

Case Report

Anterior cingulate cortex involvement in non-paraneoplastic limbic encephalitis

Kyosuke Ibi^{a,*}, Katsunori Fujii^b, Hironobu Kobayashi^a, Masayoshi Senda^a
Katsuhiko Kitazawa^a, Akihito Honda^a

^a Department of Pediatrics, Asahi General Hospital, Chiba, Japan

^b Department of Pediatrics, Chiba University Graduate School of Medicine, Chiba, Japan

Received 29 October 2018; received in revised form 26 March 2019; accepted 7 April 2019

Abstract

Background: Non-paraneoplastic limbic encephalitis is characterized by attention deficit, loss of emotion control, and impaired memory. Viral infection can cause acute encephalitis in children, occasionally exhibiting clinical features of limbic dysfunction. However, how viral infection affects the limbic system remains to be elucidated.

Case description: A 5-year-old Japanese boy was admitted to our hospital because of high fever and status epilepticus. After seizures were controlled by diazepam, he exhibited attention deficit, loss of emotion control, and impaired memory, suggesting acute limbic encephalitis. Since titers of antibodies against Coxsackie virus A10 were significantly elevated in the serum, we diagnosed him with non-paraneoplastic limbic encephalitis associated with the viral infection. Brain magnetic resonance imaging demonstrated involvement of anterior cingulate cortex as well as white matter of the frontal lobe in the acute period. After steroid pulse therapy, these brain lesions subsequently disappeared in a time-dependent manner, beginning with the frontal lobe white matter and extending to the anterior cingulate cortex, and his psychological symptoms also disappeared.

Conclusion: To the best of our knowledge, this is the first report to show the involvement of the region from the anterior cingulate cortex to the frontal lobe white matter. Clinical features such as seizures, attention deficit, loss of emotion control, and impaired memory suggest that this viral limbic encephalitis possibly extended from the frontal white matter to the anterior cingulate cortex via inter-neuronal connections in a time-dependent manner.

© 2019 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.

Keywords: Anterior cingulate cortex; Non-paraneoplastic limbic encephalitis; Magnetic resonance imaging

1. Introduction

Limbic encephalitis is characterized by seizures, impairment of short-term memory, and psychiatric symptoms such as anxiety, depression, and personality change [1]. Most cases of limbic encephalitis develop

as a paraneoplastic syndrome. The symptoms often precede the diagnosis of malignancy. However, infectious diseases and autoimmune disorders can also cause a mimic syndrome, non-paraneoplastic limbic encephalitis [2].

The involved infectious pathogens consist of herpes simplex virus, human herpes virus type 6 or 7, and other viruses. Although many neuroimaging studies on viral limbic encephalitis have been reported, how these viruses can invade the limbic system, which includes

* Corresponding author at: Department of Pediatrics, Asahi General Hospital, I-1326, Asahi-shi, Chiba 289-2511, Japan.

E-mail address: birukilat@gmail.com (K. Ibi).

regions such as the hippocampus, amygdala, and cingulate cortex, still remains unclear.

Recently, it has been emphasized that the rostral anterior cingulate cortex plays a critical role in psychiatric disorders. Altered activation the rostral anterior cingulate cortex has been reported to be critical as a neuronal mediator in children and adolescents with anxiety disorders [3]. The rostral anterior cingulate cortex is also supposed to be implicated in the pathogenesis of obsessive-compulsive disorder [4].

We herein report for the first time a case of non-paraneoplastic limbic encephalitis with involvement of the rostral anterior cingulate cortex as well as the frontal lobe white matter, associated with Cocksackie virus A10 infection.

2. Case report

A 5-year-old Japanese boy exhibited high fever, and was then admitted to our hospital because of status epileptics lasting 40 min. Soon after admission, with administration of diazepam (0.15 mg/kg, intravenously) he became alert and had no muscle weakness; thus, we diagnosed him with febrile seizure due to some viral infection. On day 5, he was discharged from the hospital, but his mother noticed he was gradually exhibiting hyperactivity and personality change. He was readmitted to our hospital on suspicion of encephalitis on day 6.

