Seizure: European Journal of Epilepsy 65 (2019) 151–158

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Diagnostic usefulness of arterial spin labeling in MR negative children with new onset seizures

So Mi Lee[a], Soonhak Kwon[b], Yun Jeong Lee[b,*]

[a] Department of Radiology, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea
[b] Department of Pediatric, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, South Korea

ARTICLE INFO

Keywords:
Arterial spin labeling
Magnetic resonance imaging
Children
New onset seizures

ABSTRACT

Purpose: Arterial spine labeling (ASL) magnetic resonance imaging (MRI) is the non-invasive measurement of cerebral blood flow that can localize the seizure focus in patients with epilepsy. The aim of this study was to identify its utility for localizing the seizure focus in children with no structural lesion on MRI.

Methods: Forty-three consecutive children who underwent electroencephalography (EEG) and structural MRI, along with ASL for evaluation of newly developed seizures, were included. ASL abnormalities were classified as hypo/hyperperfusion, based on visual assessment, and compared with the seizure focus determined by clinical information and EEG.

Results: Among the 43 patients (M 17: F 26, mean age, 6.3 ± 3.3 years), the seizure type was focal in 36 patients and generalized in seven patients. Twenty-five (58.1%) patients showed perfusion change. Out of 36 patients with focal seizure, 24 (66.7%) showed ASL abnormalities, and 19 (52.8%) showed concordance between ASL and clinical focus. Out of seven patients with generalized seizure, only one patient showed ASL abnormalities. The overall concordance revealed moderate agreement ($k = 0.542$). ASL acquisition within one day from seizure onset was the only significant associating factor with the concordance between the two ($p = 0.014$).

Conclusion: To our knowledge, this is the first study to assess the usefulness of ASL MRI to assist in localizing the seizure focus in MR-negative children with new onset seizures. The combined use of ASL with EEG and structural MRI may play an important role in the evaluation of pediatric epilepsy.

1. Introduction

Epilepsy is the most frequent and chronic neurologic disorder and carries risks of significant morbidity and mortality. Despite the introduction of new antiepileptic drugs, one-third of patients suffer from drug resistant epilepsy [1]. In these patients, especially those with focal epilepsy, surgical treatment aiming to remove the seizure focus may represent the only available option for becoming seizure free. If the magnetic resonance (MR) result does not reveal structural abnormalities, identifying the epileptogenic zone is more challenging in these patients than in those with structural abnormalities [2,3]. Unfortunately, a meta-analysis demonstrated a significantly higher proportion of MR negative cases in children compared to adults [3]. Furthermore, discrimination between monofocal and multifocal seizures is truly difficult in children, since clinical information including semiology and the pattern of EEG is often inconclusive. Even though intracranial electroencephalography (iEEG) remains the **"gold** standard" diagnostic procedure for localizing seizure focus and planning surgical resection to improve surgical outcome and minimize surgical complications, further complementary information from different modalities is needed before performing any invasive procedure. Thus, multimodal approaches combining several functional imaging methods may enable the understanding of the mechanisms underlying the epileptic process, and help achieving a more accurate localization of abnormal neuronal activities.

Nuclear medicine techniques, such as ictal and interictal single photon emission computed tomography (SPECT), and positron emission tomography (PET), are currently considered the leading imaging

Abbreviations: ASL, arterial spine labeling; CBF, cerebral blood flow; CI, confidence interval; ECTS, epilepsy with centrotemporal spike; EEG, electroencephalogram; FCD, focal cortical dysplasia; iEEG, intracranial electroencephalogram; MR, magnetic resonance; MRI, magnetic resonance imaging; ORs, odds ratios; PET, positron emission tomography; SPECT, single photon emission computed tomography; SISCOM, subtracted ictal single photon emission computed tomography co-registered with magnetic resonance imaging

* Corresponding author at: Department of Pediatrics, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, 130 Dongdeok-ro, Jung-gu, Daegu, 41944, South Korea.
E-mail address: oilily1103@hanmail.net (Y.J. Lee).

https://doi.org/10.1016/j.seizure.2019.01.024
Received 6 November 2018; Received in revised form 25 December 2018; Accepted 25 January 2019

modalities to detect perfusion and metabolic changes related to the presumed seizure focus [4]. Nevertheless, the use of PET or SPECT in a peri-ictal period is often difficult, due to the requirements of separate evaluation and administration of the radiocontrast agent. These limitations have discouraged the adoption of these techniques for the evaluation of seizures in young children.

Arterial spine labeling (ASL) is a magnetic resonance imaging (MRI) technique for assessing cerebral blood flow by magnetically labeling protons from the inflowing blood as an endogenous diffusible tracer [5]. ASL does not require an exogenous contrast agent. The signal difference between labeled and control images generates a perfusion weighted image, which can be used to evaluate regional cerebral blood flow (CBF).

The advantages of the ASL techniques, including their non-invasiveness, easy accessibility, and the absence of intravenous contrast agents, make them particularly suitable for pediatric epilepsy [6]. However, only a few case series have reported the diagnostic utility of ASL on seizure evaluation in pediatric epilepsy. Furthermore, these reports were analyzed in patients with brain structural abnormalities [7–10]. Notwithstanding the significantly higher proportion of MR negative cases in children than in adults, there has been no report on the diagnostic performance of ASL in pediatric epilepsy without obvious structural brain lesions. Therefore, we aimed to evaluate the diagnostic usefulness of ASL for seizure localization in pediatric epilepsy with MR negative findings.

2. Methods

2.1. Subjects

This study was approved by the Institutional Review Board of our institution. We retrospectively reviewed medical records and image data of consecutive patients undergoing evaluation for newly developed seizures between April 2017 and February 2018. The inclusion criteria were as follows: (1) newly developed seizure; (2) patients under 18 years of age; (3) negative structural high-resolution 3 T- MR scan; and (4) patients undergoing a set of investigations, including electroencephalogram (EEG), MRI, and ASL sequence. Since we aimed to evaluate the usefulness of ASL sequence in identifying seizure focus in children with MR negative epilepsy, we excluded the patients with abnormalities on structural MR image. The patients treated with antiepileptic drugs before the acquisition of MRI were also excluded.

