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Visualizing epileptogenic regions using the chemical exchange saturation transfer method in a patient with drug-resistant focal epilepsy: a case report

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Abstract

Background Sustained elevations in extracellular glutamate levels within astrocytes may precipitate epileptic seizures. In this report, chemical exchange saturation transfer imaging was used to measure brain glutamate concentrations in a patient who underwent focal resection surgery.

Case presentation A male Japanese patient in his 30s with drug-resistant focal epilepsy underwent preoperative assessment at our institute. Preoperative magnetic resonance imaging was performed using an ultra-high-field magnetic resonance imaging system. The results of intracranial electroencephalography and chemical exchange saturation transfer imaging were compared.

Head magnetic resonance imaging revealed no abnormalities. However, fluorodeoxyglucose-positron emission tomography revealed reduced glucose metabolism in the distal left temporal lobe. Preoperative fluorodeoxyglucose-positron emission tomography and intracranial electroencephalography indicated abnormal interictal waves and identified the seizure onset site. Ablation was performed from the distal to the basal region of the temporal lobe. Pathological examination revealed focal cortical dysplasia type IIa. Chemical exchange saturation transfer imaging delineated an elevated glutamate concentration extending from the distal tip of the left temporal lobe to the medial temporal lobe. These regions included the areas of seizure onset identified by intracranial electroencephalography and matched the extent of the resection surgery. Four months postoperatively, focal aware seizures recurred; however, no focal impaired awareness seizures were observed at 1 year postoperatively. Elevated glutamate levels were detected in the hippocampus head, suspected to be associated with residual focal aware seizures.

Conclusion Glutamate-chemical exchange saturation transfer magnetic resonance imaging was used to non-invasively measure brain glutamate concentrations, providing new insights into identifying epileptogenic zones when conventional imaging techniques fail.

Keywords Chemical exchange saturation transfer, Focal resection surgery, Drug-resistant epilepsy, Temporal lobe epilepsy, Case report

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Background

According to the World Health Organization's 2010 Global Burden of Disease Study, epilepsy ranks as the second most burdensome neurological disease in terms of disability-adjusted life years [1]. In such cases, surgical intervention is often the only viable option for seizure control.

Epilepsy surgery aims to alleviate epileptic seizures by completely removing the epileptogenic area causing the seizures [2]. Localization of the epileptogenic zone is currently on the basis of the convergence of clinical results, interictal/interictal electroencephalography (EEG), and imaging techniques. However, if the estimated epileptogenic zone does not align with the actual seizure focus, surgical efficacy may be compromised.

Sustained elevations in extracellular glutamate (Glu) levels within astrocytes can precipitate epileptic seizures [3–6]. This phenomenon is attributed to diminished glutamine synthetase activity and reduced Glu transporter expression in astrocytes [7–9].

Glu-chemical exchange saturation transfer (CEST) is a magnetic resonance imaging (MRI) technique that noninvasively visualizes Glu concentrations in the brain [10].

Anatomical MRI fails to reveal epileptogenic lesions in 20–40% of patients eligible for surgery [11]. Therefore, Glu-CEST may be valuable for localizing seizure foci in MRI-negative epilepsy.

In this report, we delineated the epileptogenic zone by quantifying Glu using the CEST method with an ultrahigh field (UHF) MRI system. This report explores the potential of CEST imaging for visualizing epileptogenic regions in a patient with drug-resistant focal epilepsy, presenting an innovative approach to enhancing preoperative assessments.

Arterial spin labeling (ASL) and the morphometric analysis program have been reported as being useful for diagnosing MRI-negative epilepsy. However, we propose that Glu-CEST MRI, which directly evaluates Glu levels, may offer superior diagnostic value for identifying the epileptogenic origin [12, 13].

This paper is the first to report the use of Glu-CEST MRI to noninvasively measure brain Glu concentrations, providing novel insights into identifying epileptogenic zones when conventional imaging techniques fail.

