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Ictal Focal Hyperperfusion Demonstrated by Arterial Spin Labeling in Child With Refractory Frontal Lobe Epilepsy: A Case Report

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Research Article

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Abstract

Background

Epilepsy is one of the most common chronic neurological diseases, despite the great variety and prevalence of antiepileptic drug treatments, one-third of epilepsies remain drug-resistant. To our best knowledge, the patient reported in this case report is the first case of children with frontal lobe epilepsy achieving rapid and non-invasive surgical localization by arterial spin labeling (ASL) with EEG.

Case presentation

A 4-year-old previously healthy girl with repeated panic attacks and generalized tonic-clonic seizures. Levetiracetam, clonazepam, oxcarbazepine, and lacosamide were successively administrated with poor outcome. Seizure control was not obtained from any of these treatments. Using the quantitative analysis system of CBF, the imaging on PLD1025ms presented a mean CBF value of 17.81ml/100g/min for the lesion, 36% of the average value of the entire right hemisphere, thus presenting abnormally significant hypoperfusion. The patient became seizure free after lesionectomy of the frontal lobe by ASL combined with electroencephalogram (EEG) rapid localization. And the histopathological diagnosis was focal cortical dysplasia (FCD) type IIa. And there was no recurrence of the seizure was observed for 6 months after the operation.

Conclusions

The positive outcome suggests that the combined use of ASL with EEG could be a beneficial option for presurgical evaluation of pediatric epilepsy.

1. Background

Epilepsy is one of the most common chronic neurological diseases, with a prevalence rate between 0.8% and 1.2%. Despite the great variety and prevalence of antiepileptic drug treatments, one-third of epilepsies remain drug-resistant, with epilepsy surgery accounting for 10 to 50 percent of these patients' consequent treatment options[1]. Presurgical evaluation of these patients with drug-resistant epilepsy is key. While MRI is the most important tool for the identification of epileptogenic structures, in the presurgical evaluation of pediatric epilepsy, 30–40% of patients can have a negative MRI finding[2]. Non-invasive or invasive examinations such as PET (positron computed tomography), SPECT (single-photon emission computed tomography), MEG (magnetoencephalography), SISCOM (subtraction ictal single-photon emission computed tomography coregistered to MRI), and SEEG (stereotaxic electroencephalography) are the preferred presurgical evaluations of epilepsy. Nevertheless, each of them has their own shortcoming and limitations.

Frontal lobe epilepsy is characterized by rapid conduction, difficulty in accurate localization of scalp EEG, and frequent, violent disturbances of the seizure pattern, which brings challenges to the preoperative

localization of the epileptogenic zone. Arterial spin labeling (ASL) as a functional magnetic resonance imaging (fMRI) takes advantage of variations in blood oxygen levels to detect changes in cerebral hemodynamics and locate epileptogenic zone without contrast agents and radiation. It has the advantages of being of fast, convenient, repeatable, without radiation, and a relatively simple operation. However, at present, only a few studies have reported the role of ASL in the localization of epileptogenic regions in temporal lobe epilepsy. In this paper, the application of ASL in the presurgical evaluation of pediatric epilepsy is successfully illustrated through a case of pediatric drug-resistant frontal epilepsy who gained seizure control via surgical resection of epileptogenic regions localizing by ASL, which could play an important role in the presurgical evaluation of pediatric epilepsy.

2. Case Presentation

2.1 Cases

Informed consent was obtained from the parents and their families, and the parents also agreed to the publication. This study was approved by the institutional review board of the West China Second University Hospital. Their clinical manifestations, electroencephalogram (EEG), brain magnetic resonance imaging (MRI), malformations, investigations of other organs, and postoperative histopathological tissue.

2.2 Patient history

A 4-year-old previously healthy girl was admitted to our hospital due to repeated seizures for 9 months. During the ictal phase, her seizures were characterized by frightened and explosive screams followed by tonic and clonic movements of the upper limbs or all four limbs with impaired awareness which would last for several minutes. Two days prior to admission, her condition worsened with more frequent seizures, up to 90 per day. On examination, her growth was found to be in the 90th percentile. The neurodevelopment was normal and no developmental delay or regression was observed. No dysmorphic features, tremor, ataxia, nor involuntary movements were observed. Cranial nerve examination findings were normal. The patient was delivered by cesarean section at 37 weeks of gestation. There was no history of hypoxic asphyxia or postnatal resuscitation. Routine cerebrospinal fluid testing, autoimmune encephalitis related antibodies, paraneoplastic syndrome related antibodies, OB, AQP4, MOG, GFAP, auto-antibodies, thyroid-related antibodies, cardiolipin antibodies, antineutrophil cytoplasmic antibody, metabolic screening, and other screening results were all negative. Levetiracetam, clonazepam, oxcarbazepine, and lacosamide were successively administrated with poor outcome. Seizure control was not obtained from any of these treatments.

2.3 EEG

Both routine EEG and video EEG (VEEG) displayed epileptiform discharges of the right frontal lobe. The VEEG showed interictal slow background activity with low-high amplitude sharp, sharp-slow, 1.5-3Hz polymorphic slow wave in the right or bilateral forehead, frontal lobe regions, and anterior temporal regions during wake-up and sleep, with or without low-amplitude sharp wave frequently emitting

individually or continuously, which can spread to adjacent leads or all leads (Fig. 1). During ictal onset, 4 clinical seizures were identified which were characterized by sudden explosive screams, deviation of both eyes to the right, followed by generalized tonic-clonic seizure for 20–30 seconds (Fig. 2). The synchronous EEG displayed right frontal epileptiform discharges which rapidly spread to the bilateral frontal area with low-medium amplitude sharp wave rhythms or sharp-slow, followed by generalized low-medium amplitude slow-waves mixed with low-amplitude fast-wave rhythms.

