A case report of anti-N-methyl-d-aspartate receptor encephalitis with chromosomally integrated human herpesvirus 6

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Case report

A case report of anti-*N*-methyl-D-aspartate receptor encephalitis with chromosomally integrated human herpesvirus 6

Short running title: anti-NMDAR encephalitis with ciHHV6

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ABSTRACT

Chromosomally integrated human herpesvirus 6 (ciHHV6) is a condition where HHV6-DNA is integrated into the host germline genome. ciHHV6 can be misdiagnosed as active HHV6 infection. We report a 30-year-old woman presenting with psychological symptoms without a history of immunodeficiency. She had an ovarian teratoma and anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies in the cerebrospinal fluid (CSF) with HHV6-DNA in the serum and CSF. The final diagnosis was anti-NMDAR encephalitis and ciHHV6 because laparoscopic oophorectomy and immunotherapy ameliorated her symptoms and HHV6-DNA was detected in her oral mucosa cells. This case suggests the need to assess whether HHV6-DNA is related to infection or ciHHV6 when HHV6-DNA is detected in the CSF of patients with encephalitis.

Keywords: anti-*N*-methyl-D-aspartate receptor encephalitis, autoimmune encephalitis, case report, cerebrospinal fluid, chromosomally integrated human herpesvirus 6

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune-mediated disorder characterized by cerebrospinal fluid (CSF) antibodies against NMDAR and complex neuropsychiatric symptoms, such as psychosis, seizures, abnormal movement, and impaired consciousness.[1]

Human herpesvirus 6 (HHV6) can cause encephalitis, especially in immunocompromised patients.[2] Clinical symptoms of HHV6 encephalitis are similar to those of anti-NMDAR encephalitis.[1,3] However, about 1% of the population is born with chromosomally integrated HHV6 (ciHHV6), wherein the entire HHV6 genome is inserted into the telomere of a chromosome in every cell.[2] ciHHV6 has not been proven to cause encephalitis; therefore, it is important to distinguish active HHV6 infection from ciHHV6 when HHV6-DNA is detected in patients with encephalitis.

Here, we describe a case with CSF positive for anti-NMDAR antibodies and HHV6-DNA, who was finally diagnosed with anti-NMDAR encephalitis and ciHHV6.

2. Case report

A 30-year-old woman developed subacute restlessness, confusion, and headache on Day 0. She inexplicably jumped from the second floor of her house on Day 39. She was taken to an emergency hospital and transferred to a psychiatric hospital because of delusion. Aripiprazole and flunitrazepam did not improve her symptoms. Electroencephalography (EEG) showed generalized slow waves and CT showed an ovarian teratoma in her left ovary (Figure 1A). Because autoimmune encephalitis (AIE) was suspected, she was transferred to our hospital on Day 67 with disorientation, visual

hallucination, persecutory delusion, delusional mood, mood lability, and agitation. She had no history of medical problems and no focal neurologic deficits. No high fever nor meningeal signs were observed. Mild pleocytosis, hyperproteinemia, and anti-NMDAR antibodies were observed in her CSF. Serum and CSF were positive for HHV6-DNA (1,500,000 and 8,100 copies/mL, respectively) but negative for other herpesvirus DNA. EEG showed a diffuse background slowing without paroxysmal activity (Supplementary Figure 1A) and brain MRI was normal (Figure 1B, C).

Considering the possibilities of HHV6 encephalitis and anti-NMDAR encephalitis, she was treated with antiviral agents and intravenous methylprednisolone followed by intravenous immunoglobulin. Laparoscopic oophorectomy for the left ovarian tumor was performed on Day 82. Subsequent plasma exchange ameliorated her symptoms. The cell numbers and protein levels in the CSF decreased to almost normal levels and her EEG became normal (Supplementary Figure 1B). Despite 6 weeks of ganciclovir treatment, blood and CSF remained positive for HHV6-DNA. Subsequently, her oral mucosa cells were also positive for HHV6-DNA. Discontinuation of ganciclovir treatment did not aggravate her symptoms. Finally, she was diagnosed with definite anti-NMDAR encephalitis and ciHHV6 (Figure 1D).[3-5]