Case presentation

Patient details and presentation

A male Japanese patient in their 30s developed epilepsy in 2017, initially attributed to behavioral anomalies during sleep. Focal epilepsy was diagnosed and controlled with levetiracetam 1500 mg and clonazepam 1 mg until 2019. However, in 2021, the patient began experiencing focal impaired awareness seizures. Owing to the occurrence of seizures approximately once per month, the patient was referred to the epilepsy department of our hospital. These seizures involved loss of consciousness following "déjà vu" sensations. At the time of referral, the patient was on four antiepileptic drugs: levetiracetam, 1500 mg; lacosamide, 300 mg; perampanel, 2 mg; and clonazepam, 1 mg. Despite using multiple antiepileptic drugs with different mechanisms of action, seizure suppression remained suboptimal, leading to the decision to implement a surgical approach. The detailed progress is summarized in Table 1.

Glu-CEST MRI

Pre-surgery MRI was performed using a UHF (7 Tesla) MRI system (MR950; GE Healthcare, Chicago, IL, USA) with a 32-channel head coil (Nova Medical,

Table 1 Summary of progress

Preoperative course	2017: onset of seizure symptoms with behavioral abnormalities during sleep 2018: start of LEV 2019: seizures suppressed by adding CZP 2021: the patient was referred to our hospital because his seizures were not controlled despite the addition of CZP, LCM, and PER
Test results	Electroencephalography: spiny waves were observed in the bilateral antero-medial temporal regions It was difficult to identify the starting point from EEG findings during seizure Head MRI: no obvious abnormal findings. No hippocampal sclerosis or atrophy FDG-PET: hypoglycemia in the left anterolateral temporal region
Surgery	Intracranial electrode implantation: subdural electrodes were implanted in the lateral and medial left temporal lobe, and in the frontal lobe. Intracranial electrodes were placed in the lateral and medial left temporal lobe, and frontal lobe. Intracranial EEG during seizure showed repeated spikes in the temporal pole followed by propagation to the lateral temporal lobe Focal resection: resection of the left lateral temporal lobe, including the temporal pole, was performed. Intraoperative hippocampal wave recordings showed a low frequency of spikes, so the hippocampus was preserved
Post-surgery	Four months postoperatively, FAS recurred. One year after surgery, FIAS disappeared

LEV, levetiracetam; LCM, lacosamide; PER, perampanel; CZP, cronazepam; EEG, electroencephalography; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose-positron emission tomography; FAS, focal aware seizures; FIAS, focal impaired awareness seizures

Houston, TX, USA) at the Center for Integrated Brain Function Research, Niigata University Brain Research Institute. T_1-weighted three-dimensional magnetization-prepared rapid acquisition gradient echo scans were acquired with the following parameters: field of view = 220 × 220 mm^2, matrix = 220 × 220, repetition time/echo time = 4.1/1.4 ms, flip angle = 4°, and slice thickness = 1 mm.

On the basis of the three-dimensional T_1 data, the CEST image slice was determined. CEST images were corrected for the B_0 field distribution using water saturation acquisition [14]. To correct for B_1 inhomogeneity, we followed the method of Cember *et al*. which leverages classification based on T_1 values and a measured effective B_1 irradiation pulse intensity distribution map to enhance CEST imaging [15]. A single-slice CEST image sequence based on fast spin echo was then acquired with the following parameters: field of view = 220 × 220 mm^2, matrix = 128 × 128, repetition time/echo time = 10,000/5.8 ms, flip angle = 70°, and slice thickness = 4 mm. CEST imaging was conducted using a pulsed CEST preparation of eight sinc pulses of 100 ms each with a 10 ms interpulse delay (total saturation time of 800 ms) and a root mean square (RMS) amplitude of 3.0 μT. A total of 31 frequencies were acquired, each spaced by 100 Hz, ranging from −1500 to +1500 Hz.