2.4 MRI

Preoperative MRI was performed with a GE Sigma 1.5T superconducting MR scanner. The cranial scan was performed with the head orthogonal coil, T1WI, T2WI, and fluid attenuation inversion recovery sequence (FLAIR). T1WI uses a spin-echo sequence, TR: 500ms, TE: 15. T2WI adopts a fast spin-echo sequence, TR: 3000ms, TE: 90ms. FLAIR sequence TI2200ms, TR: 8000ms, TE: 140ms. 3D ASL sequence TR:, TE:, PLD:1025ms. In this case, the T1WI (Fig. 3A)and T2WI(Fig. 3B) sequences showed a suspicious signal abnormality, and displayed a subtle increased FLAIR signal in the right frontal lobe (Fig. 3C). Considering that the patient's seizures were drug resistant, it was important to identify the responsible lesion and, consequently, localize the lesion as soon as possible before surgical treatment. Therefore, 3D ASL cerebral perfusion imaging was performed to locate the lesion responsible for the epileptic activity. The examination revealed two abnormally high perfusion areas in the right medial frontal lobe (Fig. 4), using cerebral blood perfusion quantitative analysis system. PLD1025ms imaging demonstrated that the mean value of cerebral blood perfusion (CBF) of the lesion was 119.14ml/100g/min, which was + 217% of the mean value of the whole brain on the right hemisphere, presenting abnormally high perfusion, which was consistent with the abnormal discharge position detected by EEG. In addition, the 3D ASL sequence demonstrated that the two hyperperfused areas in the right frontal cortex corresponded with the suspicious thickened areas in FLAIR sequences.

2.5 Surgery and Postoperative

According to the characteristics of the patient’s clinical symptomology and results from VEEG, MRI, and ASL, the lesion responsible for the patient’s drug-resistant focal epilepsy was identified in the right frontal lobe. the range of resection was determined by intraoperative EEG monitoring. Consequently, "epileptic foci resection + multiple subpial transections" was performed. The patient became seizure free following lesionectomy. Histopathological diagnosis was focal cortical dysplasia (FCD) type IIa (Fig. 5A-5B). The postoperative VEEG (Fig. 6) displayed slow waves in the left frontal and anterior temporal regions. Postoperative head MRI and ASL (Fig. 7A-7D) showed that there were two abnormally hypoperfusion areas in the right medial frontal lobe. Using the quantitative analysis system of CBF, the imaging on PLD1025ms presented a mean CBF value of 17.81ml/100g/min for the lesion, 36% of the average value of the entire right hemisphere, thus presenting abnormally significant hypoperfusion. The antiepileptic treatment of levetiracetam was continued after the operation, and no recurrence of the seizure was observed for 6 months. There was no statistically difference in orientation, comprehension, cognitive

function, mentality, memory, and daily living ability between preoperative and postoperative tests. Moreover, her motor and sensory functions do not appear to have been affected.

3. Discussion And Conclusions

Epilepsy is a chronic neurological disease that affects more than 70 million people worldwide[3] .It results from excessive electrical discharges in a group of brain cells caused by various diseases. Repeated epileptic seizures can delay the development and maturation of neurons and cause neurological diseases, which cause significant harm to the body and mind of patients. Frontal lobe seizures can have many bizarre manifestations, which are typically brief, nocturnal, and with or without loss of consciousness. They account for 20–30% of all types of focal epilepsy, second only to temporal lobe epilepsy.[4] The seizures are often frequent, sometimes up to dozens of times a day, each lasting for a short time (typically 10–20 seconds and no more than 1 minute) and often occurring during sleep. They can be secondary to generalized tonic-clonic seizures. The frontal lobe is in charge of a person's voluntary movement, speech, smell, vision, autonomic nerve function, mental activity, and more. Therefore, epileptic foci located in different frontal lobes can result in a variety of clinical symptoms. According to the anatomical location, frontal lobe epilepsy can be divided into medial frontal lobe epilepsy, basal frontal lobe epilepsy, and dorsolateral frontal lobe epilepsy. Different types of seizures may occur according to the location of origin of the discharge. For example, the supplementary motor area (SMA) is located on the inner side of the frontal lobe. An epileptic lesion in this area is typically marked by seizures displaying a "fencing posture" accompanied by vocalization or pauses in speech. Because such a lesion is located in the medial frontal lobe, the discharge often occurs in the midline and may spread to both hemispheres but may not be captured in the scalp EEG. Seizure originating from an abnormality in the cingulate gyrus are characterized by emotional changes and autonomic nerve function symptoms, such as feelings of fear, flushed face, and heart rate changes, followed by agitation and excessive exercise often accompanied by shouting. Because of its deep location, scalp EEG often fails to capture the abnormal electrical activity. In our case, the main manifestation was panic attacks, feeling of fear, and explosive screams during the seizure, followed by generalized tonic-clonic seizures, which was consistent with the above characteristics of frontal lobe epilepsy. Due to the particularity of the symptomology of frontal lobe epilepsy, the onset of seizures in different regions of the frontal lobe is relatively fixed, and EEG recording may be limited to some frontal lobe epilepsy. Therefore, clinical symptomology and imaging play an invaluable role in the diagnosis and localization of frontal lobe epilepsies. Despite the fact that more than 30 kinds of anti-epileptic drugs (AEDs) are available for epilepsy treatment, one-third of patients with epilepsy remain drug-resistant[20]. The most common histopathological findings in pediatric epileptic surgical specimens are focal cortical dysplasia (FCD), which has been reported to account for 30–70% of epilepsy surgeries in children[5]. In our case, postoperative pathology indicated FCD type IIa. Most structural epilepsies are refractory and thus surgical treatment might be the best choice for these patients suffering from these conditions. However, no obvious lesions are found on brain MRIs of many cryptogenic patients. Consequently, identification of techniques to locate the lesions prior to surgery has become the key to presurgical evaluation. Conventional MRI can provide clear and stereoscopic brain