On admission, he was restless and always excited. He couldn't sit still, shouting and running here and there. He lost his short-term memory, vocabulary, and tenderness. He could only say hello to others, unable to discriminate between right and left, and he could not even perform easy calculations, which he correctly did when he was healthy. Interestingly, these manifestations changed day by day after the initial seizure (Fig. 1). Although he exhibited the above symptoms, he did not

show any other neurological deficits. He did not experience recurrent seizures, and remained alert. Blood examination yielded normal results. Cerebrospinal fluid examination also revealed all normal as cell numbers (3 cells/mm³), protein (35 mg/dL), glucose (91 mg/dL), and IgG-index (0.585). PCR test for herpes simplex virus in the cerebrospinal fluid was negative. Electroencephalography performed five hours after the seizure on day 1 (Fig. 2) showed slow waves in the frontal lobe, which returned to the normal state on day 14. Brain magnetic resonance imaging (MRI) performed on day 8 showed high-intensity lesions on diffusion-weighted image (DWI) and low value of apparent diffusion coefficient (ADC) mapping in the frontal lobe and rostral anterior cingulate cortex (Fig. 3). We didn't see any change in T2 signal intensity and fluid-attenuated inversion recovery imaging. We didn't perform other neuroimaging examinations. Titers of antibodies against Cocksackie virus A10 were elevated 1000 times on day 11, and 2000 times on day 29. GluRe2 antibodies in blood and cerebrospinal fluid were not elevated, and no tumors were found in the abdominal cavity during ultrasound examination.

Therefore, we finally diagnosed him with non-neoplastic limbic encephalitis due to Cocksackie virus A10 infection. We treated the patient with two courses of methylprednisolone (30 mg/kg of body weight), administered intravenously for three consecutive days. Subsequently, DWI and ADC signal intensity gradually disappeared in a time-dependent manner (Fig. 4). The patient gradually returned to his normal state without any neurological deficit. We performed “Kyoto Scale of Psychological Development 2001” test on day 38. Developmental quotient (DQ) was 84, in which Cognitive-Adaptive (C-A) domain was 85, and Language-Social (L-S), 82, respectively. He passed all the tests for Postual-Motor (P-M) domain. Sub-items of Kyoto Scale of Psychological Development 2001 test

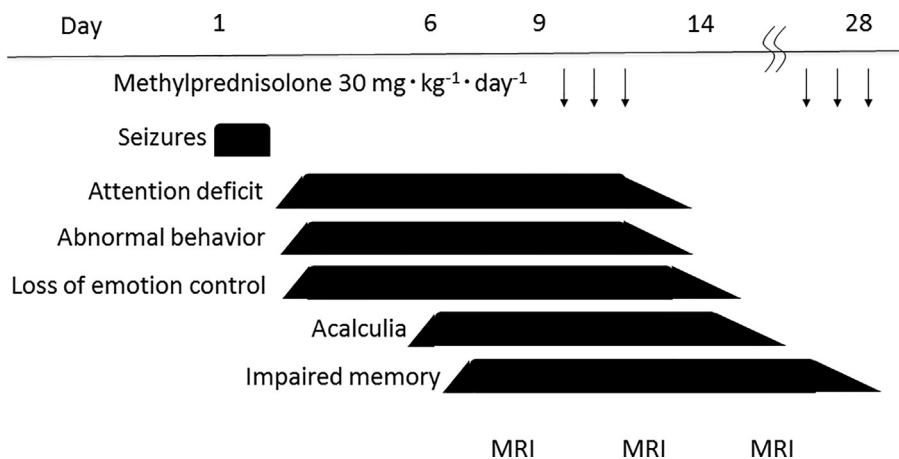


Fig. 1. Changes in clinical features of the patient in a time-dependent manner. Clinical manifestations have been demonstrated in a time-dependent manner.

