A Case of Herpes Encephalitis Occurring after Aneurysmal Coil Embolization

Kazuyuki Kuwayama, Taku Matsuda, Hirotaka Hagino, Hidekazu Taniguchi, and Yoshinobu Nakagawa

Objective: We report a case of herpes encephalitis that occurred after coil embolization of cerebral aneurysm.

Case Presentation: A 66-year-old woman underwent stent-assisted coil embolization for the recurrence of basilar tip aneurysm. She was discharged to home but noted fever 30 days after the procedure, and as she developed disorientation and disturbance of consciousness, she consulted the outpatient clinic of our hospital. MRI showed abnormal signals mainly in the mesial right temporal lobe, and with a diagnosis of herpes encephalitis based on the cerebrospinal fluid (CSF) tap test, acyclovir drip infusion was performed. While disturbance of consciousness was resolved, disorientation and short-term memory loss persisted.

Conclusion: There is a possibility that herpes encephalitis was induced by the intracranial endovascular procedure. Herpes encephalitis should be recognized as a possible complication after intracranial endovascular therapy.

Keywords ▶ herpes encephalitis, coil embolization, basilar tip aneurysm, reactivation

Introduction

Herpes encephalitis is a disease with a poor prognosis. Its mortality is 70% without treatment, and it results in severe sequelae or death in 30% of the patients even with appropriate treatment.1) Herpes encephalitis in adults is considered to be caused primarily by reactivation of latent herpes virus infection.2) While there have been sporadic reports of the occurrence of herpes encephalitis after neurosurgery,3,4 its occurrence after intracranial endovascular treatment has not been reported.

Case Presentation

The patient was a 66-year-old woman with hypertension but no history of herpetic disease. She had an episode of subarachnoid hemorrhage (Hunt and Kosnik 5) 2 years before, when she underwent coil embolization by a simple technique for basilar tip aneurysm, was discharged to home despite persistence of mild impairment of higher brain functions, and had since been followed up at our department as an outpatient. MRA performed 6 months after coil embolization demonstrated recurrence of cerebral aneurysm due to coil compaction, but the patient was observed due to mildness of the condition. However, stent-assisted re-embolization was necessitated by gradual progression of coil compaction.

Coil embolization of cerebral aneurysm

The administration of clopidogrel at 75 mg/day and aspirin at 100 mg/day was initiated 1 week before the procedure.

On right vertebral angiography, coil compaction of the basilar tip aneurysm was observed, the contrast agent filled a space of 9.9 × 9.5 × 6.1 mm, and the neck 5.6 mm in diameter mounted on the left posterior cerebral artery (Fig. 1A). A 7 Fr FUBUKI guiding catheter NV (Asahi Intecc, Thailand) was placed in the right vertebral artery. After an Excelsior SL-10 (Stryker, CA, USA) was guided into the aneurysm, an Enterprise VRD 4.0 × 30 mm (Codman, Miami, FL, USA) was placed in the basilar artery via the left posterior cerebral artery (P2), and stent-assisted coil embolization was performed using 6 GalaxyFill (Codman), 2 Galaxy Xtrasoft (Codman),

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3 Target 360 ultra (Stryker), and 5 Axium Prime3D (Medtronic, Minneapolis, MN, USA) coils. Cone beam CT confirmed adequate stent expansion and complete occlusion of the cerebral aneurysm (Fig. 1B).

**Postoperative course**

The patient complained of sensation disturbance of the left lower extremity immediately after the procedure. On the same day, 100 mg of hydrocortisone was administered once. Head MRI performed on the day after the procedure revealed a small de novo infarction in the cerebellum. On the day of the procedure, the patient developed atrial fibrillation, which persisted to the next day. Edoxaban was orally administered at 30 mg/day 1–7 days after the procedure. Head MRI was performed again 3 days after the procedure, but no change was observed in the findings compared with those on the day after the procedure. The Mini Mental State Examination (MMSE) score 5 days after the procedure was 27/30. Sensation disturbance of the left lower extremity was resolved 6 days after the procedure, and the patient was discharged to home 7 days after the procedure.

