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PEDIATRICS (L AVERILL, SECTION EDITOR)

# Utility of Arterial Spin Labeling MRI in Pediatric Neuroimaging: A Pictorial Essay

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**Abstract**
*Purpose of Review* With advances in magnetic field strength, multichannel coils and parallel imaging, arterial spin labeling (ASL) magnetic resonance imaging (MRI) is now widely available for clinical use. There is a growing body of literature on the utility of ASL in a variety of pediatric diseases that feature alterations in blood flow as part of the pathophysiologic process.
*Recent Findings* ASL can help discriminate high-grade tumors from low-grade tumors, and is especially useful to identify characteristic hyperperfusion seen in hemangioblastoma and choroid plexus tumors. In moyamoya, ASL coupled with acetazolamide challenge provides quantitative cerebral blow flow data that can inform decisions regarding revascularization surgery. In both migraine headaches and hypoxic ischemic injury (HII), there is early hypoperfusion on ASL imaging followed by hyperperfusion. Global or medial occipital hyperperfusion in the setting of HII is a poor prognostic factor. ASL can identify hypoperfusion in seizure foci, but is more useful for seizure localization with hyperperfusion in the acute setting.
*Summary* ASL perfusion imaging is a useful adjunct to conventional brain MRI in children, and should be applied in a wide variety of clinical scenarios.

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## Introduction

The evaluation of brain perfusion adds important physiologic information to conventional imaging in a wide range of settings in both children and adults, such as cerebrovascular disease, dementia, tumors, seizures, migraines and infection [1]. Perfusion imaging can be accomplished with a variety of techniques including dynamic susceptibility contrast magnetic resonance imaging (MRI), computed tomography (CT) perfusion imaging, single-photon emission computed tomography (SPECT), and positron emission tomography (PET). Arterial spin labeling (ASL) MRI, though, is uniquely positioned to assess brain perfusion without ionizing radiation or the need for intravenous injection of contrast or radiotracer.

The ASL technique was developed in the early 1990s and has become widely available for routine brain imaging in the past 10 years with advances in magnet field strength, multichannel coils, and parallel imaging [1–3]. Although there are multiple variations of ASL technique, they are all based on the same general principles. Rather than using an injected agent, ASL labels the patient's own arterial water protons to measure tissue perfusion. A control acquisition through the brain is obtained without arterial labeling. Radiofrequency pulses are then applied to the neck to saturate or invert the longitudinal magnetization of arterial water protons. After a post-labeling delay, acquisition through the brain is repeated. Subtraction of the labeled images from the control images yields the perfusion-weighted images [4, 5]. Cerebral blood flow (CBF) is displayed with color maps and can be quantitatively

measured in units of ml/100 g/min by placing a region of interest (ROI) or compared as a ratio to a ROI in the contralateral hemisphere or cerebellum. A recent white paper by Alsop et al. provides technical details for ASL acquisition and processing, with pseudocontinuous ASL emerging as the preferred technique [6••].

ASL is especially well suited to pediatric brain imaging because it is completely non-invasive and repeatable during the same imaging session as well on multiple follow-up examinations. In addition, ASL in children has greater signal-to-noise compared to adults due to increased blood flow and higher brain water content in children [7, 8]. In general, it is believed that CBF is low at birth, rapidly increases in the toddler years, peaks in mid childhood, and then declines in adolescence and early adulthood [3, 8, 9•, 10•]. Based on these observations as well as differences in patient size, we use slightly different parameters for children less than and greater than 8 years old. For younger children, we decrease the scan delay between labeling and image acquisition in the brain from 1525 to 1026 ms and slightly reduce the repetition time. On average, the ASL sequence takes 3.5 min to acquire on our three Tesla scanners.

At our tertiary care children's hospital, ASL imaging has become an integral part of our routine brain MR imaging since we introduced it 6 years ago. We have found that ASL provides valuable insights in many cases, from newborns to adolescents. Here, we present a pictorial essay highlighting the utility of ASL in children with brain tumors, moyamoya, migraine headaches, hypoxic ischemic injury, and seizures.