Demographic data including age, gender, type of seizure, seizure duration, occurrence of status epilepticus, epilepsy syndrome, psychologic assessment, EEG findings, time from seizure onset to acquisition of ASL sequence, and time from seizure onset to acquisition of EEG were collected. The acquisition time was classified by peri-ictal period, including post-ictal and interictal period.

The post-ictal state was defined by changes in behavior, motor function, and neuropsychological performance that last until the return to a presumed baseline, without time limit. Interictal periods were defined as the time between the resolution of postictal abnormalities and the beginning of the next ictal event. Status epilepticus was defined as a single seizure lasting more than 30 min, or the occurrence of two or more seizures without recovery of consciousness in between [11]. Seizure types, epilepsy types, and epileptic syndromes were classified in accordance with the International League Against Epilepsy classification and Revised terminology and concepts for organization of seizures and epilepsies [12–14].

2.2. MRI and ASL acquisition

All brain imaging was performed on a 3 T scanner (Discovery MR 750; GE Healthcare, Milwaukee, WI, USA) using a 32-channel head coil. All patients underwent transit time corrected ASL imaging in addition to structural MR sequences, including diffusion-weighted imaging. We used a pseudo-continuous 3D fast spin echo based ASL acquisition sequence, with a modified Hadamard end coding, with background suppression [15]. The images were acquired in separate blocks, each composed by seven different post-labeling delays times: 700, 922, 1178, 1481, 1853, 2335, and 3017 ms, with effective label durations of 222, 256, 303, 372, 482, 682, and 1183 ms. The following ASL protocol was applied: TR, 5548 ms; TE, 11 ms; flip angle, 111°; section thickness / spacing, 6 / 0 mm; NEX, 1; readout, 4 arms x 640 samples; field of view, 22 x 22 cm; in a plane voxel resolution, 1.72 × 1.72 mm [2]. The total acquisition time for the ASL sequence was 3 min 57 s. Due to a lack of cooperation, some of the children were sedated during data acquisition using chloral hydrate or intravenous sedative drugs including midazolam, propofol or ketamine.

2.3. Data analysis

The clinical seizure focus was determined by two experienced pediatric neurologists (LYJ, KSH) based on a localization hypothesis using clinical history, ictal semiology, psychological assessment, and EEG findings. If seizures had occurred more than once, the clinical seizure focus and seizure type were determined based on the episode of seizure immediately before the acquisition of ASL, supported by EEG findings. All structural MRI scans were confirmed as normal by two pediatric neurologists (LYJ, KSH) and one pediatric radiologist (LSM). The area of perfusion changes on the ASL sequence was reviewed separately, and the areas of hypoperfusion and hyperperfusion were classified according to the intensity of the signal by the radiologist (LSM), who was blind to the presumed seizure focus.

The degree of concordance was assessed by comparing the area of ASL changes to that of the presumed seizure focus. Concordance was defined when the presumed seizure focus overlapped entirely with the area of ASL changes, even if the area of ASL changes was more extended, and the most prominent ASL changes matched the seizure foci. If some, but not all, of the seizure focus overlapped with the area of ASL changes, this was considered as partial concordance. Discordance was defined when the seizure focus and the area of perfusion change area were in different regions of the same hemisphere or in opposite hemispheres. In addition, discordance was also assigned when there were no ASL abnormalities in patients with seizure focus.

2.4. Statistical analysis

The baseline characteristics of the study patients are summarized as mean and standard deviation (SD) for continuous variables and frequency (percentage, %) for categorical variables. The kappa coefficient was calculated to determine the degree of concordance between ASL and the clinical seizure focus. The degree of concordance was analyzed, including all cases that were partially concordant. Interpretation of the level of agreement was as follows; 0.0–0.2 slight; 0.2–0.4 fair; 0.4–0.6 moderate; 0.6–0.8 substantial; 0.9–1.0 almost perfect [16]. In order to analyze the associations between baseline variables and abnormal ASL finding, and the concordance between ASL and seizure focus, univariate and multivariate logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Results were considered statistically significant at $P < 0.05$. Statistical analyses were performed with SPSS version 18 (SPSS, Chicago, IL).

3. Results

3.1. Patient characteristics

Forty-three patients were enrolled in the study. Twenty-six patients (60.5%) were female. The mean age of the patients was 6.3 ± 3.3 years (range 0.9–16.2 years). According to EEG findings and ictal semiology shown before ASL acquisition, focal seizures were diagnosed in 36 patients, and generalized seizures in seven patients. Based on all

Table 1
Clinical profile and location of abnormalities in ASL for each patient.