Postoperatively, activities of daily living (ADL) were independent, but the patient noted fever 30 days after the procedure and exhibited loss of appetite, headache, and disorientation. As she also developed disturbance of consciousness, she consulted the outpatient clinic of our department 38 days after the procedure.

**Findings on arrival**

The state of consciousness by the Glasgow Come Scale (GCS) was E3V4M6, and there was no clear paralysis, but the patient wobbled and could not walk. Disorientation and short-term memory loss were noted. The body temperature was 38.7°C. The blood test results were as follows: white blood cell (WBC): 78.4 × 10^3/µL, hemoglobin (Hb): 11.3 g/dL, hematocrit (Hct): 31.4%, platelet (Plt): 37.9 × 10^4/µL, C-Reactive Protein (CRP): 0.12 mg/dL, Na: 123 mmol/L, K: 3.8 mmol/L, and cerebral infarction (Cl): 88 mmol/L.

Head CT showed narrowing of the right cornu inferius ventriculi lateralis (Fig. 2A).
On MRI, high-intensity areas were noted on the right mesial temporal lobe, right insula, and right frontal lobe on T2-weighted, FLAIR, and diffusion-weighted images (DWI) (Figs. 2B and 2C). The apparent diffusion coefficient (ADC) was slightly elevated at these sites (Fig. 2D).

On emergency intracranial angiography, no stenosis or occlusion was observed in the cerebral vessels including the stent lumen.

On the cerebrospinal fluid (CSF) tap test, the CSF was transparent and colorless, the cell count was 14, lymphocyte percentage was 95%, and protein level was 91.6 mg/dL. Polymerase chain reaction (PCR) test for herpes deoxyribonucleic acid (DNA) was performed (Table 1).

### Course after admission

From the MRI and CSF tap test findings, we suspected herpes encephalitis, and drip infusion of acyclovir at 10 mg/kg 3 times a day and Na correction were performed. On the next day, the sodium level was normalized to 136 mmol/L, and disturbance of consciousness was resolved. On the day after admission, the MMSE score was 21/30. Although fever (≥37°C) was resolved 8 days after admission, disorientation, and short-term memory loss showed no improvement. Five days after admission, herpes simplex virus (HSV) DNA was found to be increased in the CSF submitted on the day of admission, and a diagnosis of herpes encephalitis was made. CSF tap tests were performed 6 and 14 days after admission (Table 1).

Acyclovir was administered over 3 weeks. On head MRI performed 21 days after admission, the area of abnormal FLAIR signals was slightly narrowed compared with the state on admission, and narrowing of the right cornu inferius ventriculi lateralis disappeared. Twenty-four days after admission, no disturbance of consciousness was noted, and the patient was discharged to home with disorientation and short-term memory loss persisting. The MMSE score was improved to 26 on the outpatient visit 37 days after discharge.

<table>
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<td>27</td>
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<td>94</td>
<td>87</td>
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<td>122.4</td>
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<td>HSV DNA PCR (copy/10⁶ cells)</td>
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<td>1.1 × 10⁵</td>
<td>&lt;1.0 × 10⁴</td>
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</table>

CSF shows lymphocyte-predominant pleocytosis. The HSV DNA level was below the reference value on the test 53 days after the procedure. *Reference range: <2.0 × 10⁶ (copy/10⁶ cells); CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; HSV: herpes simplex virus; PCR: polymerase chain reaction; POD: postoperative day.

### Discussion

In adults with normal immune function, HSV1 is the cause of 90% or more cases of herpes encephalitis. HSV2 is considered to be a major causative virus of aseptic meningitis, and encephalitis occurs in 15% or more of the patients with central nervous system infection of HSV2. After the first infection, HSV enters the axon terminal of the mucosa or skin, is transported to the dorsal root or trigeminal ganglia through the axon, and lies dormant there. About two-third of the cases of herpes encephalitis are considered to be caused by reactivation of latent HSV. Fever, local trauma, physical and mental stress, exposure to ultraviolet rays, hormone imbalance, immunosuppression, and X-ray irradiation have been reported as factors related to reactivation.