## Brain Tumors

Classification and grading of brain tumors can be challenging, despite the MRI tools available including contrast enhancement, diffusion-weighted imaging, and MR spectroscopy [11••]. High-grade tumors tend to employ neovascularity to support aggressive growth, which does not necessarily correlate with the degree of contrast enhancement. ASL, however, is well suited to detect elevated microvascular density. The addition of ASL has been shown to help predict glioma grading in adults and has recently been investigated in classifying pediatric brain tumors as well. Two recent pediatric publications showed increased CBF in high-grade tumors [World Health Organization (WHO) grade III or IV] compared to low-grade tumors, although there was overlap between the two groups [11••, 12]. CBF can be measured directly, with Dangouloff-Ros et al. suggesting a cutoff of 50 ml/100 g/min to distinguish high and low-grade tumors [11••]. This value was most reliable in hemispheric tumors but showed a sensitivity of only 65% for posterior fossa tumors. An alternative technique used by Yeom et al. evaluates tumor CBF as a ratio relative to contralateral gray matter. Although relative CBF in high-grade tumors was significantly greater

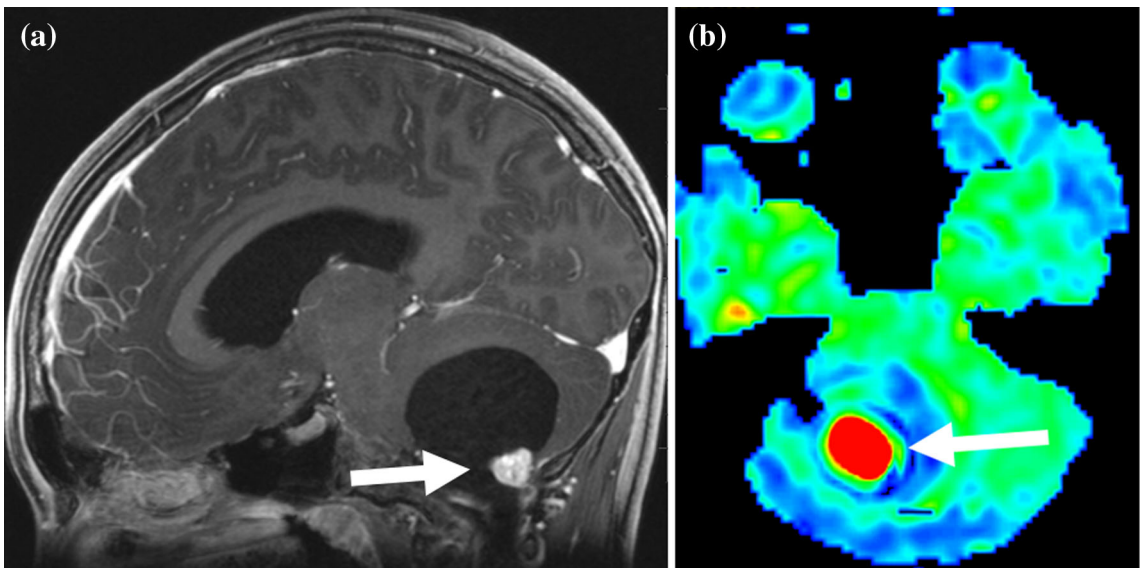


**Fig. 1** 15-year-old boy complaining of chronic headaches. Sagittal contrast-enhanced T1-weighted MR image **a** shows a posterior fossa cystic mass with an avidly enhancing mural nodule (*arrow*). The axial CBF map from ASL perfusion imaging **b** shows very high cerebral blood flow within the nodule displayed with *red* (*arrow*), while the rest of the brain perfusion appears relatively suppressed (*blue* and *green*) due to the wide color scale employed, features characteristic of hemangioblastoma (Color figure online)

than in low-grade tumors, it was widely variable (2.14 ± 1.78 and 0.60 ± 0.29, respectively) [12].