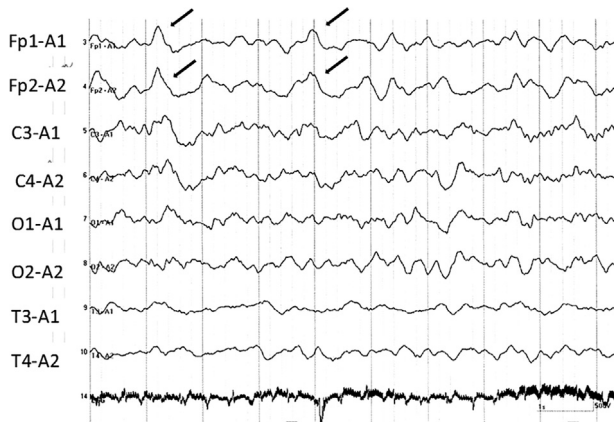


Fig. 2. Electroencephalography on day1. There were slow waves in the frontal lobe (arrows).

also showed that he could repeat four words, but not five, that he could correctly in the premorbid phase. He also could discriminate between right and left sides, which was impossible in the acute phase. The past intellectual levels were normal. Thus, current ones seem to be back to the past, without any neurological complication. Since he improved so well, he was able to go to the elementary school without any neurological complication.

We obtained informed consent from the patient and his parents for this report.

3. Discussion

We herein demonstrated for the first time involvement of the rostral anterior cingulate cortex as well as

the frontal lobe white matter in non-paraneoplastic limbic encephalitis. Since clinical manifestations included seizures on day 1 and attention deficit, abnormal behavior, loss of emotion control, acalculia, and loss of episodic memory and vocabulary in a time-dependent manner, we considered that Coxsackie virus A10 might have invaded the rostral anterior cingulate cortex from the frontal lobe.

It is often difficult to diagnose limbic encephalitis by the MR signal changes because transient restriction of diffusion in the patients with status epilepticus was occasionally observed. However, MR signal changes due to status epilepticus appear mainly in the cortical gray matter, subcortical white matter, and hippocampus [5,6]. Thus, we considered MR signal changes in our patient were caused by limbic encephalopathy.

The anterior cingulate cortex, located on the medial surface of the frontal lobes, usually plays an important role in attention, motivation, decision making, learning, and cost-benefit calculation, as well as conflict and error monitoring [7,8]. It is functionally divided into two portions, a dorsal portion for attention and a ventral one for memory [9]. Recently, rostral portion has been reported to play a critical role in pediatric anxiety and obsessive-compulsive disorders [3,4]. To the best of our knowledge, there are no reports on the continuous involvement of the rostral anterior cingulate cortex and the frontal lobe white matter in non-paraneoplastic limbic encephalitis. Thus, the observed changing clinical symptoms as well as the brain MRI and initial electroencephalographic findings obtained