In all, 27 cases of herpes encephalitis that occurred after neurosurgery have been reported to the present. Among them, 26 occurred after intracranial surgery, and 1 occurred after spinal cord surgery. Jaques et al. speculated that surgical stress, trauma, and the use of steroid promoted reactivation of HSV. Of the 27 reported cases, steroid was used postoperatively in 18 except 9 in whom there was no mention about the use of steroid. Dexmethasone has been shown in vitro to dose-dependently induce reactivation of HSV1. Since our patient postoperatively complained of mild sensation disturbance of the left foot, we used steroid in consideration of the possibility of symptoms due to perianeurysmal inflammation or edema. However, as no abnormality was noted around the aneurysm on head MRI on the day after surgery, we terminated its use thereafter. An involvement of steroid in reactivation cannot be excluded although it was used only once in a small dose. Pazin et al. reported that a positive result of laryngeal HSV culture and skin lesions were observed postoperatively either alone or in combination in 28 (50%) of the 58 patients who underwent microvascular decompression of the trigeminal nerve root and suggested...
that mild stimulation or occult trauma of the trigeminal nerve may promote reactivation of HSV. In our patient, the wall of the basilar tip aneurysm did not touch the trigeminal nerve in MRA source images. However, transient inflammation of the aneurysmal wall and peri-aneurysmal edema have been reported to occur after embolization.\(^9,10\) Moreover, as the stent was placed in the basilar artery on the proximal side of the bifurcation of the anterior inferior cerebellar artery via the left P2 the possibility of slight displacement of the basilar artery cannot be excluded. They may have stimulated the trigeminal nerve and promoted reactivation of HSV. In addition, as the patient temporarily exhibited atrial fibrillation after surgery and was managed in the Intensive Care Unit (ICU) for 4 days, this may also have enhanced the surgical stress and promoted reactivation.

In the 27 cases of herpes encephalitis that occurred after neurosurgery, the time until the onset was reportedly 1–21 days (mean: 7.8 days). In our patient, the disorder occurred 30 days after surgery, and this delayed onset may be related to the difference in the etiological mechanism of herpes encephalitis between surgical and endovascular procedures.

In herpes encephalitis, lymphocyte-predominant CSF pleocytosis is observed. The sensitivity and specificity of PCR for herpes virus DNA in CSF are \(\geq 95\%\) and \(\geq 99\%\), respectively, and it is the most important test for the definitive diagnosis. However, it must be noted that PCR may present with false-negative results in the ultra-acute period after the onset.\(^1,11\) In addition, it is impossible to make an immediate definitive diagnosis because several days are needed before the results of PCR can be obtained. Head CT findings are often normal for 4–6 days after the onset. Head MRI often shows high-intensity signals in the mesial temporal lobe and insula from an early period in T2-weighted, FLAIR, and DWI images, but head CT and MRI findings are negative in 25% of the patients.\(^12\) In our patient, narrowing of the right cornu inferius ventriculi lateralis was noted on head CT on re-admission 38 days after the procedure, but it was a non-specific finding not accompanied by attenuation change in the brain parenchyma. On the other hand, head MRI showed high-signal areas in the right mesial temporal lobe, right frontal lobe, and right insula in T2-weighted, FLAIR, and DWI images. Since these findings were observed after stent-assisted coil embolization, cerebral infarction was most suspected, but the area of abnormal signals was not in agreement with the vascular distribution, and no decrease in ADC was noted (Figs. 2B–2D), so the possibility of cerebral infarction was considered low. However, by way of precaution, we performed intracranial angiography to check if there were any abnormalities in the cerebral blood vessels. The CSF tap test showed lymphocyte-predominant pleocytosis, suggesting viral meningoencephalitis. While detection of HSV DNA by PCR is necessary for the definitive diagnosis, 4 days was necessary before the results could be obtained after submission of the sample. As has been reported previously,\(^1,12,11\) head MRI and CSF tap test were also useful for the diagnosis of herpes encephalitis in our patient.