Despite these limitations, ASL is highly useful in characterizing pediatric brain tumors in two specific situations. ASL clearly shows the highly vascular nature of hemangioblastoma and distinguishes it from the more commonly encountered pilocytic astrocytoma presenting as a posterior fossa "cyst with mural nodule" (Figs. 1, 2)

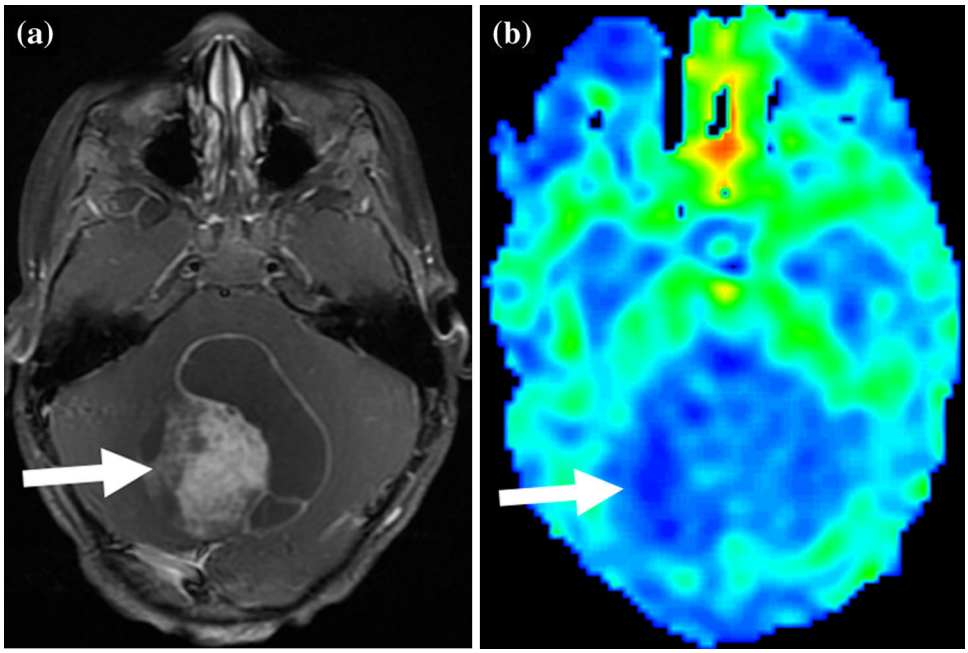


**Fig. 2** 3-year-old girl with gait disturbance and vomiting. Axial contrast-enhanced, fat-suppressed T1-weighted image **a** shows a large cystic mass in the posterior fossa with rim enhancement and a heterogeneously enhancing solid component (*arrow*). The corresponding CBF map **b** shows very low perfusion in the solid portion of the mass displayed with *deep blue* (*arrow*). At surgery, the child was diagnosed with pilocytic astrocytoma (WHO grade 1) (Color figure online)

