



Anterior Commissure Involvement in Humanherpes Virus 6 Encephalitis

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Abstract

The anterior commissure is an evolutionarily conserved nerve bundle that connects the right and left hemispheres, playing pivotal neurological roles in visual, linguistic, and olfactory functions. The authors herein describe a 16-month-old boy with high fever, lethargy, and recurrent seizures. Polymerase chain reaction (PCR) examination detected human herpesvirus 6 (HHV-6) in both the cerebrospinal fluid and the pharyngeal swabs, leading to the diagnosis of HHV-6 encephalitis. Brain magnetic resonance imaging (MRI) 4 days after disease onset distinctly revealed anterior commissure involvement on diffusion-weighted images and apparent diffusion coefficient maps, suggesting that this lesion was cytotoxic edema. After treatment with 30 mg/kg/d methylprednisolone for 3 days, the anterior commissure involvement on MRI was completely diminished. This is the first MRI report rarely showing anterior commissure involvement in encephalitis, suggesting that this lesion might be caused by direct invasion of HHV-6 or transient axonal swelling associated with inferior temporal lobe damage.

Keywords

connecting fiber, human herpesvirus 6, magnetic resonance imaging, cytotoxic edema

Received April 21, 2014. Received revised April 21, 2014. Accepted for publication June 01, 2014.

The anterior commissure is a bundle of nerve fibers that connects the bilateral hemispheres across the midline and is located in the anterior portion of the columns of the fornix.¹ Most nerve fibers connecting the 2 hemispheres pass through the corpus callosum, but a small number alternatively pass through the anterior commissure pathway, which includes those essential for language, olfactory, and visual functions.^{2,3}

A certain number of diseases involving the anterior commissure have been reported. Cerebral infarction and mild head traumatic injury can cause volume loss of the white matter, leading to a reduced size of the anterior commissure.^{3,4} Sexual orientation affects the size of the anterior commissure, owing to hormonal effects on both hemispheres in the human brain.⁵ However, there have been no magnetic resonance imaging (MRI) reports of acute encephalitis involving the anterior commissure, although some viral infections have been reported affected there. Herein, the authors describe the first brain imaging case of anterior commissure involvement in a patient with human herpesvirus 6 (HHV-6) encephalitis.

Case Summary

A previously healthy 16-month-old boy was admitted to another hospital for high fever, lethargy, and recurrent seizures. He was unconscious and had generalized seizures intermittently. Since becoming unconscious and recurrent seizures had not been resolved by medication, he was transferred to our hospital 3 days after the disease onset.

On admission, he was unconscious with high fever but no seizures. His muscles were flaccid and the deep tendon reflexes were normal without any neurological deficit. Blood examinations