3. Discussion

This is the first report of a case of anti-NMDAR encephalitis with ciHHV6. Individuals with ciHHV6 have high viral DNA levels in the blood and CSF, which can lead to ciHHV6 being misdiagnosed as active HHV6 infection and unnecessary antiviral treatment being given.[3,6] Therefore, when HHV6-DNA is detected in the CSF of patients with encephalitis, ciHHV6 should be excluded by measuring HHV6-DNA in

hair follicles or oral mucosa cells.[3,5] Moreover, other possible etiologies such as AIE should be assessed. Our patient had no history of immunodeficiency. Her symptoms and clinical course did not differ from typical anti-NMDAR encephalitis.[1] Furthermore, CSF and serum remained positive for HHV6-DNA even after ganciclovir treatment and clinical recovery. Taken together with the mucosa cell results, we concluded that she had ciHHV6.

Recent studies reported that herpes simplex encephalitis triggers anti-NMDAR encephalitis[1] and that other herpesviruses may trigger AIE.[7,8] Linnoila et al. reported three patients with encephalitis possessing HHV6-DNA and autoantibodies (one of them had anti-NMDAR antibodies) in the CSF,[7] but did not specify whether they had HHV6 infection or ciHHV6. Niehusmann et al. reported a patient with anti-glutamic acid decarboxylase antibody-positive encephalitis, ciHHV6, and active HHV6 infection assessed by transient HHV6-IgM positivity.[8] HHV6-IgM was not measured in our case because positivity for HHV6-IgM does not necessarily reflect infection and is not required to diagnose HHV6 encephalitis.[2,3]

In conclusion, HHV6-DNA can be detected in patients with AIE, and the possibility of ciHHV6 should be considered.

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Conflict of interest

The authors report no disclosures relevant to the manuscript.

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Ethical statement

Written informed consent was obtained from the patient for publication of this case

report and accompanying images. Our institution's ethics committee did not require ethics approval.

Data Availability

Further anonymized data are available upon reasonable request.

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Figure Legend

FIGURE 1

(A) Axial image of a CT scan shows fat attenuation within a cyst with calcification in the left ovary (yellow arrow). (B) Fluid attenuated inversion recovery and (C) diffusion-weighted brain MRI images taken on Day 48 show no abnormal findings. (D) Summary of the clinical course of the patient, polymerase chain reaction (PCR) analysis of human herpesvirus 6 (HHV6)-DNA, and cerebrospinal fluid (CSF) findings are shown. The onset of symptoms was set as Day 0. Following the subacute development of restlessness, confusion, and headache, she jumped from the second floor of her house on Day 39. On Day 67, she was transferred to our hospital. The patient had delusions, mood lability, and agitation. The Glasgow Coma Scale was 14 with disorientation. Her blood test was normal. In her CSF, the cell numbers and protein levels were elevated, and oligoclonal IgG bands and anti-NMDAR antibodies were positive. She was treated with intravenous methylprednisolone (IVMP) followed by intravenous immunoglobulin (IVIg) and acyclovir (ACV). After HHV6-DNA was detected in the CSF and serum, ACV was switched to ganciclovir (GCV) on Day 76. Laparoscopic left oophorectomy was performed on Day 82, and the pathological diagnosis of the left ovary was mature cystic teratoma. After the surgery, plasma exchanges (PLEX) were performed five times, and finally, her psychological symptoms resolved completely, except for slight short-term memory impairment. However, HHV6-DNA remained positive in the CSF and serum. After detecting HHV6-DNA in oral mucosa cells, she was confirmed to have chromosomally integrated HHV6, and GCV treatment was discontinued. Her symptoms have been stable for more than one year since the GCV discontinuation.

Abbreviation: R, right

Supplementary Figure 1

Electroencephalography (EEG) findings of the patient: bipolar montage. (A) EEG performed on Day 69 shows diffuse background slowing without any paroxysmal activities (before treatment). (B) EEG performed on Day 104 shows normal background activity (after treatment).