Concerning the treatment, it is recommended to administer acyclovir at 10 mg/kg/day, 3 times a day, for 2 weeks when herpes encephalitis is suspected.\(^11\) According to guidelines in Western countries, the period of acyclovir administration is extended from conventional 2 weeks to 2–3 weeks.\(^13,14\) In our patient, we suspected herpes encephalitis based on clinical symptoms, CSF tap test findings, and head MRI findings and administered acyclovir at 10 mg/kg/day 3 times a day from the day of admission. Since disorientation and short-term memory loss persisted 2 weeks after the beginning of administration, the treatment was continued for 1 week. As no change was observed in neurologic symptoms even after the additional administration, whether additional administration was necessary is unclear. In the evaluation of 27 cases of herpes encephalitis that developed after neurosurgery, all four patients who were not administered an antiviral agent died. Of the 21 patients in whom the period of antiviral drug administration was mentioned (idoxuridine in 1, acyclovir in 20), neurologic symptoms were completely resolved in five patients in whom treatment was initiated within 2 days after the onset of symptoms.\(^2,3\) Of the 16 patients in whom the antiviral therapy was initiated 3 or more days after the onset of symptoms, 6 showed complete recovery, 8 suffered permanent sequelae, and 2 died.\(^2,3\) From these results, initiation of acyclovir administration early after the appearance of symptoms is considered important to improve the prognosis. However, as clinical symptoms are non-specific, early diagnosis is difficult.\(^15\) Our patient consulted the outpatient clinic of the neurosurgic department 8 days after the onset of fever. The first postoperative follow-up examination was scheduled on that day, and while the patient and her husband noted fever, loss of appetite, and disorientation, they considered them to be poor physical condition. MRI on the visit already showed abnormalities. Despite the initiation
of acyclovir administration on the day of examination, permanent sequelae remained.

Cerebral infarction is a frequent complication after coil embolization of cerebral aneurysms, but there have also been sporadic reports of posterior reversible encephalopathy syndrome (PRES) and contrast-induced encephalopathy. PRES is supposed to be caused by vascular edema primarily in the posterior circulation due to disruption of the blood–brain barrier. It is characterized by symptoms including headache, altered consciousness, convolution, and cortical blindness. The lesion is symmetric, and the parietal and occipital lobes are affected most notably. On head MRI, high-signal intensity on T2-weighted and FLAIR images and elevation of ADC are observed, but signals on DWI are often normal. Contrast-induced encephalitis is caused by disruption of the blood–brain barrier due to repeated injection of the contrast agent in the same vessel, and focal symptoms are considered to appear due to toxicity of the contrast medium leaking out into the brain parenchyma, cortex, or subarachnoid space. Lesions occur frequently in the area supplied by the vessel in which angiography has been performed repeatedly, and high-density areas are observed on head CT immediately after the procedure, but head MRI presents no abnormalities that can explain the symptoms. On follow-up CT, high-density areas disappear rapidly, often with resolution of symptoms. In our patient, the head MRI findings resembled those of PRES, but the condition could be differentiated from PRES because the lesion was located in the unilateral frontotemporal region, high-intensity signals were detected on DWI, and abnormal signals did not disappear on follow-up MRI. Herpes encephalitis could also be differentiated from contrast-induced encephalitis because it occurred 30 days after endovascular treatment, and no high-density area was noted on head CT. While PRES and contrast-induced encephalitis are both transient disorders, herpes encephalitis has a poor prognosis if treatment is delayed, and their differentiation is important.

### Conclusion

A case of herpes encephalitis that occurred after intracranial endovascular treatment was reported. Herpes encephalitis must be remembered as a complication that may occur after intracranial endovascular procedures. Since its prognosis is poor if treatment is delayed, patients should be instructed to immediately consult if they notice abnormalities such as fever and disorientation after the procedure.

### Disclosure Statement

Neither the first author nor any of the coauthors have any conflicts of interest.

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