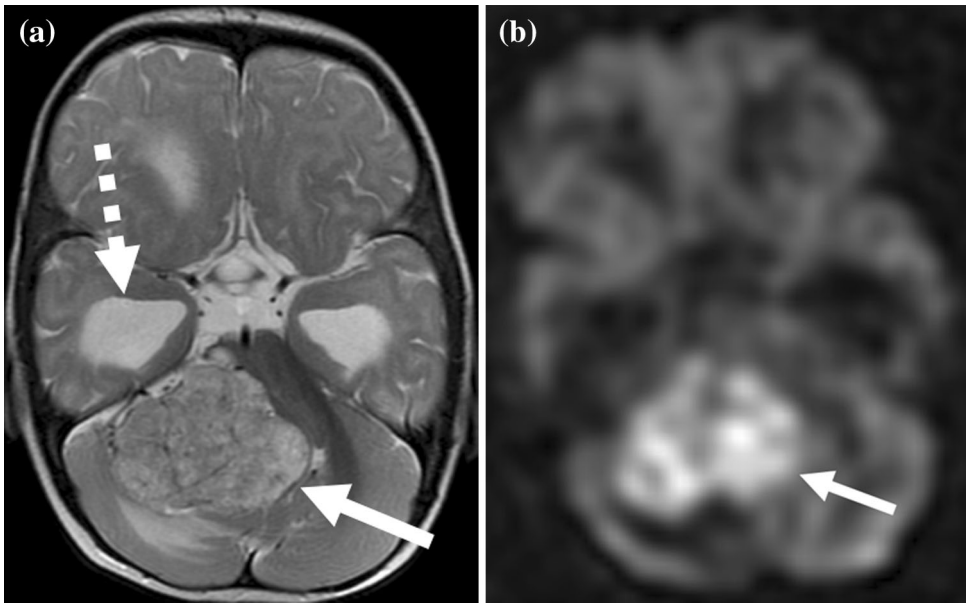


**Fig. 3** 8-month-old with bulging fontanelle. Axial T2-weighted image through the posterior fossa **a** shows a solid, heterogeneously high signal mass (*arrow*) obstructing the fourth ventricle and invading the right cerebellar hemisphere and middle cerebellar peduncle. Both temporal horns of the lateral ventricles are dilated (*dashed arrow*). Additional MRI sequences showed avid enhancement but no restricted diffusion (not shown). The corresponding perfusion-weighted ASL image (**b**), though, shows elevated perfusion (*arrow*). Features are characteristic of choroid plexus tumor, with pathology showing atypical papilloma in this case

[11••]. The solid enhancing nodule of hemangioblastoma will be "lightbulb bright" on perfusion-weighted imaging, with intensely high signal on CBF maps essentially overwhelming the signal from the rest of the brain tissue. Choroid plexus tumors also routinely show elevated perfusion, in contrast to most other brain tumors (Fig. 3). ASL is promising in distinguishing choroid plexus carcinoma from papilloma, with carcinoma exhibiting significantly higher relative CBF ratio, ranging from 1.4 to 7.96 compared to contralateral brain in published reports [12, 13•].

## Moyamoya

Moyamoya is a cerebrovascular disease characterized by progressive occlusion of the internal carotid arteries and its major branches with development of leptomeningeal collateral vessels seen as the "puff of smoke" on angiography. More common in children than adults, moyamoya can be idiopathic, associated with syndromes such as neurofibromatosis type 1 (Fig. 4), or due to sickle cell disease (Fig. 5). Perfusion imaging complements the vascular

