Case Report: Late-Onset Temporal Lobe Epilepsy Following Subarachnoid Hemorrhage: An Interplay Between Pre-existing Cortical Development Abnormality and Tissue Damage

Anna Ikawa1,2, Ayataka Fujimoto1,2*, Yoshifumi Arai3, Yoshiro Otsuki3, Toshiki Nozaki1, Shimpei Baba1, Keishiro Sato1 and Hideo Enoki1

1 Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan, 2 Department of Neurosurgery, Seirei Hamamatsu General Hospital, Hamamatsu, Japan, 3 Department of Pathology, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

Epileptogenicity following brain insult depends on various factors including severity of the resulting lesion and extent of brain damage. We report a 54-year-old female patient who developed medically refractory epilepsy resulting from the interplay of pre-existing and post-insult pathologies. She presented with subarachnoid hemorrhage (SAH) due to a ruptured aneurysm and underwent clipping surgery. Seizures started 3 months post-operatively. MRI revealed cerebral ischemia and hemosiderin deposits in the left temporal lobes, and left hippocampal atrophy was suspected. As anti-seizure medications and vagus nerve stimulation failed to control her seizures, she underwent left temporal lobe resection and placement of a ventriculoperitoneal shunt for the post-operative complication of hydrocephalus. She remains seizure-free to date. Neuropathology revealed a previously undiagnosed focal cortical dysplasia (FCD) type 1a. Brain insult likely had a second hit effect in the late onset of epilepsy in this patient with pre-existing mild MCD, in whom secondary epilepsy can be attributed to the interplay of multiple underlying pathologies.

Keywords: case report, epileptogenicity, parenchymal hemosiderosis, hippocampal atrophy, malformation of cortical development, multiple pathology

HIGHLIGHTS
- Pre-existing and post-insult pathologies induced epileptogenicity
- Late-onset medically refractory epilepsy with undiagnosed FCD

BACKGROUND
Parenchymal hemosiderosis is a risk factor for focal epilepsy after intracerebral bleeding (1, 2). Epileptogenicity due to hemosiderosis is well-known and can be related to cavernous malformation (3), brain tumor (4), or intracranial hemorrhage (5, 6). The mechanism of epileptogenicity due to...
hemosideros includes abnormalities in neurotransmission and free radical formation (7).

In neuropathology of temporal lobe epilepsy, epileptogenicity has been attributed to various lesions including hippocampal sclerosis, malformation of cortical development (focal cortical dysplasia—FCD)—and gray matter heterotopias), as well low-grade tumors (8, 9).

In daily practice, acute or remote damage resulting from a previous insult is considered as the sole cause of epileptogenicity. As many patients do not require surgery, information on etiology derives solely from magnetic resonance imaging (MRI). However, many pre-existing and yet undiagnosed factors as well as complications from an acute insult can impact the establishment of an epilepsy network by affecting the neurotransmitter system and intracellular and extracellular homeostasis. Indeed, it is common clinical experience that some patients develop epilepsy following an insult and others do not, even though they have the same degree of brain damage.

We have previously identified the presence of an underlying FCD as a significant factor associated with epilepsy in patients who developed post-traumatic epilepsy following severe head trauma (10). We postulated that multifactorial mechanisms might be involved in epileptogenicity following an insult, and this further applies to patients with chronic seizures following subarachnoid hemorrhage (SAH).

Here, we describe the management of a patient who developed epilepsy and who initially presented for medical care due to a ruptured aneurysmal SAH. In addition to multiple complications due to her SAH (which included acute ischemic stroke with hemorrhagic transformation, hemosiderosis and hydrocephalus), her seizures became medically refractory and warranted resection surgery, leading to the discovery of a previously unknown area suggestive of FCD type 1a.

**CASE PRESENTATION**

A 54-year-old right-handed female was evaluated at the Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital (Hamamatsu, Japan) due to medically refractory weekly epileptic seizures.

Past medical history was relevant for a SAH due to a ruptured left middle cerebral artery aneurysm and status post-aneurysm clipping 11 months prior. Her clinical evolution during acute care was complicated by a hemorrhagic cerebral infarction in the left temporal lobes due to symptomatic cerebral vasospasm.

Focal aware and unaware seizures started 3 months after the surgery. Seizure semiology consisted of an epigastric sensation followed by aphasia and then loss of awareness, with occasional focal to bilateral tonic-clonic seizures. The electroencephalogram (EEG) showed interictal epileptiform discharges over the left fronto-temporal region, in keeping with topography of the fronto-temporal area.