No.	Age/ gender	Time (seizure-ASL)	Time (seizure -EEG)	Epileptic syndrome	Semiology	SE	EEG	Seizure focus	ASL focus	Concordance
Focal seizure										
1	6.3/f	3 m	87 d	ECTS	Hypersalivation, impaired awareness	–	Bi CT	Lt CT	Rt P	No
2	8.8/f	8 h	29 h	ECTS	Left facial clonic movement, hypersalivation	–	Rt CT	Rt CT	Lt T	No
3	9.2/m	17 h	12 h	ECTS	Focal to bilateral tonic-clonic seizure	–	Bi CT	CT	–	No
4	6.8/m	19 h	8 h	ECTS	Focal to bilateral tonic-clonic seizure	–	Lt CT	Lt CT	Lt P	Yes
5	7.3/f	47 d	23 d	ECTS	Chewing movement with impaired awareness	–	Lt CT	Lt CT	–	No
6	11.6/f	2 h	14 h	ECTS	Lt side clonic movement	–	Rt CT	Rt CT	Rt FP (hyperP)	Yes
7	7.5/f	3 h	61 h	ECTS	Rt side clonic movement (face, upper limb)	–	Bi CT, Lt O	Lt CT	Lt FT	Yes
8	5.2/f	1 m	40 d	PS	Focal to bilateral tonic-clonic seizure, ictal vomiting	–	Lt O	Lt O	–	No
9	6.2/f	13 h	7 h	PS	Ictal vomiting, impaired awareness, Rt EBD	–	Bi O	Lt O	Lt PTO (hyperP)	Yes
10	4.6/f	18 h	10 h	PS	Ictal vomiting, EBD, impaired awareness	–	Rt O, Lt TP	Rt O	Rt PTO (hyperP)	Yes
11	3.8/m	14 d	17 d	PS	Ictal vomiting, Rt EBD, impaired awareness	–	Rt O	Lt O	–	No
12	6.9/f	17 h	40 h	PS	Lt side clonic movement, Lt EBD, vomiting	–	Bi O, P	Rt O	–	No
13	3.0/f	4 h	18 h	–	Ictal coughing, nausea, Lt EBD and Lt head version	–	Lt O	Rt O	Rt PTO	Yes
14	9.7/f	11 d	12 d	–	Rt head version and Rt EBD, oral automatism,	–	Bi TP	Lt T	Lt T, Bi P	Yes
15	7.2/f	1 m	27 d	–	Behavioral arrest, Lt EBD, oral automatism	–	normal w	Rt T	–	No
16	9.4/f	45 d	32 d	–	Behavioral arrest	–	Bi FT	F or T	Lt T	Yes (partial)
17	11.6/f	7 d	7 d	–	Behavioral arrest, oral automatism	–	normal w	F or T	Rt PT	Yes (partial)
18	3.2/m	5 h	21 h	–	Oral automatism, Lt EBD, tonic posture of both upper limb	Yes	normal s	Rt F or T	Bi F	Yes (partial)
19	7.1/f	24 h	2 d	–	Vocalization, Rt arm dystonia, Lt EBD and Lt head deviation	–	normal s	Lt F	Lt FT	Yes
20	0.9/f	8 h	28 h	–	Rt EBD, Rt arm dystonia	Yes	Lt T	Lt T	Lt T	Yes
21	7.3/m	8 h	9 h	–	Ictal vomiting, Rt EBD, behavioral arrest	–	normal w	Rt T	Rt P	Yes (partial)
22	11.7/f	2 m	2m	–	Lt facial clonic movement with impaired awareness	–	normal w	Rt F	–	No
23	7.6/m	8 h	14 d	–	Tonic posture of both upper limb	–	Bi F	F	Rt T	Yes (partial)
24	6.1/m	29 h	4 h	–	Ictal dysphagia, Rt facial clonic movement	Yes	Bi F	Lt F	–	No
25	1.8/m	3 h	63 d	–	Rt EBD, impaired awareness	–	Bi F	Lt FT	Lt FT	Yes
26	16.2/m	5 d	5 d	–	Focal to bilateral tonic-clonic seizure	–	Bi F	–	–	No
27	9.1/f	6 h	43 h	–	Tonic posture of both upper limb	–	Bi F, Lt FP	F	Lt FT	Yes (partial)
28	4.9/f	51 h	4 h	–	Rt arm clonic movement with impaired awareness	–	Bi O, Rt F	Lt F	–	No
29	6.6/m	56 h	31 h	–	Rt side clonic movement, Rt EBD	Yes	Diffuse	Lt F	Rt T	No
30	4.4/m	12 h	25 h	–	Ictal vomiting, Lt facial and arm clonic movement	–	Lt TP	Rt FT	Lt TP	No
31	6.8/f	12 d	13 d	–	Ictal vomiting Rt EBD and Rt head version	–	Lt FT	Lt FT	Lt FTO	Yes
32	1.8/f	52 h	24 h	–	Hypermotor, partially responsive	–	normal w	F	–	No
33	7.5/f	4 h	23 h	–	Ictal vocalization, Focal to bilateral tonic-clonic seizure	–	Lt P	Lt P	Lt P	Yes
34	6.3/m	50 d	60 d	–	Upper eye ball deviation, atonic posture	–	Mid P	P	Rt P	Yes (partial)
35	0.9/f	24 h	26 h	FS plus	Rt facial twitching	Yes	Normal s	Lt F	Rt FT	No
36	7.1/m	16 d	3 d	FS plus	Behavioral arrest	Yes	Normal ws	–	–	No
Generalized seizure										
37	8.7/m	1 m	7 d	–	Atonic seizure	–	normal w	–	–	Yes
38	6.5/f	41 h	28 h	–	Generalized tonic seizure	–	normal w	–	–	Yes
39	6.5/f	24 h	24 h	CAE	Absence seizure	–	3 Hz generalized	–	–	Yes
40	1.3/f	24 h	24 h	EMA	Myoclonic atonic seizure, brief tonic seizure	–	Diffuse or Bi O	–	Lt FT	No
41	2.7/m	2 m	45 d	FS plus	GTCs	–	normal s	–	–	Yes
42	1.8/m	16 h	8 h	CwG	GTCs	–	normal s	–	–	Yes
43	1.7/m	24 h	18 h	CwG	GTCs	–	normal s	–	–	Yes

ASL, arterial spin labeling; ECTS, self-limited epilepsy with centrotemporal spike; Bi, bilateral; CAE, childhood absence epilepsy; CwG; benign convulsion with mild gastroenteritis; EBD, eyeball deviation; EEG, electroencephalography; EMA, epilepsy with myoclonic atonic seizures; F, frontal; FP, fronto-parietal; FS plus, febrile seizure plus; FT, fronto-temporal; GTCs, generalized tonic clonic seizure; hyperP, hyperperfusion; Lt, left side; O, occipital; P, parietal; PS, Panayiotopoulos syndrome; RC, Rolandic cortex; Rt, right side; s, sleep record; T, temporal; TP, temporo-parietal; w, waking record.

available information, the presumed seizure focus was discernible in 34 patients. Six patients were diagnosed as having status epilepticus at the period of the evaluation. Epilepsy syndrome was diagnosed in 17 of the 43 (39.5%) patients: Panayiotopoulos syndrome (n = 5), self-limited epilepsy with centrotemporal spike (benign childhood epilepsy with centrotemporal spike, ECTS) (n = 7), febrile seizure plus (n = 3), epilepsy with myoclonic atonic seizure (n = 1), childhood absence epilepsy (n = 1). Three patients were diagnosed as benign convulsions with mild gastroenteritis. The interval from seizure onset to ASL acquisition ranged from 2 h to 90 days. The number of patients having ASL sequence acquired within 3 days, 2 days, and 1 day from seizure onset was 28, 25, and 18, respectively. ASL was performed during the post-ictal period in 25 patients, and during the interictal period in 18 patients. The interval from seizure to EEG acquisition ranged from 4 h to 87 days. In addition, EEG was performed during the post-ictal period in 25 patients, and during interictal period in 18 patients. Sedatives were used in 25 patients during MRI acquisition. Table 1 details the patient clinical profiles and ASL findings.

