduncle (B) regions. (C) shows T2 weighted MRI signal abnormality in the right parietal region (arrow) 11 days after presentation. (D) CT head shows laminar necrosis (arrow) in the right parietal lesion 37 days after presentation.

WBCs/mm^3, 18 RBCs/mm^3, protein 69 mg/dl and glucose 71 mg/dl (serum glucose 111 mg/dl) with negative HSV-1/HSV-2 PCR. Therefore acyclovir was discontinued. Serum sodium level improved to 131 by fluid restriction and patient's clinical status improved with unremarkable neurology exam except for mild confusion. Hyponatremia was determined to be caused by syndrome of inappropriate antidiuretic hormone secretion (SIADH) with some contribution from chlorthalidone use. Our impression was the seizures were caused by hyponatremia decreasing seizure threshold in a pre-existing right temporal lesion thought to be inflammatory or traumatic in nature. Patient was discharged in stable condition to inpatient rehabilitation facility and prescribed to take levetiracetam.

Eleven days after initial admission patient was re-admitted with altered mental status, left sided weakness and facial twitching. Repeat MRI noted a new T2 hyperintense non-enhancing lesion in the right parietal region (arrow in Figure 1C). Upon arrival patient was somnolent and hard to arouse, but followed simple commands and answered in short sentences. Patient also had profound left side weakness. Patient subsequently became unresponsive and was intubated to protect the airway. CSF studies were repeated and this time showed 20 WBCs/mm^3, 1 RBC/mm^3, glucose 58 mg/dl (serum glucose 137 mg/dl), protein 80 mg/dl. This time PCR test was positive for HSV-1 viral particles. Patient completed 21-days course of IV acyclovir. A repeat CT head 37 days following initial presentation showed evolution of necrosis in the right parietal lobe (arrow in Figure 1D). Patient's neurologic function gradually improved and patient was able to follow commands and mouth words. Patient was discharged to long term acute care facility 41 days after initial presentation. Three months after discharge patient had significant improvement close to the baseline except for mild problems with short term memory and balance.

3. Discussion and conclusion

This is one of the first case reports where two false negative HSV PCR results were followed with a third PCR confirming presence of HSV. It provides a platform to discuss challenges of diagnosing HSV encephalitis. In retrospect patient's SIADH was probably caused by the intracranial infection. Patient's history of ipsilateral corneal transplant raises the possibility that source of HSV was the transplanted cornea retrogradely transported through cranial nerve V [4].

Diagnosis of HSV encephalitis is through integration of clinical information, imaging data and CSF analysis results. Altered level of mentation, focal neurological deficits and seizure are common initial clinical presentations. Over 90% of patient will have one of the above-mentioned findings and fever [5]. In elderly or immunocompromised patients fever may not be present, as was the case for our patient. Brain MRI typically shows T2 hyperintense lesions in unilateral temporal, insula, or cingulate cortex [6], however sensitivity changes from 86% within 48 h [7] to 100% in 3–10 days [8] after onset of symptoms. Focal EEG abnormalities, namely lateral discharges, have been reported to occur in all patients, although they are nonspecific [2]. CSF can be normocellular in 22% of patients, which is generally associated a lower protein level and viral load, and lower frequency of MRI abnormalities [9].

PCR test for HSV with 96–98% sensitivity and a very high specificity [3] has replaced brain biopsy as the gold standard. However, there are

increasing reports of false negative cases: in one instance [10] an 88-year old male presented with 1 months of behavioral and cognitive changes and focal seizure. Brain MRI showed vasogenic and cytotoxic changes in the right temporal cortex. Workup led to two negative HSV PCRs leading to cessation of treatment and ultimately patient's death with the diagnosis ultimately made through brain autopsy. A very early negative PCR may be related to early parenchymal replication with insufficient copies of viral DNA in the CSF [11]. Testing very late in the disease can also cause false negative PCR [12]. Therefore the Infectious Disease Society of America guidelines recommends repeating the PCR in 3–7 days if there is high clinical suspicion for HSV encephalitis [13].

An alternative cause for false negative PCR is presence of PCR inhibitors in the sample. Heme factor inhibits DNA polymerase, part of the feedback inhibition regulating hemoglobin synthesis in erythrocytes [14]. In addition, heme products such as hemin, bilirubin and bile salts inhibit PCR. Lactoferrin due to DNA interaction, immunoglobulins, as well as anticoagulants such as EDTA and heparin are also known to inhibit PCR [15]. If presence of PCR inhibitors is suspected, a CSF sample can be mixed with internal control to assess PCR inhibition. As far as we know no such assay was performed for our patient.