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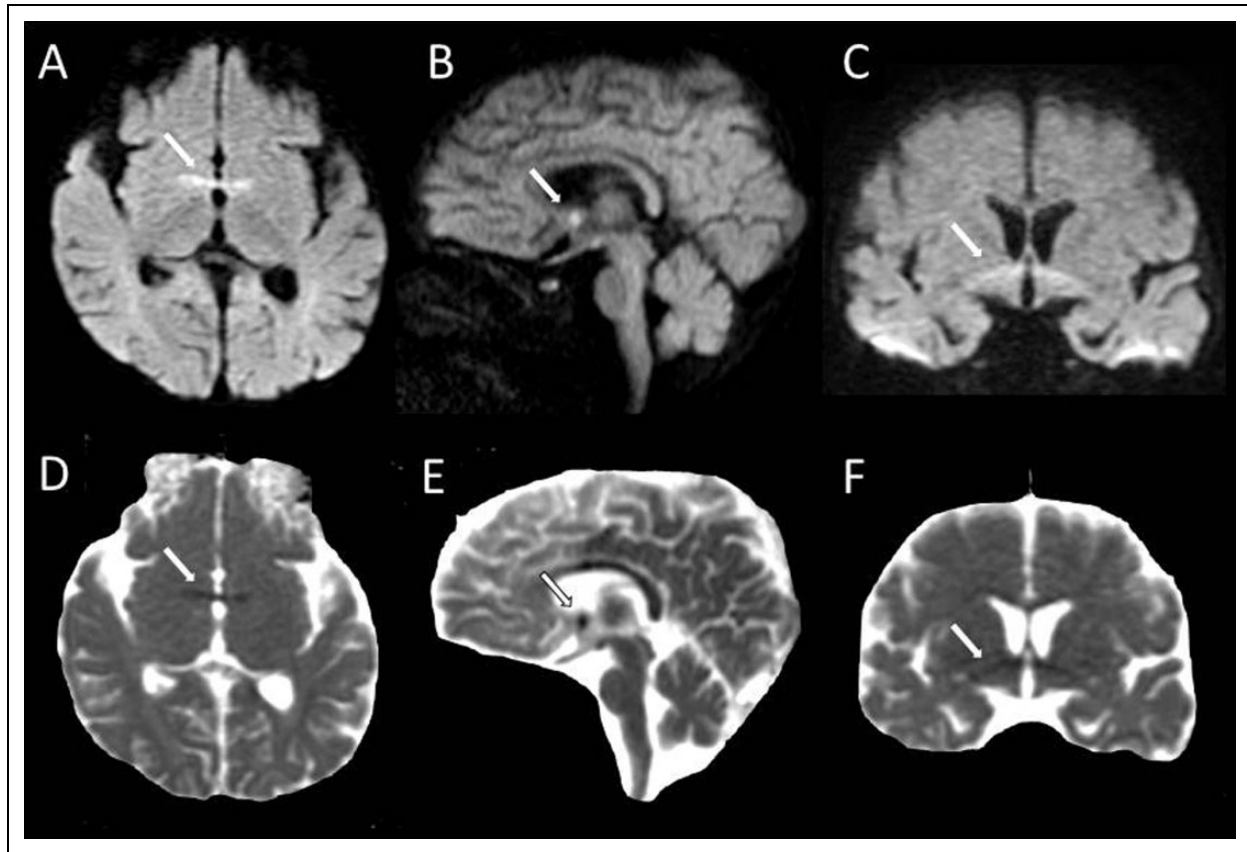


Figure 1. Axial diffusion-weighted images and apparent diffusion coherent values in a patient with human herpesvirus 6 encephalitis who showed anterior commissure involvement representing cytotoxic edema. This linear lesion was clearly detected on (A) axial (white arrow), (B) sagittal (white arrow), and (C) coronal images (white arrow) on diffusion-weighted images, and (D) axial (white arrow), (E) sagittal (white arrow), and (F) coronal images (white arrow) for apparent diffusion coherent values.

showed elevated levels of aspartate aminotransferase at 752 U/L (normal range: 13-33), alanine aminotransferase at 412 U/L (8-42), lactate dehydrogenase at 877 U/L (119-229), ferritin at 1408 U/L (50-200), and soluble interleukin-2 receptor at 2085 ng/mL (127-582), suggesting that he had moderate hypercytokinemia. Cerebrospinal fluid examinations were unremarkable. Brain MRI 4 days after disease onset clearly revealed anterior commissure lesions on diffusion-weighted images and apparent diffusion coefficient maps (Figure 1A-F), suggesting cytotoxic edema. Electroencephalogram showed a diffuse low voltage while awake, with no focal spikes or sharp waves. Bacterial cultures including of blood, sputum, urine, and cerebrospinal fluid gave negative results. The polymerase chain reaction (PCR) detected HHV-6 in both the cerebrospinal fluid and the pharyngeal swabs. Since the authors could not find any other evidence of an antecedent infection or causative etiology, the authors finally diagnosed him as having HHV-6 encephalitis associated with anterior commissure involvement. The authors treated him with 30 mg/kg/d methylprednisolone for 3 days, after which he recovered from becoming unconscious. General muscle weakness gradually improved. After 1 month, the follow-up brain MRI showed complete resolution of the anterior commissure lesions, and he was discharged from our hospital with no neurological complications.

Discussion

The authors described a boy of 16 months of age with HHV-6 encephalitis associated with an anterior commissure lesion. The MRI clearly demonstrated anterior commissure involvement due to increased intensity on diffusion-weighted imaging and reduced intensity on an apparent diffusion coefficient map, suggesting cytotoxic edema. To our knowledge, this is the first MRI report of anterior commissure involvement in encephalitis, which was transient and left no atrophy.

