

## Round-1

*Dear Reviewer,*

Thank you for your comments.

*We sincerely addressed the reviewer's comments as follows:*

1. The biggest issue in this paper is demonstrating correlation between encephalitis that occurred 23 years ago and current white matter abnormalities. Authors have provided little evidence that the encephalitis was the cause of the white matter abnormalities. It could have been due to any other infection or insult, for which the medical history may not be available. Please give as detailed a response as possible.
3. Was this patient in follow up by the authors for 23 years? How were day-7 (post-encephalitis) MRI images available?

*Answers:*

The patient was initially admitted to a local hospital with a high fever and headache 23-year ago. He developed neurological symptoms as mental change, visual disturbance, and weakness, according to medical history. The first MRI was conducted 7-day after onset. He was then transferred to a tertiary hospital to treat his symptoms and was diagnosed with scrub typhus encephalitis.

The patient visited our hospital to examine neurological sequelae. In our hospital, the first MRI was conducted at 2-year after onset. A neuroradiologist examined the MRI images and the copy of the day-7 MRI images that the patient has brought. It once again confirmed the previous diagnosis of scrub typhus encephalitis. We followed up the patient with MRI at 14- and 23-year after onset. Based on his medical history and the MRI findings, including diffusion tensor tractography, we were able to conclude the final diagnosis as an injury of the Papez circuit following scrub typhus encephalitis.

We agree that the direct correlation between encephalitis that occurred 23-year ago and current white matter abnormalities would be reinforced if we could provide the patient's initial medical documents 23-year ago, including laboratory findings and history of the eschar. However, it is beyond our scope because the medical record retention period has been terminated after ten years.

*We added the sentence in the history of present illness.*

He was diagnosed with encephalitis following scrub typhus 23 years ago. The patient complained of poor memory.

→ ~ of poor memory. **The patient was initially admitted to a local hospital with a high fever and headache 23-year ago. He developed neurological symptoms as mental change, visual disturbance, and weakness, according to medical history. The first MRI was conducted 7-day after onset. He was then transferred to a tertiary hospital to treat his symptoms and was confirmed as scrub typhus encephalitis.**

2. Institutional Review Board approval number MUST be put in manuscript in the methods section.

*Answer:*

We placed the Institutional Review Board approval number in the methods section. Our study was approved by the Institutional Review Board (No. 2018-06-010).

*We added the word in the history of present illness.*

→ *Imaging examinations*

This study was approved by the Institutional Review Board of \*\* \*\* and written informed consent was obtained from the patient for the publication of this manuscript (**No. 2018-06-010**).

*Additionally, we revised parts of the manuscript as follows.*

three dimensionally → three-dimensionally

1. Abstract

1-1. The Core tip of the abstract:

Diffusion tensor tractography allow us to investigate the integrity of white matter (WM) three dimensionally. ~ Using a diffusion tensor tractography, we confirmed injury of the Papez circuit in a patient who have suffered from cognitive impairment following encephalitis of scrub typhus 23 year ago.

→ Diffusion tensor **tractography** allows us to investigate the integrity of white matter (WM)

**three-dimensionally**. ~ Using a diffusion tensor tractography, we confirmed **the** injury of the Papez circuit in a patient who **has** suffered from cognitive impairment following encephalitis of scrub typhus 23 **years** ago.

## 2. Method:

### 2-1. *Imaging examinations of the method*

To reconstruct the Papez circuit, the following were locations were considered as the regions of interest (ROIs)

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### 2-2. Legend of figure:

Compared with the findings of the 7-day MRI, the results of MRI performed 23 years ago indicate expanded lesions of encephalomalacic changes with marked dilated of both ventricles.

→ Compared with the findings of the 7-day MRI, the results of MRI performed 23 years ago indicate expanded lesions of **encephalomalacic** changes with marked dilated of both ventricles.

## 3. The Discussion:

3-1. In our case, relative to the initial MRI findings, we found expanded medial temporal lesion in the follow-up MRI.

→ In our case, relative to the initial MRI findings, we found **an** expanded medial temporal lesion in the follow-up MRI.

## **Round-2**

*Dear Reviewer,*

Thank you for your comments.

*We sincerely addressed the reviewer's comments as follows:*

Reviewer #1: I had provided several comments previously. The authors have responded to

many of the comments but they have not provided conclusive evidence linking the initial episode 23 years ago and Papez Circuit Injury, as they themselves acknowledge. In the absence of definite evidence, the title of the article is highly misleading. Please change it to: Association between Scrub Typhus Encephalitis and Diffusion Tensor Tractography Detection of Papez Circuit Injury: A Case Report. Similarly, please make the appropriate changes throughout the text that reaffirm that absolute confirmation is not possible, but it may be due to encephalitis. In the absence of evidence, it would be scientific misconduct to claim otherwise. Please use guarded language as your manuscript stands on very shaky grounds. Using language that you "confirmed the injury" is inappropriate.