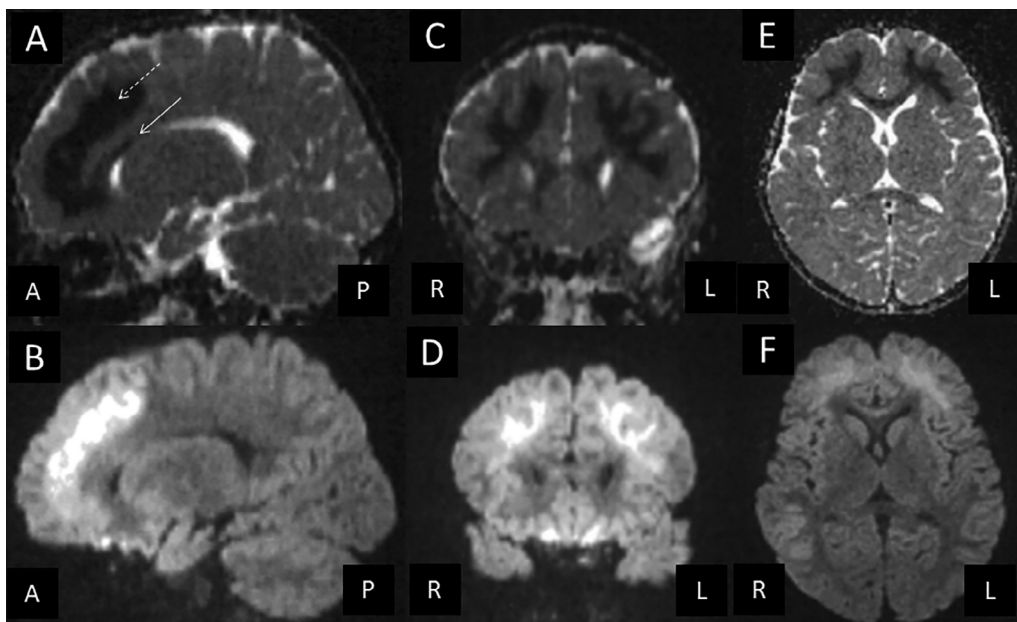


Fig. 3. Involvement of the anterior cingulate cortex and frontal lobe white matter. ADC maps (A, C, E) and diffusion-weighted images (B, D, F) on day 8 are shown in sagittal (A, B), coronal (C, D), and axial (E, F) views. The solid and dashed arrows indicate the rostral anterior cingulate cortex and frontal lobe white matter, respectively. R: right, L:left, A:anterior, P:posterior.

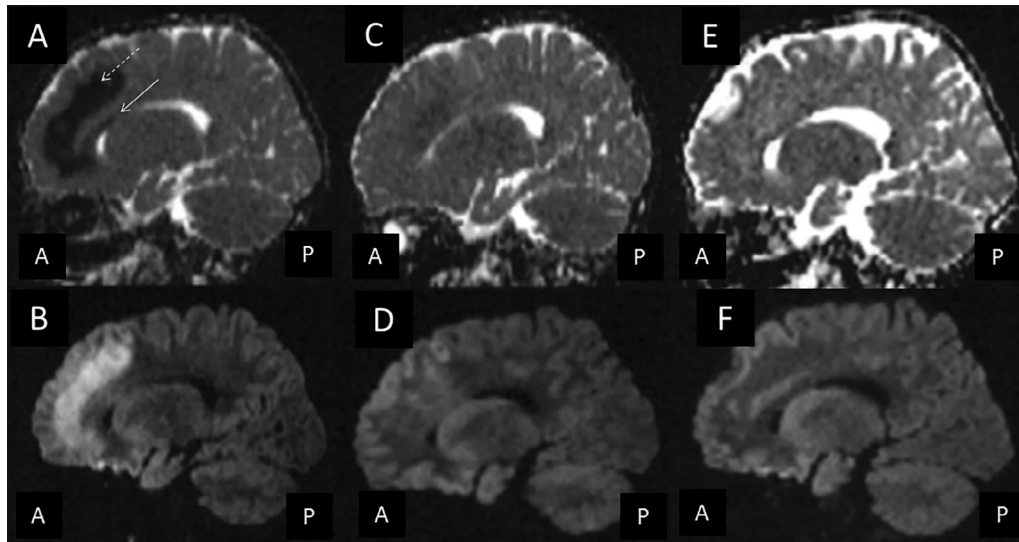


Fig. 4. Time-dependent changes in anterior cingulate cortex involvement. The DWI and ADC signals disappeared in a time-dependent manner, as shown by findings at days 8 (A, B), 11 (C, D), and 15 (E, F). The solid and dashed arrows indicate the rostral anterior cingulate cortex and frontal lobe white matter, respectively. A:anterior, P:posterior.

in this patient are useful to understand the role of the rostral anterior cingulate cortex in humans.