anatomy images and identify structural abnormalities in the brain, which is an effective method for imaging examination of structural epilepsy. However, in the presurgical evaluation of pediatric epilepsy, the occurrence of negative findings in MRI can be as high as 30–40%[2], compared with 15–30% of adults with refractory focal epilepsy[6]. Therefore, it is essential to find ways to improve the positivity rate of MRI in patients with refractory focal epilepsy for presurgical evaluation. PET is an important assessment for presurgical localization of the epileptic foci. Especially when a MRI is negative in a patient with focal epilepsy, multiple lesions, or discrepancies between MRI and EEG during seizures, further PET examination is required. The percentage of successful PET localizations in childhood epilepsy is high in children with FCD, with a sensitivity rate of 70–90% [7]. Nevertheless, PET is radioactive and expensive. The accuracy of the examination has a great deal to do with the individual state of the patient. For example, glucose level, now PET is used more glucose F18, and a lot of external environment on the impact of patients is closely related. This is not conducive to their own comparison. SPECT imaging is very useful in localizing epileptic foci, especially in patients with negative MRI findings. Nevertheless, the injection time requirement for the contrast agent during the ictal phase limits the application of SPECT in clinical practice. MEG is a brain function detection technology that detects the electromagnetic signals in the brain. It is most commonly used in the localization of epileptic foci and brain functional areas. Compared with traditional EEG, MEG has a higher temporal and spatial resolution. However, MEG also has some shortcomings, such as its blind area of detection, low sensitivity to localization of deep lesions, complex data processing in later stages, expensive equipment, and the need for patient cooperation restricts its use in young children. SEEG is an invasive examination, and surgical procedures carry risks of damage to vascular and nerve bundles, infection, electrode rupture, and more. The response rate of SEEG is the lowest in patients with normal MRI, and the complication rate of the permanent neurological deficit is 2.5% [8]. SISCOM is an emerging neuroimaging method, combining the advantages of SPECT functional imaging and MRI anatomical positioning, it is also effective at localizing epileptic lesions, especially for MRI negative patients. SISCOM increases the sensitivity of SPECT by about 70% [9]. Its main limitation lies in its inability to explain the normal physiological changes between scans, and its current clinical application is limited due to its technical and personnel requirements.

Functional magnetic resonance imaging (fMRI) is currently used to determine lesions in the cortex and predict postsurgical language and memory outcomes. In 2017, the American Academy of Neurology (AAN) evaluated the diagnostic accuracy and prognostic value of fMRI in determining functional hemispheres and predicting postsurgical language and memory outcomes in practice guidelines. As a noninvasive test, fMRI has gradually replaced the Wada test in many centers [10]. ASL is a kind of fMRI technique that reflects the tissue perfusion with magnetic markers of water protons within the arterial blood as an endogenous tracer. When blood flows into the tissue, it changes the overall magnetization of the tissue, which can be detected by the MRI device and then labels spins in the arterial blood. The free-diffusing endogenous tracer, labeled blood spins, is also called ASL. The ASL technology collects the labeled image and the reference image separately, and quantitatively calculates the perfusion by subtracting the two images. With the advancement of technology, the application of ASL in the central nervous system is no longer limited to the measurement of cerebral blood flow (CBF). Its special imaging

principle can also reflect the process of cerebral blood flow perfusion, allowing for its wider application in cerebrovascular imaging. Currently, it is mainly applied for the diagnosis of neurovascular diseases (such as ischemic cerebrovascular disease, acute cerebral ischemic stroke, and transient ischemic attack), brain abscess, infection, inflammation, trauma, brain function disease, and neurodegeneration diseases (such as temporal lobe epilepsy, Alzheimer's disease, and Parkinson's disease).