1. In the absence of definite evidence, the title of the article is highly misleading. Please change it to: Association between Scrub Typhus Encephalitis and Diffusion Tensor Tractography Detection of Papez Circuit Injury: A Case Report

**We changed the title of our manuscript as follow.**

Injury of the Papez Circuit Following Scrub Typhus Encephalitis Detected Using Diffusion Tensor Tractography: A Case Report

→ Association between Scrub Typhus Encephalitis and Diffusion Tensor Tractography Detection of Papez Circuit Injury: A Case Report

2. Similarly, please make the appropriate changes throughout the text that reaffirm that absolute confirmation is not possible, but it may be due to encephalitis. In the absence of evidence, it would be scientific misconduct to claim otherwise. Please use guarded language as your manuscript stands on very shaky grounds. Using language that you "confirmed the injury" is inappropriate.

**We revised our manuscript as follow.**

**1. Abstract**

BACKGROUND

We aimed to report herein, for the first time, diffusion tensor tractography (DTT) findings in a chronic patient with cognitive impairment following scrub typhus encephalitis, which revealed injury to the Papez circuit of the WM.

→**For the first time, we aimed to report** diffusion tensor tractography (DTT) findings in a chronic patient with cognitive impairment following scrub typhus encephalitis, which revealed injury to the Papez circuit of the WM.

#### CASE SUMMARY

~ Mini-Mental Status Examination score, 14; and grip strength (right/Left [kg]), 32.3/31.3.

→Mini-Mental Status Examination score, 14; and **handgrip** strength (right/**left** [kg]), 32.3/31.3.

**Core tip:** The Papez circuit consists of mainly white matter and is known play a critical role of cognition. Using a diffusion tensor tractography, we confirmed the injury of the Papez circuit in a patient who has suffered from cognitive impairment following encephalitis of scrub typhus 23 years ago.

→ The Papez circuit consists **mainly** of **the** white matter and is known **to** play a critical role **in** cognition. Using a diffusion tensor tractography, we **detected** the injury of the Papez circuit in a patient **with** cognitive impairment following encephalitis of scrub typhus **23-year** ago.

## 2. INTRODUCTION

Recently, studies have reported that diffusion tensor tractography (DTT), derived from diffusion tensor imaging (DTI), has the capacity to visualize neural tracts, including the Papez circuit, three-dimensionally [7-9].

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## CASE PRESENTATION

### *History of present illness*

He was then transferred to a tertiary hospital to treat his symptoms and was confirmed as scrub typhus encephalitis.

→ He was then transferred to a tertiary hospital to treat his symptoms, **and the** diagnosis of scrub typhus encephalitis **was confirmed.**

### *Personal and family history*

No special previous medical history was reported.

→ No special personal and **family histories were found.**

### *Physical examination*

Physical examination showed narrow visual fields; however, he could read books and newspapers. His motor power on both extremities was intact without any pain. But fine movements of ~.

→ Physical examination **revealed** narrow visual fields; however, he could read books and newspapers. His motor power on both extremities was intact without any pain.

### *Laboratory examinations*

~ as follows: grip strength (right/Left [kg]): 32.3/31.3; two-point discrimination test (right/Left [mm]): and 5/absence; monofilament test (right/Left [mm]): 3.22/absence.

-- as follows: handgrip strength (right/**left** [kg]), 32.3/31.3; two-point discrimination test (right/**left** [mm]), 5/absence; **and** monofilament test (right/**left** [mm]),3.22/absence.

### *Imaging examinations*

This study was approved by the Institutional Review Board of \*\* \*\*

→This study was approved by the **institutional review board of Ulsan University Hospital,**

~ as the regions of interest (ROIs)<sup>[6]</sup>: the thalamocortical tract–cingulate gyrus (seed ROI), anterior limb of internal capsule (target ROI 1) and the anterior thalamic nuclei (target ROI 2)~

→ as the regions of interest (ROIs)<sup>[6]</sup>: the thalamocortical tract–cingulate gyrus (seed ROI), **the** anterior limb of **the** internal capsule (target ROI 1) ~

~ the mammillothalamic tract–anterior thalamic nucleus (seed ROI) and the portion of isolated mammillothalamic tract (target ROI 1),

→ the mammillothalamic tract–anterior thalamic nucleus (seed ROI) and the portion of **the** isolated mammillothalamic tract (target ROI 1),

the cingulum–middle portion of the cingulum (seed ROI) and the posterior portion of the cingulum (target ROI) on coronal images.

→ the cingulum–**the** middle portion of the cingulum (seed ROI) and **the** posterior portion of the cingulum (target ROI) on coronal images.