In humans, there are 5 interhemispheric nerve bundles, namely, corpus callosum, anterior commissure, hippocampal commissure, posterior commissure, and habenular commissure.¹ Among these, the anterior commissure is the most evolutionarily conserved nerve bundle, which connects bilateral olfactory tracts and temporal lobes.³ Although this anterior commissure is the oldest, its pathological change has not been well reported, contrary to the case of the corpus callosum, which widely connects the 2 hemispheres. Previous reports have suggested that the anterior commissure is highly vulnerable to direct impact of trauma, progressive axonal injury, and myelin degeneration.³⁻⁵ These pathologic events would actually cause a reduced size of the anterior commissure on brain imaging.^{3,4}

In animals, some conditions have been reported to cause anterior commissure abnormalities. Prenatal stress can alter the size of the rostral anterior commissure in rats.⁶ Perinatal administration of testosterone induces hypertrophy of the anterior commissure in adult rats.⁷ Fetal alcohol exposure can alter the size of the mid-sagittal commissure in rats.⁸ These abnormalities essentially correlated with changes in the size of the anterior commissure. Thus, in both humans and animals, cerebral events would result in size differences in the anterior commissure.

There are 3 significant findings in this report. First, this is the first MRI report associated with signal abnormality of the anterior commissure on diffusion-weighted images and apparent diffusion coefficient maps, suggesting that these lesions were cytotoxic edema. Since the corpus callosum, another major interhemispheric nerve bundle, often exhibits abnormalities in MRI signal owing to drugs,⁹ epileptic seizures,¹⁰ and high-altitude cerebral edema,¹¹ the signal abnormality of the anterior commissure might have been due to a similar mechanism. Second, this anterior commissure lesion was transient and actually left no nerve bundle atrophy, indicating that it was a reversible change. All previous reports on the anterior commissure have described irreversible size reduction, such as postischemic and post-traumatic changes.^{3,4} Thus, our case is interesting in terms of its pathogenesis showing transient signal abnormality. Third, the patient was as young as 16 months of age, indicating that he had a developmentally immature brain undergoing myelin and synapse formation. Since the vulnerability of the anterior commissure to mild head trauma has also been reported in children, the anterior commissure involvement of this patient might have resulted from the immaturity of the brain by some mechanism. Apart from this cerebral vulnerability, transient hypercytokinemia might have been synergistically responsible for the reversible anterior commissure lesion seen in this patient.

The HHV-6 is known to cause exanthema subitum in infancy, which is usually self-limited but occasionally develops into encephalitis in children or in immunocompromised hosts.^{12,13} Brain MRI usually shows medial temporal lobe lesions in immunocompromised hosts.¹⁴ However, in children, various brain imaging patterns have been reported, for example, acute necrotizing encephalopathy and diffuse brain swelling, not limited to the medial temporal lobe itself.¹⁵ Although this patient did not show any brain lesion other than in the anterior commissure, HHV-6 infection would probably have somehow affected the underlying pathogenesis.

Interestingly, the [11C] (R)-PK11195 positron-emission tomography imaging study after herpes virus encephalitis has already reported microglial activation in the anterior commissure.¹⁶ Since inferior medial temporal lobes were also affected in that study, nerve fiber connections might contribute to the involvement of the anterior commissure. The reason as to why our patient presented the unique involvement of anterior commissure still remains unclear. Thus, further investigation will be required to elucidate it.

In summary, the authors demonstrated for the first time the unique transient involvement of the anterior commissure in HHV-6 encephalitis. Since the anterior commissure connects the inferior temporal lobes and the olfactory area, HHV-6, which usually affects the bottom of the temporal lobes, might affect connecting nerve bundles like the anterior commissure. Since this anterior commissure involvement disappeared after 1 month and no volume reduction remained, this involvement was supposed to have been transient cytotoxic edema caused by cortical damage or direct invasion.

Acknowledgments

The authors are grateful to doctors who are related to this patient for assistance with the therapy. The authors also thank the patient and his family with great sincerity.

Author Contributions

KF performed design and analysis and interpretation of MRI data and was the author of the first draft of the manuscript. HI, KN, HH, and NS performed a case conception and a critical review of the manuscript. HU performed a critical review of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the Chiba University ethical committee board.

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