B_0 and B_1 corrected CEST images were used to calculate the Glu-CEST MRI using the following equation:, where S (−3.0 ppm) denotes the signal intensity after the saturation pulse with an offset of −3.0 ppm from the water peak, and S (+3.0 ppm) represents the signal intensity after the saturation pulse with an offset of +3.0 ppm from the water peak. Glutamate exhibits a CEST effect at approximately +3.0 ppm downfield from the bulk water resonance [16].

$$Glu - CESTMRI = (S(-3.0ppm) - S(+3.0ppm))/S(-3.0ppm),$$

Observations

The patient exhibited no obvious paralysis, sensory disturbances, or other abnormal neurological findings. In addition, there was no history of cerebrovascular or cardiovascular disease that could have contributed to loss of consciousness.

Interictal EEG revealed sharp waves localized at F7 and F8, although seizure recordings failed to demonstrate a distinct onset pattern. MRI revealed no evident abnormalities, while magnetoencephalography identified a cluster of dipoles within the left insular cortex. Fluorodeoxyglucose-positron emission tomography (FDG-PET) indicated reduced glucose metabolism in the left temporal pole. Neuropsychological testing showed normal intellectual and memory functions.

All tests were performed without administering sedatives or other medications. FDG-PET was performed after the patient fasted for at least 6 hours. These tests were performed 1 year before surgery.

On the basis of the findings, epileptogenic regions were suspected within the left frontal and temporal lobes. However, the precise focus could not be determined, making it difficult to differentiate between medial and lateral lobe epilepsy. Consequently, intracranial subdural electrodes were implanted in the lateral and basal regions of the left frontal lobe, the lateral aspect of the left temporal lobe, and the medial temporal lobe. Interictal intracranial EEG revealed discrete spikes from the basal left temporal lobe, anterior to the left parahippocampal gyrus, and from the lateral aspect of the left temporal lobe. During three recorded intracranial EEG seizures, a pronounced spike was identified in electrodes located between the distal portion of the left temporal lobe and the parahippocampal gyrus, followed by propagation to the lateral temporal cortex (Fig. 1A). Subsequently, anterior temporal lobectomy was performed, encompassing the distal tip of the left temporal lobe, the basal region, and the middle and inferior temporal gyri (Fig. 1D and E). Intraoperative EEG recordings from the surface of the amygdala and hippocampus revealed no discernible spikes from the amygdala, with sporadic low-frequency spikes detected in the posterior aspect of the hippocampus. Therefore, the language-dominant hippocampus and amygdala were preserved to prevent postoperative verbal memory loss.

Postoperative MRI indicated no obvious neurological deficits (Fig. 1E). Focal aware seizures (FAS) recurred 4 months postoperatively; however, no focal impaired awareness seizures were observed 1 year postoperatively. During evaluation 1 year after surgery, the patient was classified as Engel Class Ib. There were no postoperative neurological abnormalities, and psychological tests showed no deterioration.

Glu-CEST MRI was performed the day before intracranial EEG electrode placement. It delineated an elevation in glutamate concentration extending from the left temporal pole to the medial temporal lobe. Subsequently, a 1 × 8 strip electrode was positioned in the corresponding area, revealing a prominent spike in EEG activity at seizure onset from the electrode proximate to the region with heightened Glu concentration (Fig. 1A–C). The region exhibiting increased Glu concentration, as identified by Glu-CEST MRI, was encompassed within the resection area (Fig. 1D and E). Histopathological examination of the resected tissue revealed focal cortical dysplasia type IIa (FCD type IIa).

FCD type IIa causes drug-resistant epilepsy and is characterized by histopathologic findings of dysmorphic