(Figure 1A). Probabilistic DTT of the Papez circuit revealed that the left thalamocortical tract and the right mammillothalamic tract could not be reconstructed;

→(Figure 1A). Probabilistic DTT of the Papez circuit revealed that the left thalamocortical tract and **right** mammillothalamic tract could not be reconstructed;

## DISCUSSION

In this study, using DTT, we found that cognitive impairments in a chronic patient with encephalitis of scrub typhus were strongly associated with injury of the Papez circuit.

→ In this study, using DTT, we found that cognitive impairments in a chronic patient with encephalitis of scrub typhus were strongly associated with **Papez circuit injury**.

It has been debated since a long time~

→ It has been debated **for** a long time~

Only two cases studies of scrub typhus encephalitis have reported abnormal findings on MRI that were indicative of deep WM involvement [12,13].

→ Only two **case** studies of scrub typhus encephalitis **had** abnormal **MRI findings** indicative of deep WM involvement [12,13].

Using DTT, this study findings exclusively confirms injury of two major WM areas –

→ Using DTT, our study findings exclusively **detect** the injury **in** two major WM areas –

This finding suggests the possibility of a secondary Wallerian degeneration of the Papez circuit, following the direct WM lesions, although we could not perform follow-up DTT to confirm this possibility.

→ This finding suggests the possibility of a secondary Wallerian degeneration of the Papez circuit, following the direct **WM lesions. However**, we could not perform follow-up DTT to confirm this possibility.

~ [14-16]. Using DTT, these studies showed complete Wallerian degeneration of the fornix and cingulum within 2-4 mo postoperatively.

→ ~ [14-16]. Using DTT, these studies showed complete Wallerian degeneration of the fornix and cingulum within 2-4 **months** postoperatively.

~ via interhemispheric components[15,16].

→ ~ *via* **the** interhemispheric components[15,16].

~ following encephalitis, concomitant injuries of the thalamocortical tract, mammillothalamic tract, and fornix were demonstrated, along with serial cognitive impairment.

→ ~ following encephalitis, concomitant injuries of the thalamocortical tract, mammillothalamic tract, and fornix were demonstrated, along with **severe** cognitive

impairment.

Regarding cognition following encephalitis, a 3.7-year follow-up study reported only a 12.8% frequency of dementia<sup>[18]</sup>. However, these findings have limited application to our patient,

→ Regarding cognition following encephalitis, a 3.7-year follow-up study reported only a 12.8% **incidence** of dementia<sup>[18]</sup>. However, these findings have limited application **in** our patient,

By reconstructing the CST using DTT data, we found relative preservation of the both the CSTs. Overall, we simultaneously analyzed the relation between the integrity of the Papez circuit and CST and the neurological manifestations~.

→ By reconstructing the CST using DTT data, we found relative preservation **of both CSTs**. Overall, we simultaneously analyzed the **relationship** between the integrity of the Papez circuit and CST, and the neurological manifestations ~.

~, which might aid the development of rehabilitative strategies for restoring function and normal activities of daily of life after brain injury.

→ ~, which might **help develop** rehabilitative strategies for restoring function and normal activities of **daily life** after brain injury.

## TREATMENT

not applicable. → Not applicable

## OUTCOME AND FOLLOW-UP

not applicable. → Not applicable

## **Figure Legends**

Figure 1 (A). Initial and follow-up magnetic resonance imaging (MRI) shows multiple lesions in the parietal, temporal, and occipital lobe of both hemispheres. Compared with the findings of the 7-day MRI, the results of MRI performed 23 years ago indicate expanded lesions of encephalomalacic changes with marked dilated of both ventricles. Figure 1 (B). Diffusion

tensor tractography of the Papez circuit and corticospinal tract (CST). In the Papez circuit, the left thalamocortical tract and right mammillothalamic tract show destruction (yellow arrows). In addition, the anterior part of the fornix shows injury (purple arrows). Both CSTs of both the hemispheres appear relatively intact.

→**Figure 1 Serial magnetic resonance imaging and diffusion tensor tractography of a chronic patient with cognitive impairment after scrub typhus encephalitis.** A: **Magnetic resonance imaging shows** multiple lesions in the parietal, temporal **and** occipital **lobes** of both hemispheres. Compared with the findings of the 7-day MRI, **the 23-year MRI findings** indicates expanded lesions of encephalomalacic changes with marked **dilation** of both ventricles; B: Diffusion tensor tractography of the Papez circuit and corticospinal tract (CST) **reveals discontinued of** the left thalamocortical and right **mammillothalamic tracts in** the Papez circuit (yellow arrows). In addition, the anterior part of the fornix **is not observed in both hemispheres** (purple arrows). **The CSTs of both hemispheres appear** relatively i