A Reversible Lesion of Corpus Callosum Splenium with Adult Influenza Associated Encephalopathy: a case report

En Kimura, MD, PhD; Sadahisa Okamoto, MD; Yuji Uchida, MD, PhD; Tomoo Hirahara, MD; Tokunori Ikeda, MD; Teruyuki Hirano, MD, PhD; Makoto Uchino MD, PhD.

Correspondence:

En Kimura M.D., Ph.D.

Author Affiliations:

Department of Neurology, Graduate School of Medical Sciences, Kumamoto University

1-1-1 Honjo, Kumamoto, 860-0811, Japan

TEL : +81-96-373-5893  FAX : +81-96-373-5895

E-mail  enkimura-ku@umin.net
ABSTRACT

An influenza virus associated encephalopathy is severe and poor prognoses in childhood. Adult case reports were still quite rare. Especially, none of them was presenting quite mild subcortical encephalopathy with reversible lesions of corpus callosum splenium.

A previously healthy 35-year-old man was affected by acute progressive tetraplegia, transcortical motor aphasia, and mild dullness of his consciousness soon after alleviation of high fever, while recovering a type A influenza virus receiving an Oseltamivir phosphate. The initial magnetic resonance imaging study at day 1 showed lesions in symmetrical diffuse white matter and on the central portion of corpus callosum splenium, which resolved on follow-up studies at day 8 and day 146. His neurological deficits mostly recovered within following 12 hours during a Methyl-predonisolone pulse therapy. The levels of Interleukin-6/-10 in his blood and cerebrospinal fluid were elevated, and rapidly decreased at day 8.

It is important for clinicians to recognize that, even in adulthood, the subcortical encephalopathy during a therapeutic process of Influenza type A infection can occur in conjunction with a reversible lesion of corpus callosum, which may recover quickly. In addition, cytokines storm in the blood system and corticospinal cavity may play an important role in this pathoetiolo.
Case presentation

The influenza virus associated encephalopathy (IAEE)[1-4] is known as severe and poor prognoses in especially childhood under the age of 5 years, such as an acute necrotizing encephalopathy, Reye's syndrome, hemorrhagic shock and encephalopathy, which are the typical dreaded and often fatal complications.[5, 6] Although the great effective improvement in therapeutic approaches, the rates of mortality (31.8 %) and disability (27.7 %) are still quite high. Recently, the number of patients with IAEE in childhood has increased in Japan.[3, 7] However, the adult case reports were still quite rare. Considering pathoepigenesis, the IAEE is suggested to be a pro-inflammatory cytokine-related disease.[8] The serum and CSF cytokines levels, especially IL-6 (interleukin-6), IL-10 (interleukin-10), and soluble TNF receptor 1 (sTNFR1), were markedly increased in most of severe IAEE cases. Moreover, in the therapeutic approaches, the anti-influenza therapies, such as a selective Neuraminidase inhibitor (Oseltamivir phosphate), corticosteroid pulse, and hypothermia, were quite effective to cure IAEE patients.[9] On the other hand, there are some reports demonstrating a variety of MRI findings of IAEE, especially pretty mild cases, such as two child patients recovered without any neurological deficit.[10] Those MR imaging presented a lesion in the central portion of the corpus callosum splenium that was quite similar
with this adult case. In addition, recently these reversible lesions caused by some
different pathoetiologies were reviewed.[11] The clinical features of those patients
were relatively mild CNS manifestations and complete recovery within 1 month.

Here we report a quite mild case of an adult IAEE who has recovered without any
neurological deficit. The complete flow-up study of MR imaging and the serum/CSF
cytokines assay are presented. His brain MR imaging finding reveals reversible lesion
of the central portion of his corpus callosum splenium.

A previously healthy 35 years old man got a type A influenza virus infection. He had a
high fever with mild painful throat, myalgia, and arthralgia of his whole body. He was
diagnosed an influenza type A infection with a positive signs of an influenza antigen
detection kit (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan) from his throat swab,
commonly used at outpatient clinics in Japan. He started taking a capsule of
Oseltamivir phosphate (100 mg/capsule × 3 times) within 24 hours from his beginning
of high fevers. The next day, he had an acute progressive tetraplegia, and transcortical
motor aphasia with mild dullness of his consciousness, then transferred to our
emergency room.

Initial MR imaging study at day1 (fig. 1a) showed lesions in whole white matter and
especially on the central portion of the corpus callosum splenium with slightly hyper intensity on T2-weighted, FLAIR, and markedly high signal intensity on diffusion-weighted images. These findings resolved completely on follow-up study at day 8 and day 146 (fig. 1b).

His cerebrospinal pressure was high (235 mmH$_2$O), but cytological and biochemical analysis of cerebrospinal fluid was within normal rages: number of cells was 3/3 mm$^3$, which were all monocytes, protein level was 30.6 g/dl, and glucose level was 67 mg/dl. Influenza genome was not detected by polymerase chain reaction (PCR) with specific primer pair in his CSF samples form both day1 and day8. Blood count showed mild thrombocytopenia (12.0 $\times$ 10$^4$ /ml) and leukopenia (2,500 /ml). Electroencephalography showed normal basic activity with no paroxysmal discharge. He was treated with Methyl-prednisolone pulse therapy (1,000 mg/day for 3 days). He got improved quickly. After 2-week-rehabilitations, he recovered fully and discharged on foot at day 24.