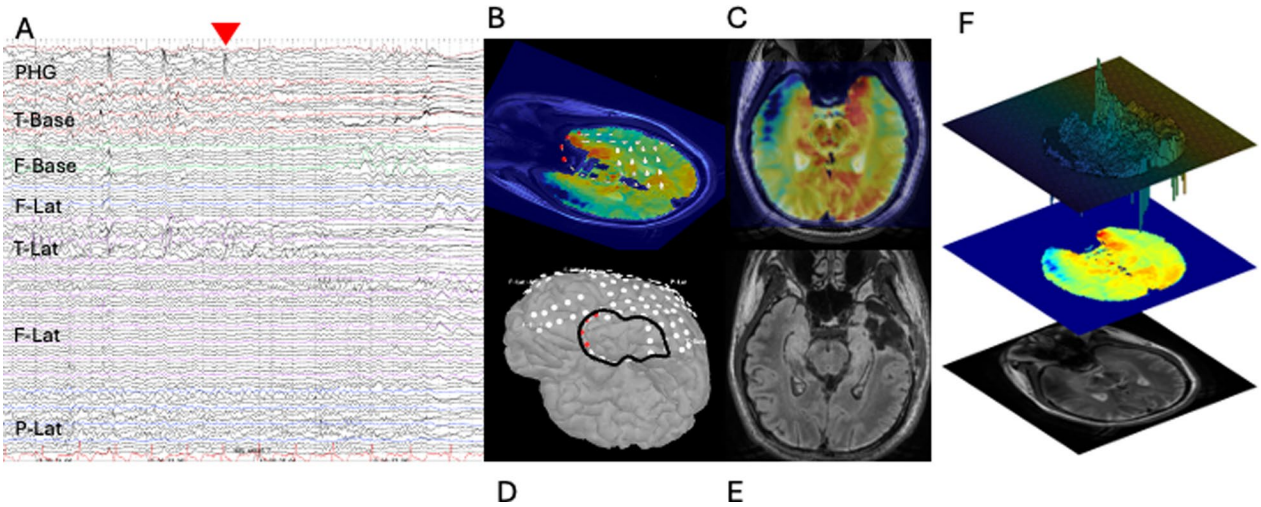

Fig. 1 Intracranial EEG during an epilepsy attack shows a leading spike in the electrodes placed between the tip of the temporal lobe and parahippocampal gyrus (**A**, arrow). The electrodes where the leading spike was observed (**B**, **D**) are close to the area where the glutamate concentration was increased on glutamate chemical exchange saturation transfer magnetic resonance imaging. The red circle indicates the electrode at which the spike was detected. The black frame indicates the area to be removed (**D**). The area where focal ablation of the left temporal lobe tip, temporal lobe base, and middle and inferior temporal gyrus was performed is shown based on the ictal electroencephalography origin area on intracranial electroencephalography (**D**). The hippocampus was preserved, and the area with increased glutamate concentration depicted on glutamate chemical exchange saturation transfer magnetic resonance imaging (**C**) was resected (**E**). Glutamate chemical exchange saturation transfer magnetic resonance imaging shows that glutamate concentrations were the highest in the tip of the temporal lobe, followed by the head of the hippocampus (**F**). Glu-CEST, glutamate chemical exchange saturation transfer; MRI, magnetic resonance imaging; PHG, parahippocampal gyrus; T-Base, temporal base; F-Base, frontal base; F-Lat, frontal lateral; T-Lat, temporal lateral; P-Lat, parietal lateral; T2WI, T2-weighted imaging

neurons and absence of balloon cells. Complete resection of the focal area is expected to suppress seizures; however, MRI often shows no abnormalities. The resected area was associated with abnormal EEG activity during seizures and an elevated Glu concentration as detected by Glu-CEST MRI**.**

In addition, Glu-CEST MRI revealed an increased Glu concentration within the hippocampal head, albeit at a lower magnitude than that in the left temporal pole (Fig. 1C and F). The highest Glu concentrations were observed in the tip of the temporal lobe, followed by the head of the hippocampus (Fig. 1F).

The Glu-CEST results suggested that the residual seizures were caused by the preserved hippocampal head and may be useful for considering additional surgical treatment in the future.

Discussion

In this report, an electrode positioned at the distal tip of the temporal lobe, where both a leading spike and low-amplitude fast activity were detected on intracranial EEG, closely approximated the location of elevated Glu concentrations identified by Glu-CEST MRI. Despite using a single-slice image, the alignment of Glu-CEST MRI findings with intracranial EEG data suggests the epileptogenic properties of the region with elevated Glu concentration. The postoperative seizure-free period confirmed the efficacy of resecting the region identified by Glu-CEST MRI.