3.2. ASL findings

Out of 43 patients, 25 (58.1%) showed the area of perfusion change; hypoperfusion was found in 22 patients and hyperperfusion in three patients (Table 1). All three patients showing a hyperperfusion area on the ASL sequence had an image scan within one day from seizure onset (2, 13, and 18 h from seizure onset). Of the 36 patients with focal seizure, abnormal perfusion areas on the ASL sequence were identified in 24 patients (66.7%). Among the 34 patients whose seizure foci were localizable by clinical information and the EEG findings, 24 patients (70.6%) showed focal areas of perfusion change on the ASL sequence. Eighteen of the 26 (78.3%) patients with focal epileptiform discharges on the interictal EEG showed perfusion change on the ASL sequence. Of the seven patients with generalized seizure, only one patient with epilepsy with myoclonic-atonic seizures showed perfusion change on the ASL. This patient showed focal as well as diffuse or generalized polyspike discharges on interictal EEG and presented various seizure types such as myoclonic-atonic, myoclonic, and tonic seizures.

3.3. Concordance between ASL and seizure focus

Among the 25 patients whose abnormal perfusion areas were determined by ASL sequence, the area of the clinical seizure focus was concordant with the location of the perfusion change on the ASL sequence in 19 (76%), including seven patients showing partial concordance. In seven patients with concordance, the areas of perfusion change were larger than that of the seizure focus. Among the 18 patients showing both ASL change and epileptiform discharges on interictal EEG, ASL abnormalities were concordant with the location of epileptiform discharges in 13 (72.2%). In eight of the 15 patients with bilateral epileptiform discharges on EEG, ASL changes were confined to one hemisphere, providing lateralization information. Of 10 patients without focal epileptiform discharges on EEG, but diagnosed as focal seizure by ictal semiology, six showed an area of perfusion change, and four showed concordance between ASL and clinical seizure focus (Fig. 1). The overall concordance between ASL and clinical seizure focus revealed moderate agreement. (k = 0.542).

3.4. ASL findings in epilepsy syndromes

Of the 17 patients with epilepsy syndrome, abnormal perfusion areas on ASL sequence were determined in nine patients: Panayiotopoulos syndrome n = 2/5, ECTS n = 5/7, febrile seizure plus n = 1/3, and epilepsy with myoclonic atonic seizures n = 1/1. Among the nine patients with epileptic syndrome showing perfusion change on ASL sequence, two (n = 2/2) patients with Panayiotopoulos syndrome (Fig. 2) and three (n = 3/5) patients with ECTS showed concordance between ASL and the clinical seizure focus. In the two patients with Panayiotopoulos syndrome, ASL revealed hyperperfusion changes on the area consistently with, but more extensively than the seizure focus, including the parietal, temporal, and occipital lobe. Five of the seven patients with ECTS showed perfusion change in area near ipsilateral (n = 3) or contralateral (n = 2) rolandic cortex on ASL.

3.5. The associating factors of ASL finding and concordance between ASL and seizure focus

We used logistic regression analysis to estimate the associations between baseline variables and ASL findings (Table 2). Univariate analysis revealed that perfusion change on ASL was significantly associated with ASL acquisition within one day from seizure onset (OR 7.5, 95% CI 1.7–32.8, p = 0.007), focal seizure (OR 12.0, 95% CI 1.3–111.3, p = 0.029), and focal epileptiform discharges on EEG findings (OR 4.0, 95% CI 1.1–14.6, p = 0.039). After adjusting for other confounders, including acquisition within one day from seizure onset, status epilepticus, age, gender, focal epileptiform discharges on EEG findings, and sedation, multivariate analysis showed no significant factor associated with abnormal ASL finding.

In the univariate logistic regression analysis performed to estimate the associating factors for concordance between seizure focus and altered perfusion region on the ASL, ASL acquisition within one day (OR 4.5, 95% CI 1.1–17.4, p = 0.032) and within two days from seizure onset (OR 4.0, 95% CI 1.1–14.7, p = 0.034), and ASL acquisition during postictal period (OR 4.0 95% CI 1.1–14.7, p = 0.034) were significantly associated with concordance (Table 3). Multivariate analysis showed ASL acquisition within one day from seizure onset as the only factor significantly associated to concordance (OR 8.98, 95% CI 1.57–51.51, p = 0.014).

4. Discussion

We analyzed the perfusion abnormalities on ASL in pediatric patients with acute seizures who did not show structural abnormalities in structural MRI. We found that ASL was able to identify regions of perfusion change in more than half of the patients (58.1%), and the perfusion changes on ASL were concordant in 19 out of 36 patients (52.8%) with focal seizure and six out of seven patients (85.7%) with generalized seizure. These results yielded a moderate concordance (k = 0.542) with the clinical seizure focus based on semiology and EEG findings.

Our results support ASL as a safe and easily accessible imaging modality, that can be used to assist with the localization of seizure focus in pediatric epilepsy without structural brain lesions in the clinical practice. However, in our study, we could not compare directly the efficacy of ASL with that of interictal PET or ictal/interictal SPECT on the localization of seizure foci. In the previous literature, the sensitivity of ictal SPECT was reported to vary from 81 to 90% and that of PET from 30 to 80%, depending on the lobes and age. [4; 17] One study reported that postictal perfusion change on ASL offered similar or better localization compared to ictal SPECT in 60% of cases (9/15) and interictal PET in 71% of cases [17]. In another study, ASL showed a very good concordance with PET (k = 0.84) and a fair concordance with subtracted ictal SPECT co-registered with MRI (SISCOM) (k = 0.28) [18]. These studies suggested that ASL is a technique comparable to SPECT and PET in the localization of the seizure focus.