The nutrient supply and metabolism of brain tissue are inseparable from the supply of cerebral blood flow, so the relationship between brain function and cerebral blood flow perfusion is very close. Magnetic resonance perfusion imaging is a functional imaging method that has been rapidly developed in recent years to reflect the microvascular distribution and blood perfusion in tissues at the molecular level. This technology can semi-quantitatively and quantitatively reflect tissue hemodynamic information of tissues through related parameters and has a high spatial and temporal resolution, so it is particularly suitable for evaluating the hemodynamics of lesions in the microscopic field. ASL can obtain CBF perfusion images without the need for exogenous contrast agents or tracers, which is extraordinarily suitable for patients (especially children) with repeated examinations, follow-ups, and post-treatment evaluations[11]. ASL has great advantages in pediatric application because children have higher brain water content and hematocrit than adults, which increases the number and longevity of tracers, and thus the signal-to-noise ratio (SNR). Also, due to the incomplete gasification of the paranasal sinuses in children, the susceptible artifacts in the skull base are reduced, thus improving the image quality [11]. ASL and PET are consistent in the evaluation of patients with epilepsy, especially in MRI-negative patients [12]. Aboelsafa et al. reported a prospective study on ASL in identifying epileptic areas in MRI-negative patients. ASL was used to calculate the asymmetry index percent (AI%) and the percent asymmetry factor (AF%) of different regions on both sides of the brain and showed an accuracy of 95.78% and 98.14% respectively, and through ASL combined with MRS, 100% sensitivity, 98.45% specificity, and 98.86% accuracy are achieved [13]. Nevertheless, at present the actual application of ASL in the presurgical evaluation of epilepsy is still rare. Several studies have reported that the localization value of ASL, such as in MRI negative children with new onset seizures, mesial temporal lobe epilepsy, non-lesional focal impaired awareness seizures, intractable epilepsy, partial epilepsy status, and localizing the seizure onset zone [13–19]. Epilepsy can induce cortical hyperperfusion during seizures, especially following repeated seizures or status epilepticus. The relative hypoperfusion that occurs during the interictal phase may indicate local brain atrophy and gliosis. Studies had shown that the epileptogenic zone can be hyperperfused during the ictal phase, and the high signal gradually can become a low signal after one week[16]. It may be that the hyperexcitability of neurons in the epileptic area at the early stage of epilepsy results in metabolic and functional changes leading to increased local CBF. With the prolonged course of the disease, local cerebral blood flow may be reduced due to the loss of local neurons. This suggests that ASL has potential advantages in follow-up evaluation of epilepsy [14]. Although current reports of hyperperfusion acquisition time during an episode are inconsistent, it may last for hours or even days. Lee et al. reported that ASL perfusion changes were observed 2 hours to 90 days after the seizure, and the ASL perfusion changes were excessive within 1 day after the seizure ended [15]. Changes in cerebral blood flow state may be affected by multiple factors, including cerebral perfusion pressure, carbon dioxide level, type of

structural abnormalities, duration of seizures, seizure frequency, and epileptic focus. In our case, the child underwent an MRI examination immediately after repeated seizure episodes. No obvious abnormalities were found in routine MRI, while ASL indicated that the epileptogenic lesion presented significant hyperperfusion changes, which was consistent with clinical symptoms and VEEG. It may be caused by abnormal changes in the metabolism and function of neuronal overexcitement during an epileptic seizure, resulting in significantly increased CBF in corresponding brain regions, which is largely consistent with literature reports [16]. Therefore, ASL can be used to locate epileptic lesions noninvasively in conjunction with EEG results. EEG has a certain diagnostic value for brain diseases, especially in patients with focal epilepsy, but it is limited to variety certain conditions and is susceptible to various factors. In this case, ASL combined with EEG was used to accurately identify the epileptogenic zone of the patient with DRE. Postsurgical ASL and EEG indicated that the lesion was resected, which was further validated by the fact that the patient was seizure free after the lesionectomy. Furthermore, the motor, sensory, cognitive, and language functions were not affected. These results lay a foundation for the identification and accurate localization of epileptic lesions through the use of ASL combined with EEG and also suggests that ASL cerebral perfusion imaging can be an alternative to PET imaging and localization, with the added advantages of being safer, cheaper, and faster. Moreover, ASL is relatively stable and less affected by the patient's natural state.

In recent years, ASL has emerged as a new magnetic resonance imaging method for measuring cerebral blood flow. The main principle behind the technology is that labeled hydrogen protons in the arterial blood can be used as an endogenous contrast agent. The cerebral blood flow can be non-invasively and quantitatively measured. It is characterized by simplicity, no radiation, high spatial resolution, and good reproducibility, and it has been successfully applied in clinical studies of many types of diseases. At present, ASL is rarely used to assist in localizing epileptogenic regions in MRI negative children with focal epilepsy. We believe that ASL could have increasingly broad applications in the study of pediatric epilepsy with the advancement of related technology and research. There were some limitations in our study. First, it is a case report with a small number of cases. Second, we don’t compare the sensitivity of ASL with that of ictal/interictal PET, because PET is currently the most accepted standard for preoperative evaluation of epilepsy surgery. Third, the range of resection was determined by intraoperative EEG monitoring without SEEG. However, to our best knowledge, this is the first case of the use and consequent analysis of the ASL technique in identifying the epileptogenic regions in pediatric frontal lobe epilepsy patients with an MRI negative finding. The ASL technique is characterized by short acquisition time, low price, and no radiation as compared to SPECT and PET-CT. ASL combined with EEG could be an effective alternative option to assist with the localization of epileptogenic zones. And we need more prospective studies in a larger number of patients to determine the location of ASL in epileptogenic lesions, especially in the pediatric patients.

Abbreviations

ASL=arterial spin labeling, EEG=electroencephalogram, PET =positron computed tomography, SPECT=single-photon emission computed tomography, MEG=magnetoencephalography, SISCOM=subtraction ictal single-photon emission computed tomography coregistered to MRI, SEEG=stereotaxic electroencephalography, fMRI=functional magnetic resonance imaging, VEEG=video EEG, FCD=focal cortical dysplasia, FLAIR=fluid attenuation inversion recovery sequence, CBF=cerebral blood perfusion, SMA=supplementary motor area, AEDs=anti-epileptic drugs.