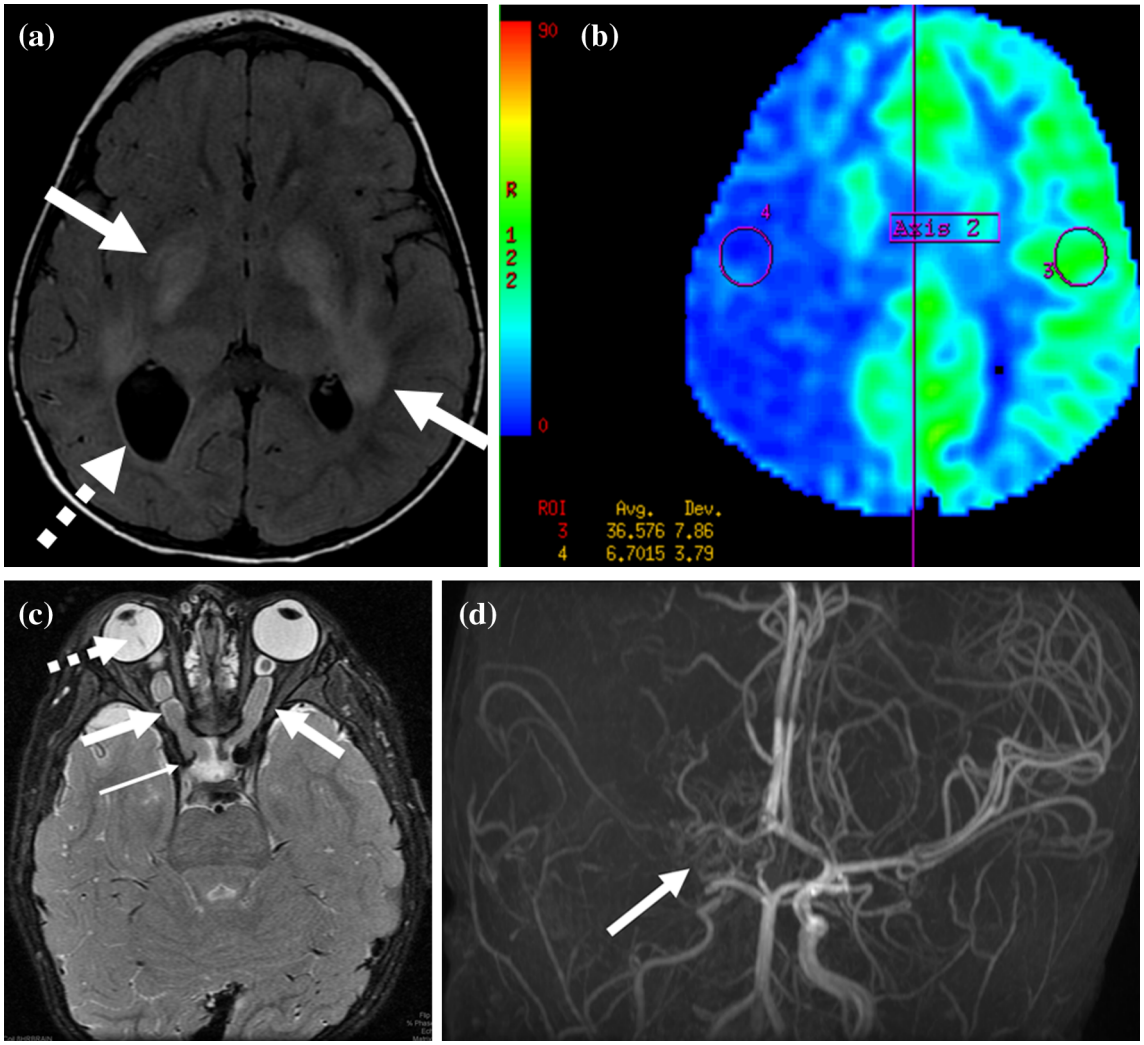


**Fig. 4** 21-month-old girl with unequal pupils and absent right-sided red reflex. Axial fluid attenuated inversion recovery (FLAIR) image through the level of the basal ganglia **a** shows relatively symmetric high signal in the globus pallidus, posterior thalamus and corona radiata bilaterally (*arrows*), as well as ex vacuo dilation of the atrium of the right lateral ventricle (*dashed arrow*). Corresponding diffusion-weighted image showed no abnormality (not shown). ASL was included in the brain MRI protocol (**b**), showing markedly reduced perfusion in the right cerebral hemisphere with approximately one-sixth of the cerebral blood flow compared to the contralateral side. Subsequently, the child was called back for additional imaging of the orbits and MR angiogram (MRA). Axial T2-weighted, fat-suppressed image through the globes **c** shows bilateral optic nerve enlargement (*arrows*) as well as right-sided retinal detachment (*dashed arrow*). Proteinaceous subretinal fluid was better demonstrated as high signal on FLAIR images (not shown). Coronal maximum intensity projection of the MRA **d** shows classic features of moyamoya, with truncation of the internal cerebral artery (ICA), numerous small lenticulostriate collaterals (*arrow*), and lack of normal MCA branches. Upon further detailed review, a very small caliber ICA flow void can be seen on the T2-weighted image as well (**c**, *thin arrow*). The child was diagnosed with neurofibromatosis type 1, which can be rarely complicated by vasculopathy throughout the body including moyamoya