Several recent studies have evaluated the utility of ASL in children with seizures. However, sample sizes in these studies were small, and most investigations focused on the utility in patients with structural abnormalities such as focal cortical dysplasia (FCD) and cortical tubers [7–10,19]. In one study of nine children, hypoperfusion on ASL was co-localized with structural MRI abnormalities in all cases, with PET hypometabolism in 5/6 cases, and with histologically proven FCD type IIb in 5/5 cases [7]. Another study evaluated the perfusion characteristics of

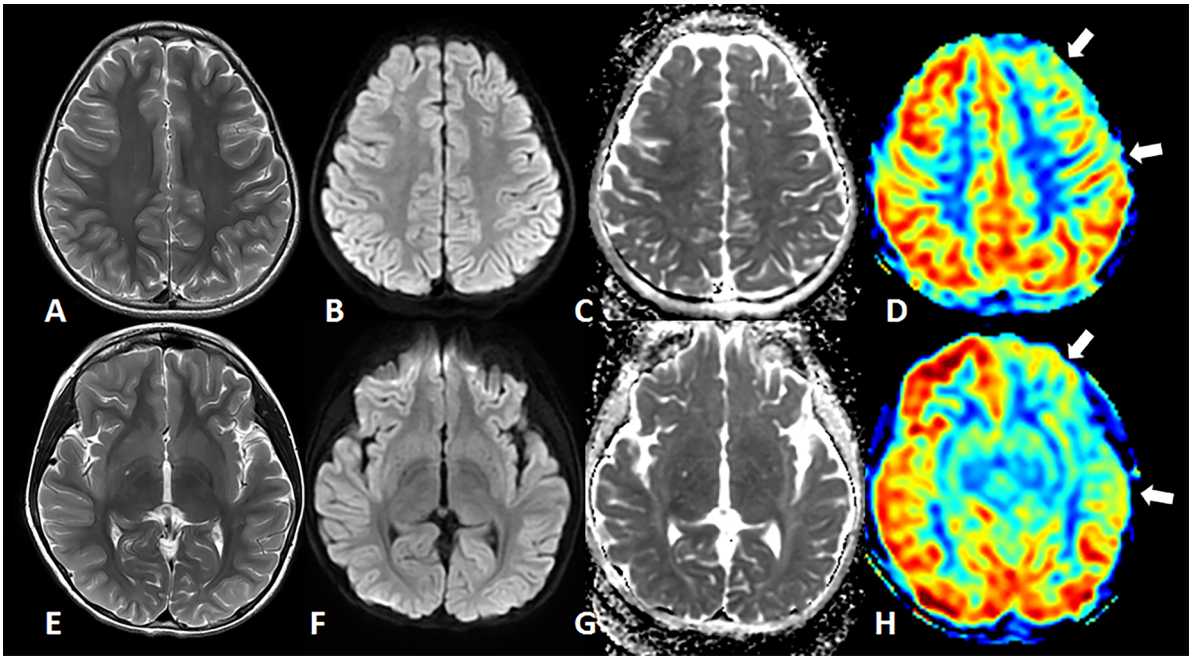

Fig. 1. Patient 19: A 7-year-old girl presenting focal impaired awareness seizure (ictal vocalization followed by impaired awareness, right arm dystonia, left eyeball deviation, and left head deviation). Her interictal EEG result was normal. Axial T2-weighted images (A, E), diffusion weighted images (B, F), and apparent diffusion coefficient images (C, G) show no abnormal focal lesion in the brain parenchyma. ASL perfusion MR images (D, H) depict a hypoperfusion in the left fronto-temporal lobes (arrows). In this patient, clinical seizure focus was in the left frontal area.

cortical hamartoma in tuberous sclerosis using ASL and analyzed the correlation between the perfusion value and seizure frequency [9]. Our study is the first to evaluate the diagnostic utility of ASL in a considerably large group of MR-negative pediatric patients with acute seizures. In addition, we focused on ASL potential to provide information about the location of the seizure focus at the first visit, prior to more invasive studies. The lower concordance rate in our study compared to previous results may be explained by the exclusion of the patients with brain structural abnormalities in our study[7; 17; 20]. Our results agree with a previous study in adults, showing that hypoperfusion change on ASL was concordant with the electro-clinical diagnosis in 11/20 MR negative individuals with refractory focal seizures. The concordance between visually assessed ASL and electro-clinical diagnosis in this adult study revealed a moderate agreement (k = 0.406). [21]

The acquisition of ASL is more sensitive in children compared to adults. Higher CBF and higher blood velocity in the carotid artery compared with adults results in reduced relaxation time and transit effects. Moreover, water content of the brain is higher in children [22]. This results in an increased equilibrium MR signal and improves pediatric ASL signal through increased tracer concentration and lifetime [23]. Given their benefits in terms of image quality, their greater accessibility and the dispensability of intravenous contrast agents, ASL methods may be ideally suited for pediatric perfusion imaging [24,25].

In the present study, we could observe the perfusion status on ASL in epilepsy syndromes. Some of the patients with Panayiotopoulos syndrome had a broad perfusion change on parietal, temporal, and occipital areas on ASL, which might suggest alterations not only in the regions of seizure origin, but also in the seizure propagation pathway, implying the presence of a complex altered network. The pathophysiology of autonomic manifestations in Panayiotopoulos syndrome has not been clearly elucidated. One hypothesis suggested the presence of variable and widely spread epileptogenic foci acting upon a temporarily hyperexcitable central autonomic network, irrespective of the cortical area of origin of the seizure [26]. Our finding might reflect seizure propagation, which may give origin to ictal autonomic manifestations, eye deviation, and long-lasting impairment of consciousness (Fig. 2) [27]. Five out of seven patients of ECTS showed perfusion change in the centrotemporal area on ASL. This result is consistent with the theory that epileptogenic zone in ECTS involves neuronal networks within the sensory motor cortex surrounding the central figure bilaterally [28]. Perfusion changes on the contralateral centrotemporal region in our study might be explained by the EEG features of ECTS, which may shift contralateral or bilateral foci. These findings suggest that ASL may be useful for a better understanding of widespread epileptic networks as well as single seizure foci in epilepsy syndromes.