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the

corresponding author on reasonable request.

Ethics declarations

Ethics approval

This study was approved by the institutional review board of the Public Health and Clinical Center of Chengdu. The requirement for informed consent was obtained from the patient's parents. There is no conflflict of interest exists in the submission of this manuscript, and manuscript is approved by all authors for publication.

Consent to participate

Informed consent was obtained from the patient.

Consent for publication

Consent for publication was obtained from all participants to the study. Data were published anonymously.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Jia Zhang: Conceptualization, Methodology, Data collection, Writing-Original draft preparation; Yang Li: Writing-Original draft preparation; Peter Galer: Writing- Reviewing and Editing; Huan Luo: Data collection, Writing-Original draft preparation. Zeshan Yao: Tectological support, Writing- Reviewing; Jing Gan: Conceptualization, Supervision, Writing- Reviewing and Editing.

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Figures

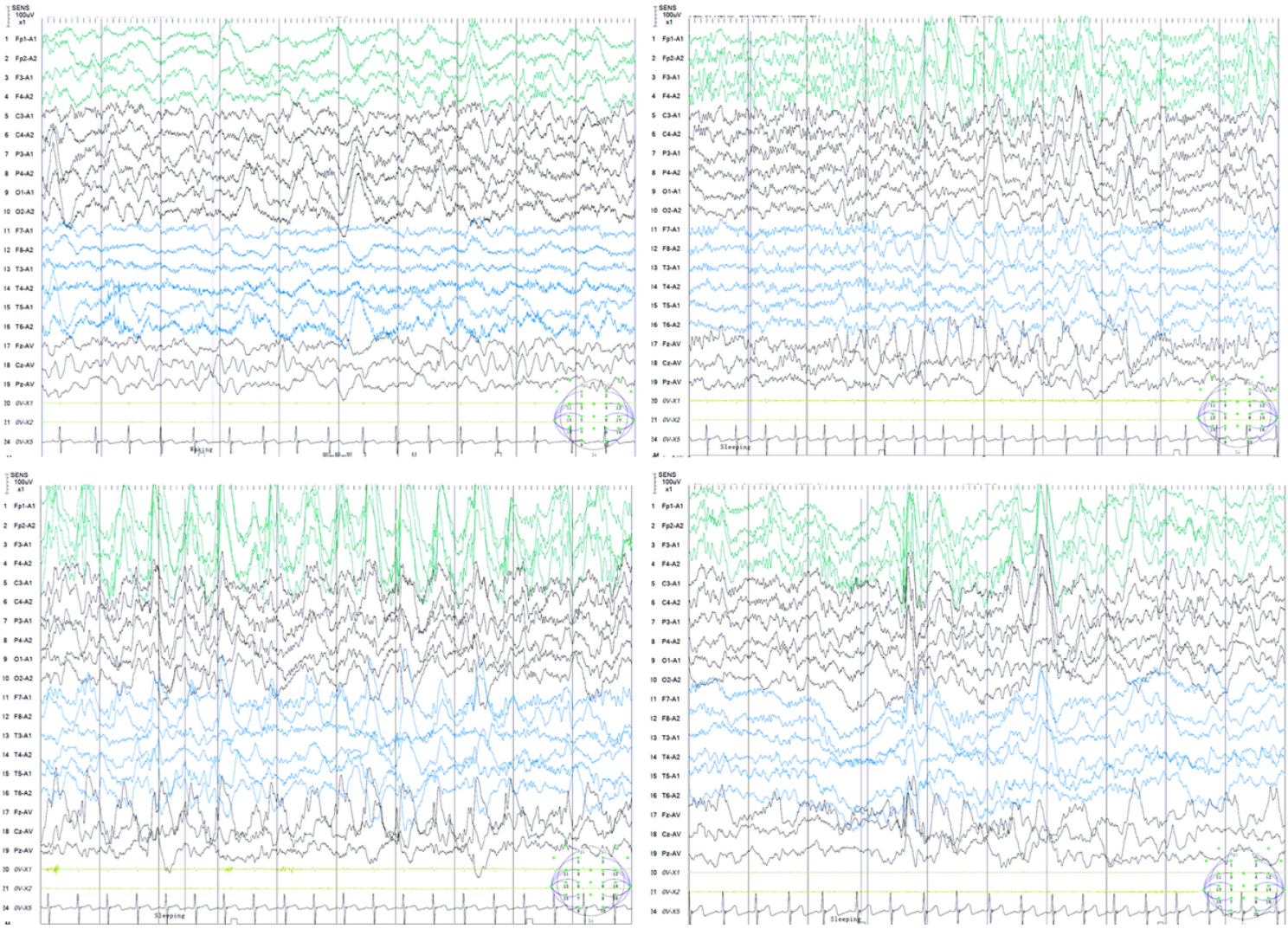

Figure 1

Preoperative interictal VEEG. The VEEG displays interictal slow background activity with sharp slow waves dominating in sleep, which can spread to adjacent leads or all leads.