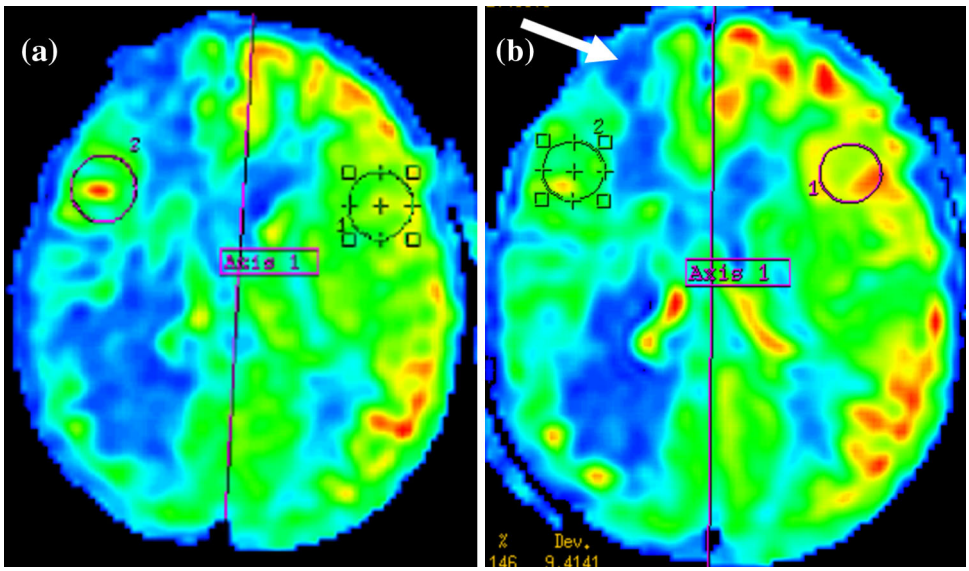


**Fig. 5** 11-year-old girl with sickle cell disease complicated by moyamoya and right-sided hemorrhagic infarction. An acetazolamide ASL challenge study was performed to assess for potential benefit from proposed temporal artery synangiosis surgery. Preoperatively, an area in the right frontal lobe showed type 3 response to acetazolamide. Prior to acetazolamide administration (**a**), CBF in the right frontal region of interest (ROI) measures 57 ml/100 g/min while the contralateral ROI measures 69 ml/100 g/min. After acetazolamide, CBF in the right frontal lobe paradoxically decreased to 48 ml/100 g/min while the contralateral side increased appropriately to 93 ml/100 g/min (not shown). After revascularization surgery, there is mildly improved perfusion to the right frontal region at baseline (**b**), with CBF mildly increasing from 50 to 64 ml/100 g/min with acetazolamide challenge. Chronic encephalomalacia in the adjacent anterior frontal lobe remains poorly perfused (*arrow*)

anatomic imaging obtained with MR angiography, providing physiologic correlation and insight into the brain's autoregulatory mechanisms. ASL compares favorably with other brain perfusion imaging techniques in the setting of moyamoya and is especially useful for the many follow-up examinations these patients undergo throughout their lives [14–17].

Arterial spin labeling can show vascular territories suffering from poor perfusion, despite normal appearance on conventional MR images [18]. Furthermore, ASL can demonstrate improved perfusion following revascularization surgery [19–21]. ASL is especially powerful when coupled with an acetazolamide challenge, designed to test the brain's vascular reserve [22••, 23]. In the setting of impaired blood flow as seen in arterial occlusive disease such as moyamoya, autoregulatory vasodilation leads to increased cerebral blood volume and mean transit time, allowing CBF and oxygen extraction fraction to remain constant [24]. When the autoregulatory mechanisms of the brain are already overwhelmed in the setting of severe chronic vascular stenosis or occlusion, however, "misery perfusion" is seen in response to increased demand with reduced CBF and increased oxygen extraction fraction. Acetazolamide, which acts as an intracranial vasodilator, mimics this physiologic scenario [15]. In the normal, type 1 response to acetazolamide challenge, there is normal brain perfusion at rest and physiologic increase in CBF after acetazolamide administration of approximately 30–40% [23]. In type 2 response, portions of the brain show reduced perfusion at rest but do still have some vasodilatory reserve and demonstrate increased perfusion after acetazolamide. In type 3 response, though, there is autoregulatory failure with reduced perfusion at rest and no response or even paradoxical decrease in perfusion with acetazolamide. Vascular territories demonstrating type 3 response are at high risk for ischemia and most likely to benefit from revascularization surgery (Fig. 5) [24].