In our study, five patients with focal seizure and one with generalized seizure showed abnormal perfusion area on ASL, discordant with their clinical seizure foci. Two of them were diagnosed as ECTS, which may have bilateral foci. In two patients, interictal epileptiform discharges were diffuse or absent. One patient with epilepsy with myoclonic atonic seizures was classified as generalized seizures based on clinical semiology, but also showed focal epileptiform discharges in interictal EEG. The other one showed focal epileptiform discharges and perfusion changes on the left hemisphere, but the seizure focus was determined to be on the right side based on clinical semiology. Our results were based on a retrospective analysis, using initial assessments including semiology and the interictal EEG, routinely performed for new onset seizures. This might lead to the lower accuracy of ASL in localization of seizure focus in the clinical setting. However, we assume that further knowledge about seizure semiology, with video EEG recording and invasive studies, will be helpful in confirming the seizure focus in these cases.

In the present study, perfusion changes on ASL were observed for a considerably long time. Hypoperfusion change on ASL was found 2 h - 90 days after seizure cessation, whereas hyperperfusion changes on ASL were identified within 1 day after seizure cessation. Previous studies assessing CBF in relation to seizures yielded inconsistent results about reporting hypoperfusion and hyperperfusion depending on the acquisition time. Several studies reported that hyperperfusion could persist for several days, even though ictal EEG findings and clinical seizures showed complete improvement [10,20,29]. However, another study showed hyperperfusion 1–5 hours after seizures and hypoperfusion interictally [30]. These conflicting results may be influenced by different

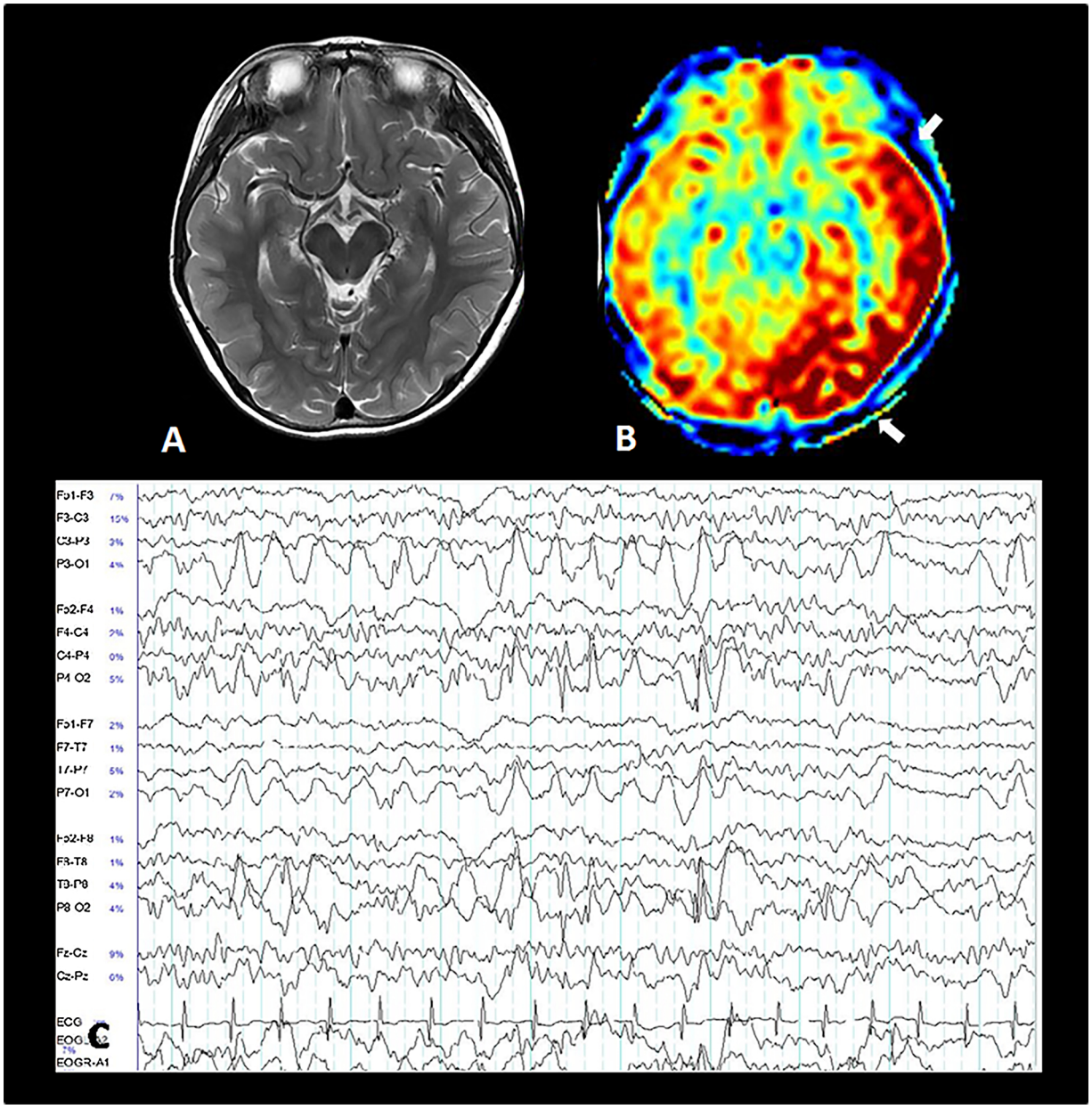

Fig. 2. Patient 9: A 6-year-old girl diagnosed as Panayiotopoulos syndrome. She presented focal impaired awareness seizure (ictal vomiting and right eyeball deviation with impaired awareness) at the time of evaluation. Axial T2-weighted image (A) shows no focal lesion in the brain parenchyma. ASL perfusion MR image (B) depicts a hyperperfusion in the left occipito-temporal regions (arrows). Interictal EEG (C) shows focal spike on predominance right and left occipital region.

Table 2
Odds ratios estimating the association of clinical profile with perfusion change on ASL sequence.