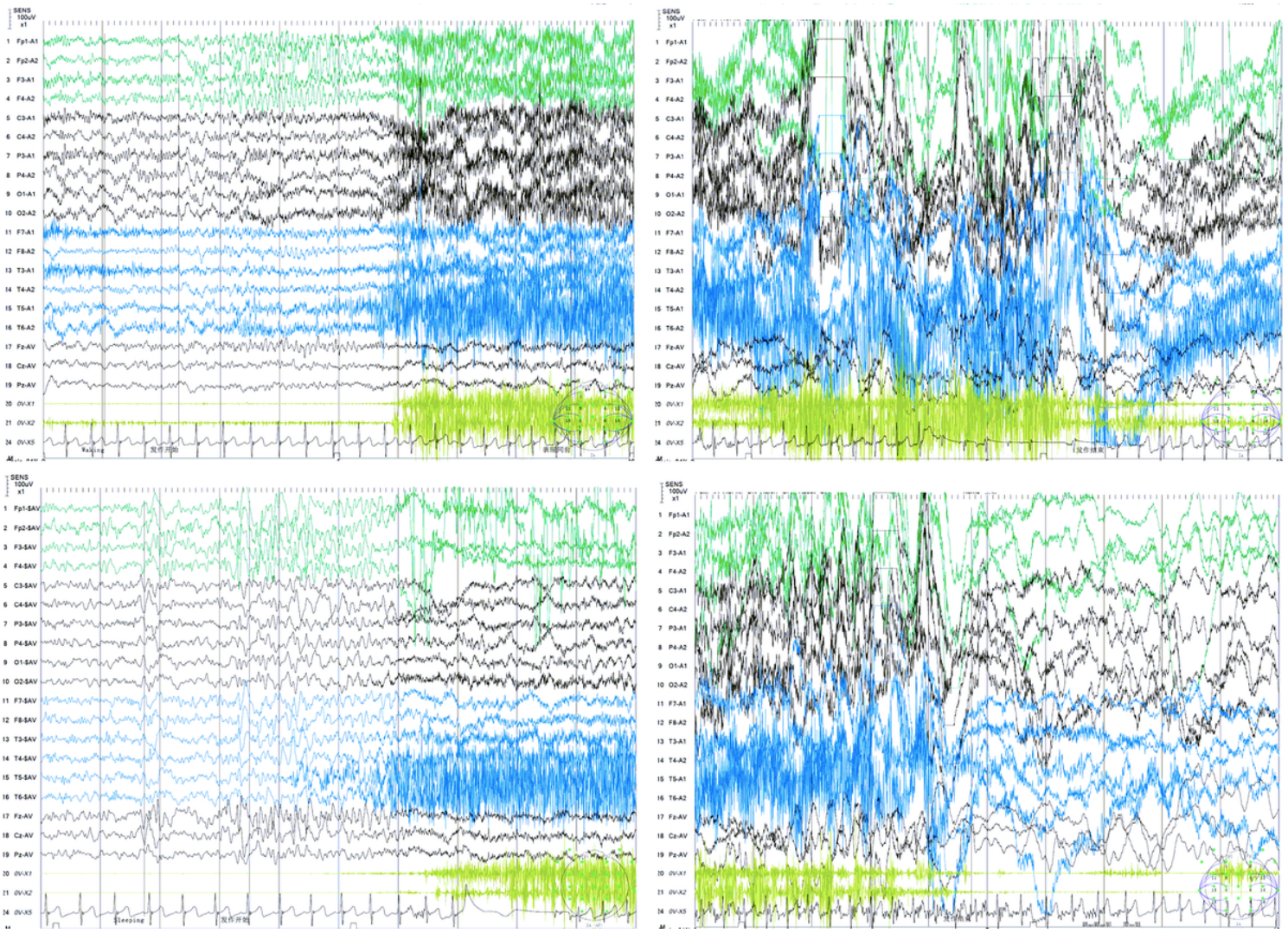

Figure 2

Preoperative ictal VEEG. The VEEG shows the epileptiform discharge in the right frontal area which rapidly spread to the bilateral frontal area. Extensive slow-waves continued to discharge after the seizure.