FDG-PET and magnetoencephalography are commonly used as preoperative noninvasive tests for identifying epileptic foci [17]. The hypoglycemic areas depicted by FDG-PET represent regions of reduced function due to repeated epileptic seizures and are often more extensive than the actual epileptogenic areas [18].

Although magnetoencephalography can delineate epileptogenic sources by detecting spikes during ictal and interictal periods, it does not always indicate the precise seizure onset zone, particularly in cases of deep epileptogenesis, such as medial temporal lobe epilepsy [19].

Glu-CEST MRI offers high spatial resolution, enabling the assessment of Glu concentrations across extensive brain regions. Previous studies have demonstrated its utility in localizing epileptic foci, particularly in cases of nonlesional temporal lobe epilepsy [20]. In our case, the region with elevated Glu concentration on Glu-CEST MRI exhibited epileptogenic properties. The coexistence of neocortical lesions within the temporal lobe and hippocampal sclerosis, known as dual pathology, complicates surgical decision-making. However, postoperative seizure suppression rates are comparable between patients undergoing selective hippocampal resection and

those undergoing hippocampal resection with amygdalectomy after anterior temporal lobectomy. The optimal surgical method and extent of temporal lobectomy remain under debate [21]. Conversely, complete resection in cases of dual pathology correlates with improved seizure outcomes [22]. In the present case, MRI did not reveal any hippocampal lesions, while FDG-PET indicated no hippocampal hypometabolism. However, since the seizures were accompanied by déjà vu, FAS, and impaired consciousness, the possibility of medial temporal lobe epilepsy was considered. Despite extensive preoperative examinations, no findings suggested a hippocampal focal point. No EEG abnormalities were detected from electrodes placed in the parahippocampal gyrus near the hippocampus. Preservation of the hippocampus was warranted owing to the minimal frequency of spikes and the potential risk of verbal memory impairment. FAS recurred 9 months postoperatively, possibly originating from the hippocampus, highlighting the relationship between Glu concentrations detected by Glu-CEST MRI and epileptogenicity.

The remaining FAS are of the déjà vu type, suggesting that hippocampal sparing contributed to the seizures.

If a patient with MRI-negative epilepsy demonstrates decreased glucose metabolism on FDG-PET and an increased Glu concentration in the same region on Glu-CEST MRI, it strongly indicates the presence of an epileptogenic focus. This information can assist in planning intracranial EEG electrode placement.

A limitation of this study is that it reports only a single case using the single-slice Glu-CEST MRI technique, which does not allow for whole-brain evaluation. Since single-slice imaging may miss epileptogenic regions outside the scan area, multi-slice or whole-brain imaging is necessary to improve reliability. Future research should therefore aim to evaluate this method using whole-brain imaging.

Conclusion

This case demonstrates that Glu-CEST MRI can noninvasively identify epileptogenic sites in patients with nonlesional epilepsy, thereby potentially guiding surgical planning and improving seizure outcomes.

Abbreviations

CEST	Chemical exchange saturation transfer
EEG	Electroencephalography
FAS	Focal aware seizures
FDG-PET	Fluorodeoxyglucose-positron emission tomography
Glu	Glutamate
MRI	Magnetic resonance imaging
MTR	Magnetization transfer ratio
UHF	Ultrahigh field

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Not applicable.

Author contributions

YI designed the study, developed the main conceptual ideas, and outlined the proof. TO, TO, MW, HK, and KH collected the data. MF aided in interpreting the results and contributed to the manuscript. HI conceived the basic concept, revised the manuscript, and supervised the project. YI wrote the manuscript with support from MO and AK. All authors discussed the results, commented on the manuscript, and approved the final version.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study has been approved by the institutional review board of NHO Nishiniigata Chuo Hospital (Approval number: 2226) and Niigata University (2022-0270). The participant provided a written informed consent statement prior to participation in the study.

Consent for publication

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

The authors declare that they have no competing interests.

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