The levels of cytokine in his blood serum and CSF were assayed at the time point of pre- and post-treatment with Methyl-prednisolone, which methods were described previously.[8] In the blood serum, IL-6 and IL-10 were elevated at day 1 (pre-treatment) and decreased at day 8 (post-treatment). In the CSF, IL-6 levels were
remarkably high (19.6 pg/ml) at day 1 and got recovered at day 8 (Table 1 and supplemental data). The level of IL-6 and IL-10 in the serum and CSF was correlated with his clinical coarse.

We presented a case of adult IAEE with transient reversible CNS manifestations and MR imaging findings revealing reversible lesion of T2 prolongation and reduced diffusion in the central portion of his corpus callosum splenium. Actually, our first impression of this distinctive MR imaging was an ADEM, which is a first prior differential diagnosis. We decided a corticosteroid pulse as the first choice therapy. Those findings were rapidly disappeared while recovering with his clinical symptoms, although the lesion at white matter was recovered later and slowly.

Recently, two child cases of quiet mild IAEE with similar MRI findings were reported.[10] These patients developed symptoms soon after the onset of influenza and also quickly recovered completely without any functional defect. The mechanism of the reversible lesion of those cases was considered the transient intramyelinic edema. The over-released pre-inflammatory cytokines, such as IL-6,[3, 4, 8] might play an important role in the pathogenesis. Our cytokines assay supported this theory. At least the elevation of the IL-6 and IL-10 levels in his blood serum and CSF were
detected. An acute cytokine storm in blood stream and CSF cavity might trigger the vaso-dilatations following reversible vasogenic edema of myelin. In addition, similar MR findings in the central splenium of the corpus callosum have been reported[11] in some cases of infectious encephalitis/encephalopathy other than IAEE, such as rotavirus,[12] O-157 *Escherichia coli*,[13] and *Salmonella enteritidis*.[14] Nonetheless different causative agents in these reports, the clinical manifestations and MR findings were nearly identical to two child cases, and also this adult case.

Moreover, we discuss a possible effect of Oseltamivir phosphate. This selective Neuraminidase inhibitor might influence development of a pathological mechanism that was considered vasogenic edema followed by “cytokine storm”. It might assist to aggregate influenza virus particles on the surface of blood cells, endothelial cells, or maybe arachnoid cells. These aggregates might temporally stimulate to increase the releasing pro-inflammatory cytokines form those cells. Authors never complain the “risk” of taking the Oseltamivir phosphate. We have considered that early treatment with Oseltamivir phosphate were still useful to make his clinical symptoms milder than it should have been.

Finally, this case was diagnosed as a quite mild IAEE. An ADEM, other CNS disorders, or some side effects of therapeutic agents, all have been ruled out from his
final diagnosis. The cytokines storm in blood system and corticospinal cavity played an important role in this pathoetiology.

**Conclusions**

We have reported a quite mild adult IAEE case, with follow up MR imaging studies of an interesting reversible lesion at central splenium of the corpus callosum. The cytokines storm in blood system and corticospinal cavity played an important role in this pathoetiology.

**List of abbreviations**


**Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by
the Editor-in-Chief of this journal.

**Competing interests**

None declared.

**Authors' contributions**

EK was the primary physician/neurologist, conceived of the original study, organized and analyzed data, and prepared draft of the manuscript. SO, YU and TH were consulting neurologists, evaluated MRI data, assisted with manuscript editing, and contributed to the original idea of treating this patient with Methyl-prednisolone. TI performed clinical assessments. TH consulted on clinical evaluations and response to therapy. MU organized and analyzed data, helped write and edit, and wrote the final draft of the manuscript.

**Acknowledgements**

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secretarial assistance.

References


Figure 1

**MR imaging showed a transient signal in the central splenium of the corpus callosum.**

a) The MR imaging on day 1, T1 weight images, FLAIR images, T2 weight images, and DWIs. FLAIR images, T2WIs, and DWIs show lesions in the central splenium of the corpus callosum and symmetric bilateral white matter, but unclear in T1WI. b) The time course of MR imaging shows the lesions of corpus callosum had resolved on a FLAIR and T2WI at day 8. Following study on day 146 showed that all MRI findings of these lesions almost faded away.

Figure 2

*Clinical course and Cytokines shift*
Top, a clinical course of this case was shown. He had a high fever with mild painful throat, myalgia, and arthralgia. Soon after taking 3 capsules (300 mg) of Oseltamivir phosphate, fever had gone, but then followed by dullness of consciousness, transcortical motor aphasia, and tetraplegia, without sensory disturbance. During corticosteroid pulse therapy, all the neurological deficits were disappeared. Bottom, a graph shows the time course of IL-6 and IL-10 levels in his blood serum and CSF.

Table 1

The cytokine, especially IL-6 and IL-10, levels in CSF and serum significantly increased.

<table>
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<th>Post-treatment serum</th>
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</table>

Cytokine assay study of Blood serum and CSF at the time point of pre- and post-treatment with Methyl-prednisolone. In his serum, IL-6 and IL-10 were elevated at day 1 (pre-treatment) and decreased at day 8 (post-treatment). In his CSF, IL-6 levels were remarkably high (19.6 pg/ml) at day 1 and got recovered at day 8.
Figure 1 (a)

T1WI  FLAIR  T2WI  DWI

(b)

T2WI

FLAIR
day 1  day 8  day 146
Figure 2. Clinical course and cytokines

- Oseltamivir (75mg) total 3 cap (225 mg)
- Methylpredonisolone 1g x 3 day
- Rehabilitation

Neurological deficit

Fever

Clumsiness

Discharge

Back to work

Figure 2