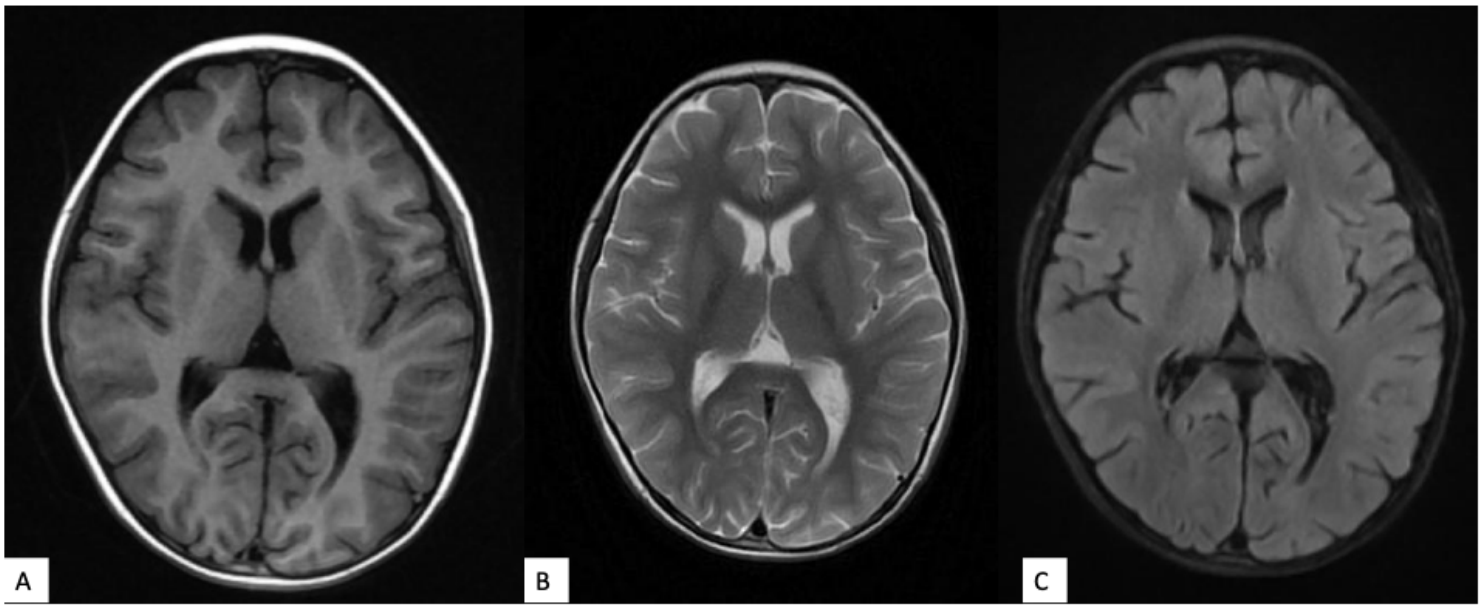

Figure 3

Preoperative head MRI. The T1WI (A) and T2WI (B) sequences showed suspicious signal abnormalities, with a subtle increased FLAIR (C) signal in the right frontal lobe (yellow arrows).

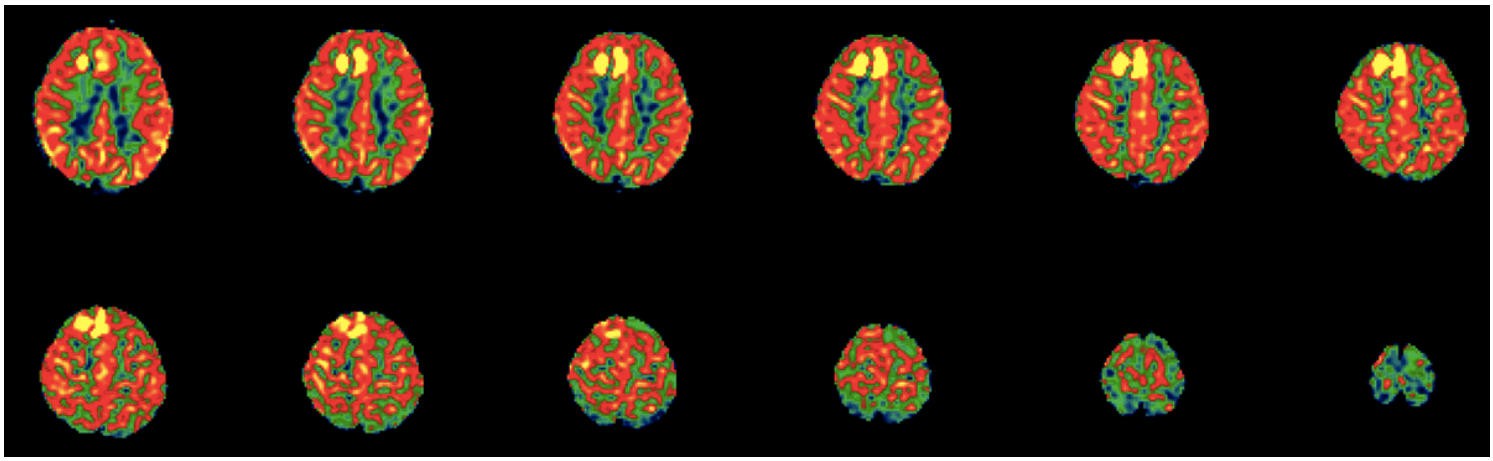

Figure 4

Preoperative ASL. ASL perfusion MRI depicts two hyperperfusion in the right medial frontal lobe, which is consistent with the epileptiform discharge position detected by VEEG and the suspicious thickened areas in FLAIR sequences.