In our case the hyponatremia on initial presentation and negative HSV PCR results deviated our focus to electrolyte abnormalities. Patient improved after resolution of hyponatremia but in the meantime also received 3 days of IV acyclovir that probably contributed to the clinical improvement. A positive PCR occurred after appearance of a new parietal lesion, suggesting progression of parenchymal infection provided CSF with enough viral load for PCR to turn positive. One can argue that by holding antivirals after two negative PCR tests our medical decision contributed to progression of HSV infection and subsequent positive HSV PCR results; this is obviously not desired. In summary, this case supports the argument that in cases of multiple negative PCR results, it is important to complete treatment with antiviral therapy if clinical setting, and electrographic or imaging findings are suggestive of HSV encephalitis.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] R.J. Whitley, S.J. Soong, R. Dolin, G.J. Galasso, L.T. Ch'ien, C.A. Alford, Adenine arabinoside therapy of biopsy-proved herpes simplex encephalitis. National Institute of Allergy and Infectious Diseases collaborative antiviral study, N. Engl. J. Med. 297 (1977) 289–294.

[2] J.P. Bewersdorf, U. Koedel, M. Patzig, K. Dimitriadis, G. Paerschke, H.W. Pfister, et al., Challenges in HSV encephalitis: normocellular CSF, unremarkable CCT, and atypical MRI findings, Infection 47 (2019) 267–273.

[3] F.D. Lakeman, R.J. Whitley, Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group, J. Infect. Dis. 171 (1995) 857–863.

[4] J.H. LaVail, K.S. Topp, P.A. Giblin, J.A. Garner, Factors that contribute to the transneuronal spread of herpes simplex virus, J. Neurosci. Res. 49 (1997) 485–496.

[5] R.E. Levitz, Herpes simplex encephalitis: a review, Heart Lung 27 (1998) 209–212.

[6] F.C. Chow, C.A. Glaser, H. Sheriff, D. Xia, S. Messenger, R. Whitley, et al., Use of clinical and neuroimaging characteristics to distinguish temporal lobe herpes simplex encephalitis from its mimics, Clin. Infect. Dis. 60 (2015) 1377–1383.

[7] A. Al-Shekhlee, N. Kocharian, J.J. Suarez, Re-evaluating the diagnostic methods in herpes simplex encephalitis, Herpes 13 (2006) 17–19.

[8] J. Granerod, N.W. Davies, W. Mukonoweshuro, A. Mehta, K. Das, M. Lim, et al., Neuroimaging in encephalitis: analysis of imaging findings and interobserver agreement, Clin. Radiol. 71 (2016) 1050–1058.

[9] A.W. Saraya, S. Wacharapluesadee, S. Petcharat, N. Sittidetboripat, S. Ghai, H. Wilde, et al., Normocellular CSF in herpes simplex encephalitis, BMC Res. Notes 9 (2016) 95.

[10] A.A. Mendez, A. Bosco, L. Abdel-Wahed, K. Palmer, K.A. Jones, A. Killoran, A fatal case of herpes simplex encephalitis with two false-negative polymerase chain reactions, Case Rep. Neurol. 10 (2018) 217–222.

[11] A.A. Weil, C.A. Glaser, Z. Amad, B. Forghani, Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result, Clin. Infect. Dis. 34 (2002) 1154–1157.

[12] K. McCabe, K. Tyler, J. Tanabe, Diffusion-weighted MRI abnormalities as a clue to the diagnosis of herpes simplex encephalitis, Neurology 61 (2003) 1015–1016.

[13] A.R. Tunkel, C.A. Glaser, K.C. Bloch, J.J. Sejvar, C.M. Marra, K.L. Roos, et al., The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America, Clin. Infect. Dis. 47 (2008) 303–327.

[14] A. Akane, K. Matsubara, H. Nakamura, S. Takahashi, K. Kimura, Identification of the heme compound copurified with deoxyribonucleic acid (DNA) from bloodstains, a major inhibitor of polymerase chain reaction (PCR) amplification, J. Forensic Sci. 39 (1994) 362–372.

[15] W.A. Al-Soud, P. Radstrom, Purification and characterization of PCR-inhibitory components in blood cells, J. Clin. Microbiol. 39 (2001) 485–493.