	Abnormal ASL (n = 25)	Normal ASL (n = 18)	Univariate OR (95% CIs)	P –value	Multivariate OR (95% CIs)	P-value
Interval from seizure onset to ASL < 1 day	15/25 (60.0 %)	3/18 (16.7 %)	7.5 (1.72–32.80)	**0.007**	5.48 (0.92–32.56)	0.062
Interval from seizure onset to ASL < 2 days	17/25 (68.0 %)	8/18 (44.4 %)	2.66 (0.76–9.30)	0.127		
Interval from seizure onset to ASL < 3 days	19/25 (76.0 %)	9/18 (50.0 %)	3.17 (0.86–11.65)	0.083		
ASL acquisition during postictal period	17/25 (68.0 %)	8/18 (44.4 %)	2.66 (0.76–9.30)	0.127		
Status epilepticus	4/25 (16.0 %)	2/18(11.1 %)	1.52 (0.25–9.38)	0.650	1.73 (0.12–25.43)	0.691
Age (months)	71.44 ± 39.9	76.7 ± 43.8	0.99 (0.97–1.02)	0.540	0.99 (0.97–1.02)	0.495
Gender (female)	16/25 (64.0 %)	10/18 (55.6 %)	1.42 (0.41–4.90)	0.577	1.66 (0.27–10.23)	0.584
Focal seizure	24/25 (96.0 %)	12/18 (66.7 %)	12.0 (1.29–111.32)	**0.029**	6.92 (0.44–109.54)	0.170
Epileptiform discharges on EEG	19/25 (76.0 %)	8/18 (44.4 %)	3.96 (1.07–14.62)	**0.039**	1.86 (0.31–10.36)	0.520
Sedation during ASL acquisition	13/25	12/18	0.54 (0.15–1.90)	0.338	0.81 (0.11–5.68)	0.828

ASL, arterial spin labeling; CIs, confidence intervals; EEG, electroencephalography; OR, odds ratio.

Table 3
Odds ratios estimating the association of clinical profile with concordance.

	Concordance (n = 25)	Discordance (n = 18)	Univariate OR (95% CIs)	P –value	Multivariate OR (95% CIs)	P –value
Interval from seizure onset to ASL < 1 day	14/25 (56.0 %)	4/18 (22.2 %)	**4.46 (1.14–17.41)**	**0.032**	**8.98 (1.57–51.51)**	**0.014**
Interval from seizure onset to ASL < 2 days	18/25 (72.0 %)	7/18 (38.9 %)	**4.04 (1.11–14.66)**	**0.034**		
Interval from seizure onset to ASL < 3 days	18/25 (72.0 %)	10/18 (55.6 %)	2.06 (0.58–7.37)	0.268		
ASL acquisition during postictal period	18/25 (72.0 %)	7/18 (38.9 %)	**4.04 (1.11–14.66)**	**0.034**		
Status epilepticus	2/25 (8.0 %)	4/18 (22.2%)	0.30 (0.05–1.88)	0.201	0.28 (0.02–3.92)	0.344
Age (months)	71.2 ± 39.5	77.1 ± 44.2	1.00 (0.98–1.011)	0.642	1.00 (0.98–1.02)	0.957
Gender (female)	10/25 (40.0 %)	11/18 (38.9 %)	0.96 (0.28–3.30)	0.941	1.08 (0.19–6.26)	0.930
Focal seizure	19/25 (76.0 %)	17/18 (94.4 %)	0.19 (0.02–1.71)	0.209	0.14 (0.01–2.05)	0.136
Epileptiform discharges on EEG	15/25 (60.0 %)	12/18 (66.7%)	0.75 (0.21–2.66)	0.656	0.36 (0.06–2.25)	0.364
Sedation during ASL acquisition	14/25	11/18	0.81 (0.24–2.78)	0.738	0.56 (0.08–3.90)	0.559

ASL, arterial spin labeling; CIs, confidence intervals; EEG, electroencephalography, OR, odds ratio.

subject characteristics that modify CBF, including cerebral perfusion pressure, carbon dioxide level, type of structural abnormalities, seizure duration, seizure frequency, and seizure foci [31]. Interestingly, in the present study, ASL acquisition within one day from seizure onset was the only significant factor associated to concordance between ASL and seizure focus. Similar to our result, several studies suggested that the timing of the ASL acquisition is highly related to the accuracy of ASL for identifying the seizure focus. One animal study reported that postictal hypoperfusion and hypoxia could be consistently seen at the seizure onset zone up to 60 min following seizures [32]. In a human study from the same group, cerebral perfusion was measured using ASL subtraction technique, and hypoperfusion was seen in 15/21 (71.4%) patients, with 12/15 (80%) showing concordance with the location of the presumed seizure onset zone, within 60 min of seizure termination. However, most patients who had late postictal ASL scans (> 60 min) showed no significant hypoperfusion [17]. In another study, the overall accuracy was higher in patients whose ASL perfusion were acquired at ≤ 3 days compared to > 3 days. (82% vs. 50%) [20]. In order to identify accurate seizure onset zone, further prospective studies are needed to define suitable conditions and the time window of ASL acquisition under video EEG monitoring.

There were some limitations in our study. First, since it was a retrospective analysis with consecutive patients undergoing initial evaluation for newly developed seizures, none of the patients underwent video EEG and MRI was not performed during simultaneous EEG monitoring, we had to rely on experienced neurologists' diagnostic approach, which was based on seizure semiology, interictal EEG, and neuropsychological testing. Second, we could not confirm the histopathological findings of clinical seizure focus, since none of the patients underwent surgery. Third, we could not compare the sensitivity of ASL with that of ictal/interictal SPEC or PET, the preexisting functional technique. Additionally, the data analysis in our study was performed via visual inspection. This might often under-recognize flow abnormalities, particularly in subtle, scattered, or diffuse CBF change. However, our study was aimed to validate the usefulness of ASL in the evaluation of first seizures in the clinical practice, which should be easily accessible and discernible by visual inspection. Also, we aimed to find ASL potential by providing complementary information about seizure focus, prior to more invasive studies, including iEEG and ictal SPECT.

More prospective studies using quantification methods in a larger number of patients are needed to determine the contribution of ASL to the localization of seizure focus and understanding epileptogenesis in the pediatric population.

To our knowledge, This is the first study to analyze the usefulness of ASL technique in identifying seizure onset focus in pediatric patients with newly developed seizures and negative MR. ASL appears to be an effective modality to assist with the localization of the seizure focus. Compared to preexisting functional imaging techniques such as SPECT and PET, the ASL technique has several benefits, including short acquisition time and the fact that a radiocontrast agent is not needed. Furthermore, ASL can produce repetitive measurements during the ictal and interictal period. Therefore, ASL can be an advantageous, additional tool for the initial evaluation of newly onset seizures for a better assessment of pediatric epilepsy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

We have no conflicts of interest to declare.