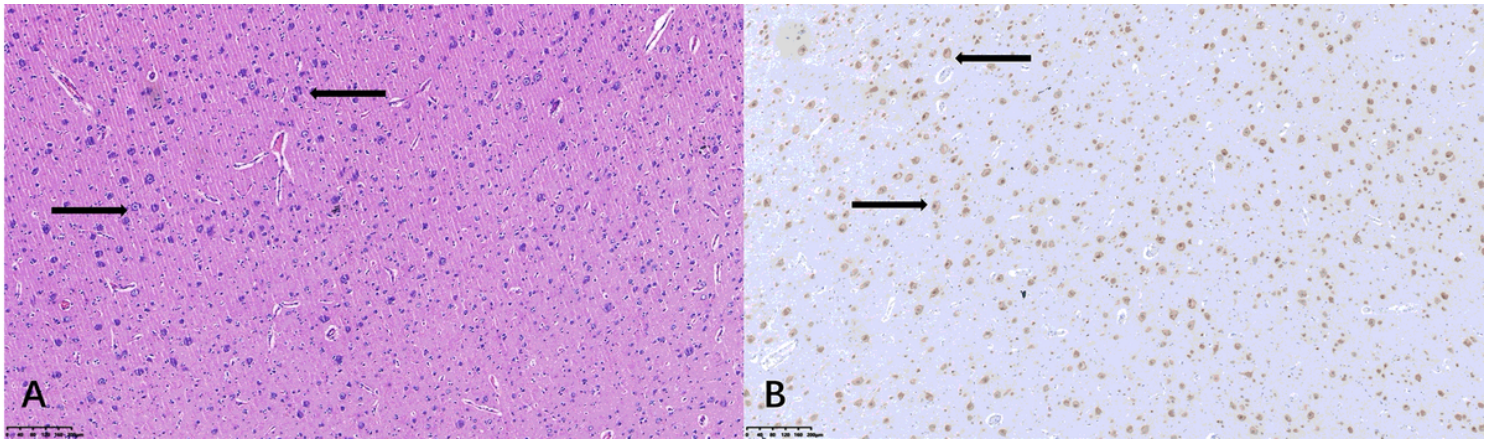

Figure 5

Postsurgical histopathology. Histopathological diagnosis was FCD type IIa (dyslamination and dysmorphic neurons).

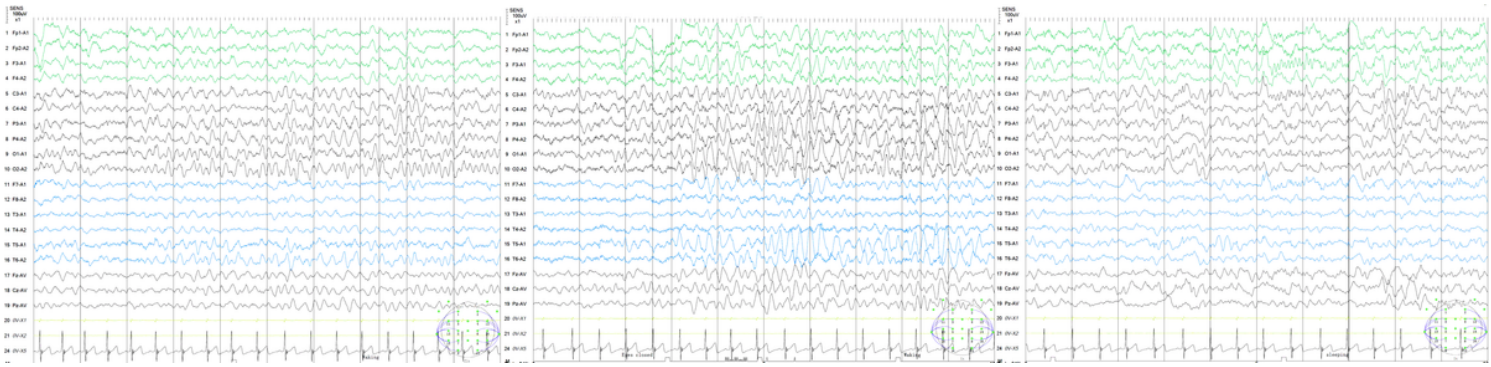

Figure 6

The postoperative VEEG displays slow waves in the left frontal and anterior temporal regions.

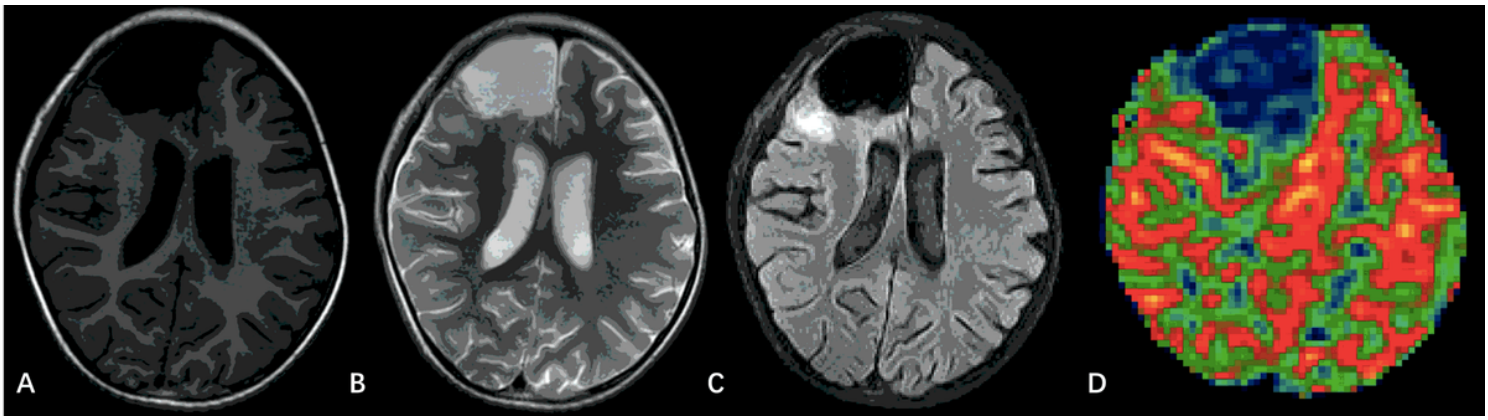

Figure 7

The postoperative MRI and ASL imaging demonstrates that there are two abnormally hypoperfusion areas in the right medial frontal lobe.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Parametertable.pdf
- renamed4e06b.pdf