Brain MRI performed for non-paraneoplastic limbic encephalitis has widely been reported. Most studies report high signal in the mesial temporal lobes, either unilaterally or bilaterally, particularly on T2-weighted MRI or fluid-attenuated inversion recovery [10]. These lesions are usually demonstrated clearly by axial imaging; however, sagittal imaging is also useful, especially to demonstrate a lesion in the anterior cingulate cortex.

In this case, we assume that the patient first had damage to the frontal lobe, which then progressed to the limbic system. Upon observing the sagittal view of the ADC map, the route via which the damage had progressed through the brain was visually confirmed (Fig. 2). The hypothesis that arises from these MRI observations is that the sagittal view in both ADC map and DWI shows the inter-neuronal connection from the frontal lobe to the limbic system.

The limitations of this report are that the images shown here are not sufficiently clear and the possible explanation provided for the pathology was based on mere speculation. Furthermore, in our case, electroencephalography showed slow waves in the frontal lobe on day 1, but the slow waves disappeared on day 14. Although these slow waves might be from seizure itself, we considered it could be influenced by anterior cingulate cortex involvement in the encephalitis, which was clearly demonstrated in MRI. Although our hypothesis must be confirmed by additional studies with better MR imaging quality, the MRI data from the case reported here may reveal an approach to show the significance of the involved circuit in the limbic system.

This is the first report to show the involvement of the anterior cingulate cortex in non-paraneoplastic limbic encephalitis, being continuous with the involvement of the frontal lobe white matter. Clinical features such as seizures, attention deficit, loss of emotion control, and impaired memory suggest that this viral limbic encephalitis was possibly progressed from the frontal white matter to the anterior cingulate cortex via inter-neuronal connections in a time-dependent manner.

Acknowledgement

We thank many related co-medicals and the patient's family.

Funding

None.

References

- [1] Luu P, Posner MI. Anterior cingulate cortex regulation of sympathetic activity. *Brain* 2003;126:2119–20.
- [2] Pellkofer HL, Kuempfel T, Jacobson L, Vincent A, Derfuss T. Non-paraneoplastic limbic encephalitis associated with NMDAR and VGKC antibodies. *J Neurol Neurosurg Psychiatry* 2010;81:1407–8.
- [3] Swartz JR, Phan KL, Angstadt M, Klumpp H, Fitzgerald KD, Monk CS. Altered activation of the rostral anterior cingulate cortex in the context of emotional face distractors in children and adolescents with anxiety disorders. *Depress Anxiety* 2014;31:870–9.
- [4] Brennan BP, Tkachenko O, Schwab ZJ, Juelich RJ, Ryan EM, Athey AJ, et al. An examination of rostral anterior cingulate

- cortex function and neurochemistry in obsessive-compulsive disorder. *Neuropsychopharmacology* 2015;40:1866–76.
- [5] Kim JA, Chung JI, Yoon PH, Kim DI, Chung TS, Kim EJ, et al. Transient MR signal changes in patients with generalized tonic-clonic seizure or status epilepticus: periictal diffusion-weighted imaging. *Am J Neuroradiol* 2001;22:1149–60.
- [6] Amelia M, Luisa S. Brain magnetic resonance in status epilepticus: a focused review. *Seizure* 2016;38:63–7.
- [7] Apps MA, Rushworth MF, Chang SW. The anterior cingulate gyrus and social cognition: tracking the motivation of others. *Neuron* 2016;90:692–707.
- [8] Shenhav A, Botvinick MM, Cohen JD. The expected value of control: an integrative theory of anterior cingulate cortex function. *Neuron* 2013;79:217–40.
- [9] Stevens FL, Hurley RA, Taber KH. Anterior cingulate cortex: unique role in cognition and emotion. *J Neuropsychiatry Clin Neurosci* 2011;23:121–5.
- [10] Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: new developments and future challenges. *Lancet Neurol* 2011;10:759–72.