References

[1] Laxer KD, Trinka E, Hirsch LJ, Cendes F, Langfitt J, Delanty N, et al. The consequences of refractory epilepsy and its treatment. Epilepsy Behav 2014;37:59–70.
[2] Bast T. Outcome after epilepsy surgery in children with MRI-negative non-idiopathic focal epilepsies. Epileptic Disord 2013;15:105–13.
[3] Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res 2010;89:310–8.
[4] Desai A, Bekelis K, Thadani VM, Roberts DW, Jobst BC, Duhaime AC, et al. Interictal PET and ictal subtraction SPECT: sensitivity in the detection of seizure foci in patients with medically intractable epilepsy. Epilepsia 2013;54:341–50.
[5] Haller S, Zaharchuk G, Thomas DL, Lovblad KO, Barkhof F, Golay X. Arterial spin labeling perfusion of the brain: emerging clinical applications. Radiology 2016;281:337–56.
[6] Andreucci M, Solomon R, Tasanarong A. Side effects of radiographic contrast media: pathogenesis, risk factors, and prevention. Biomed Res Int 2014;2014:741018.
[7] Blauwblomme T, Boddaert N, Chemaly N, Chiron C, Pages M, Varlet P, et al. Arterial spin labeling MRI: a step forward in non-invasive delineation of focal cortical dysplasia in children. Epilepsy Res 2014;108:1932–9.
[8] Kuya K, Fujii S, Miyoshi F, Ohno K, Shinohara Y, Maegaki Y, et al. A case of acute encephalopathy with biphasic seizures and late reduced diffusion: utility of arterial spin labeling sequence. Brain Dev 2017;39:84–8.
[9] Pollock JM, Whitlow CT, Tan H, Kraft RA, Burdette JH, Maldjian JA. Pulsed arterial spin-labeled MR imaging evaluation of tuberous sclerosis. AJNR Am J Neuroradiol 2009;30:815–20.
[10] Mabray P, Thewamit R, Whitehead MT, Kao A, Scafidi J, Gaillard WD, et al. Increased cerebral blood flow on arterial spin labeling magnetic resonance imaging can localize to seizure focus in newborns: a report of 3 cases. Epilepsia 2018;59:e63–7.
[11] Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993;270:854–9.
[12] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Boas WVE, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51:676–85.
[13] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:512–21.
[14] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:522–30.
[15] Dai W, Shankaranarayanan A, Alsop DC. Volumetric measurement of perfusion and

arterial transit delay using hadamard encoded continuous arterial spin labeling. Magn Reson Med 2013;69:1014–22.
[16] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
[17] Gaxiola-Valdez I, Singh S, Perera T, Sandy S, Li E, Federico P. Seizure onset zone localization using postictal hypoperfusion detected by arterial spin labelling MRI. Brain 2017;140:2895–911.
[18] Sierra-Marcos A, Carreno M, Setoain X, Lopez-Rueda A, Aparicio J, Donaire A, et al. Accuracy of arterial spin labeling magnetic resonance imaging (MRI) perfusion in detecting the epileptogenic zone in patients with drug-resistant neocortical epilepsy: comparison with electrophysiological data, structural MRI, SISCOM and FDG-PET. Eur J Neurol 2016;23:160–7.
[19] Wintermark P, Lechpammer M, Warfield SK, Kosaras B, Takeoka M, Poduri A, et al. Perfusion imaging of focal cortical dysplasia using arterial spin labeling: correlation with histopathological vascular density. J Child Neurol 2013;28:1474–82.
[20] Kim BS, Lee ST, Yun TJ, Lee SK, Paeng JC, Jun J, et al. Capability of arterial spin labeling MR imaging in localizing seizure focus in clinical seizure activity. Eur J Radiol 2016;85:1295–303.
[21] Boscolo Galazzo I, Mattoli MV, Pizzini FB, De Vita E, Barnes A, Duncan JS, et al. Cerebral metabolism and perfusion in MR-negative individuals with refractory focal epilepsy assessed by simultaneous acquisition of (18)F-FDG PET and arterial spin labeling. Neuroimage Clin 2016;11:648–57.
[22] Dobbing J, Sands J. Quantitative growth and development of human brain. Arch Dis Child 1973;48:757–67.
[23] Wang J, Licht DJ. Pediatric perfusion MR imaging using arterial spin labeling. Neuroimaging Clin N Am 2006;16:149–67. ix.
[24] Stojanov D, Aracki-Trenkic A, Benedeto-Stojanov D. Gadolinium deposition within the dentate nucleus and globus pallidus after repeated administrations of gadolinium-based contrast agents-current status. Neuroradiology 2016;58:433–41.
[25] McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 2015;275:772–82.
[26] Panayiotopoulos CP, Michael M, Sanders S, Valeta T, Koutroumanidis M. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. Brain 2008;131:2264–86.
[27] Leal AJ, Nunes S, Martins A, Secca MF, Jordao C. Brain mapping of epileptic activity in a case of idiopathic occipital lobe epilepsy (Panayiotopoulos syndrome). Epilepsia 2007;48:1179–83.
[28] Pittau F, Mégevand P, Sheybani L, Abela E, Grouiller F, Spinelli L, et al. Mapping epileptic activity: sources or networks for the clinicians? Front Neurol 2014;5.
[29] Matsuura K, Maeda M, Okamoto K, Araki T, Miura Y, Hamada K, et al. Usefulness of arterial spin-labeling images in periictal state diagnosis of epilepsy. J Neurol Sci 2015;359:424–9.
[30] Pizzini FB, Farace P, Manganotti P, Zoccatelli G, Bongiovanni LG, Golay X, et al. Cerebral perfusion alterations in epileptic patients during peri-ictal and post-ictal phase: PASL vs DSC-MRI. Magn Reson Imaging 2013;31:1001–5.
[31] Telischak NA, Detre JA, Zaharchuk G. Arterial spin labeling MRI: clinical applications in the brain. J Magn Reson Imaging 2015;41:1165–80.
[32] Farrell JS, Gaxiola-Valdez I, Wolff MD, David LS, Dika HI, Geeraert BL, et al. Postictal behavioural impairments are due to a severe prolonged hypoperfusion/hypoxia event that is COX-2 dependent. Elife 2016;5.