Levetiracetam, Zonisamide, Valproic acid, and Lamotrigine did not control her seizures, thus fulfilling criteria for drug-resistant seizures (11, 12). The patient was considered a candidate for surgical intervention and was offered the option of either resection surgery or vagus nerve stimulation (VNS). In view of focal aware seizures, the possibility of effective application of the magnet at the onset of seizures to abort their progression was preferred by the patient and her family. Therefore, she underwent VNS implantation at the age of 55-years and 3 months. VNS reduced her seizure intensity and frequency from weekly to monthly, and aiming at seizure freedom, the patient thereafter elected to undergo resection surgery.

Pre-surgical evaluation included MRI, 2-\[^{18}\text{F}\]\text{fluoro-2-deoxy-D-glucose (\[^{18}\text{FDG}\]-PET), and video EEG monitoring (VEEG). MRI showed T2 signal hyperintensity lesions in the frontal and temporal lobes, with hemosiderin deposits in the temporal area, as well as severe left hippocampal atrophy. \[^{18}\text{FDG}\]-PET showed hypometabolism in the left frontal and temporal lobe (Figure 1). VEEG captured her habitual seizures with loss of awareness preceded by an epigastric sensation and aphasia, arising electrographically from the left fronto-temporal area.

Based on the comprehensive pre-surgical evaluation, we hypothesized that her seizures were consistent with mesial temporal lobe epilepsy with a generator in the mesial temporal lobe structures from her dominant hemisphere, and we performed Spencer’s anteromedial temporal lobectomy (a left hippocampal and amygdala resection with a temporal lobectomy from the middle temporal gyrus) (13, 14) at age 56. Surgery was complicated by subacute hydrocephalus at post-operative week 1, and she underwent ventriculoperitoneal shunting. She has remained seizure-free for more than 2-years, and remains on Levetiracetam monotherapy.

Neuropathology revealed a small number of ectopic neurons in the white matter of the temporal lobe, as well as satellite oligogenesis growth, suggestive of FCD type 1a (Figure 2). Despite MRI evidence of hippocampal atrophy, the hippocampal specimen showed no neuronal loss or gliosis in CA sectors or in the dentate gyrus, and thus, no neuropathological diagnosis of hippocampal sclerosis could be confirmed.

**DISCUSSION**

In this patient, her late-onset epilepsy was at first attributed to prior SAH complicated with left frontal and temporal ischemic stroke with hemorrhagic transformation due to severe vasospasm. However, upon development of drug resistance and partial response to VNS, a full work-up for possible resection surgery, including resection of a generator in the mesial temporal structures, was postulated based on MRI signs that indicated hippocampal atrophy. Although hippocampal pathology did not confirm the presence of hippocampal sclerosis, the decision for resection surgery as the next step in this patient’s management revealed FCD 1a in the temporal neocortex. This pre-existing and not yet diagnosed epileptogenic lesion could play a role in the development of epilepsy in this patient, as not all

Abbreviations: EEG, electroencephalogram; \[^{18}\text{FDG}\], 2-\[^{18}\text{F}\]\text{fluoro-2-deoxy-D-glucose; MCD, malformation of cortical development; MRI, magnetic resonance imaging; PET, positron emission tomography; SAH, subarachnoid hemorrhage; VEEG, video electroencephalogram; VNS, vagus nerve stimulation.}
Many patients, like ours, will present with recurrent seizures that develop following the diagnosis of an insult, such as stroke, head trauma, or tumors (15–21). The current use of terms such as “post-stroke epilepsy,” “post-traumatic epilepsy,” and “brain tumor-related epilepsy” can guide our management decisions and allows us to provide patients and families an overview of the predicted outcome. However, the interplay with other underlying known and unknown neuropathological factors might lead to unexpected directions, and attention needs to be paid to patients with rather poor clinical evolution.

An imbalance between excitatory and inhibitory neurotransmission causing epileptic seizures (22–24) is a common mechanism in the various etiologies of epilepsy. It is however possible that even in the presence of a highly epileptogenic brain lesion such as FCD, epileptogenicity and clinically manifested seizures in some patients only occur after a second hit/insult. Indeed, the “two-hit theory” (25) or “multiple-hit theory” (26) may explain this situation (27, 28). In our patient, seizures became controlled after resection surgery, including resection of the cortical malformation and of areas bearing hemosiderin deposits.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by Submission of this case report was approved by the ethics review board at Seirei Hamamatsu General Hospital, and
written informed consent was obtained from the patient. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception, validation, design, acquisition of data, or analysis and interpretation of data.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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