## Migraine

Migraine headaches are common in childhood, with reported prevalence of 4–10% in school-aged children [25]. The cause of migraines is still not fully understood, but neurovascular constriction followed by hyperemia plays a role and can be imaged with ASL. This feature can be an important clue to the diagnosis of migraine in children who present with atypical aura symptoms. Hemiplegic migraine is especially worrisome, with patients presenting with stroke-like symptoms of weakness, numbness, aphasia, and confusion. A rare subtype of migraine with aura, hemiplegic migraine can be sporadic or inherited in an autosomal dominant fashion. Multiple causative genes encoding ion transport proteins have been associated with familial hemiplegic migraine, which tends to have an earlier onset in young childhood [26].

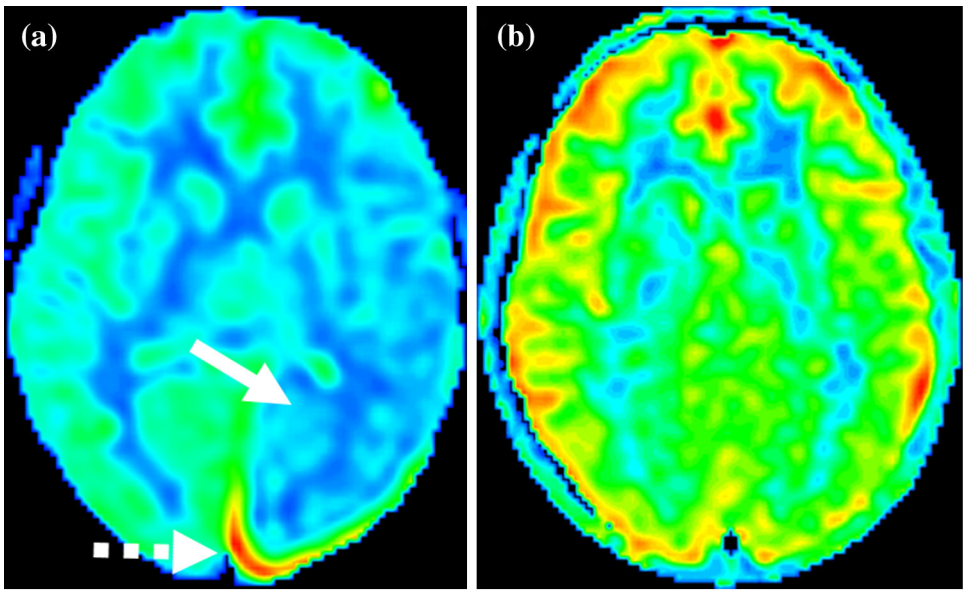


**Fig. 6** 13-year-old boy presenting to the emergency department with headache and altered mental status, diagnosed with migraine with atypical aura. MRI was performed within 6 h of symptoms, with normal anatomic and diffusion-weighted images. CBF map from ASL imaging **a** shows markedly reduced perfusion in the left hemisphere (*arrow*) most heavily involving parietal, occipital, and temporal lobes and not conforming to a vascular territory. There is a rim of hyperperfusion at the occipital pole (*dashed arrow*), indicating delayed transit of labeled protons in leptomeningeal vessels. CBF map obtained 5 weeks later **b** shows return of normal, symmetric brain perfusion

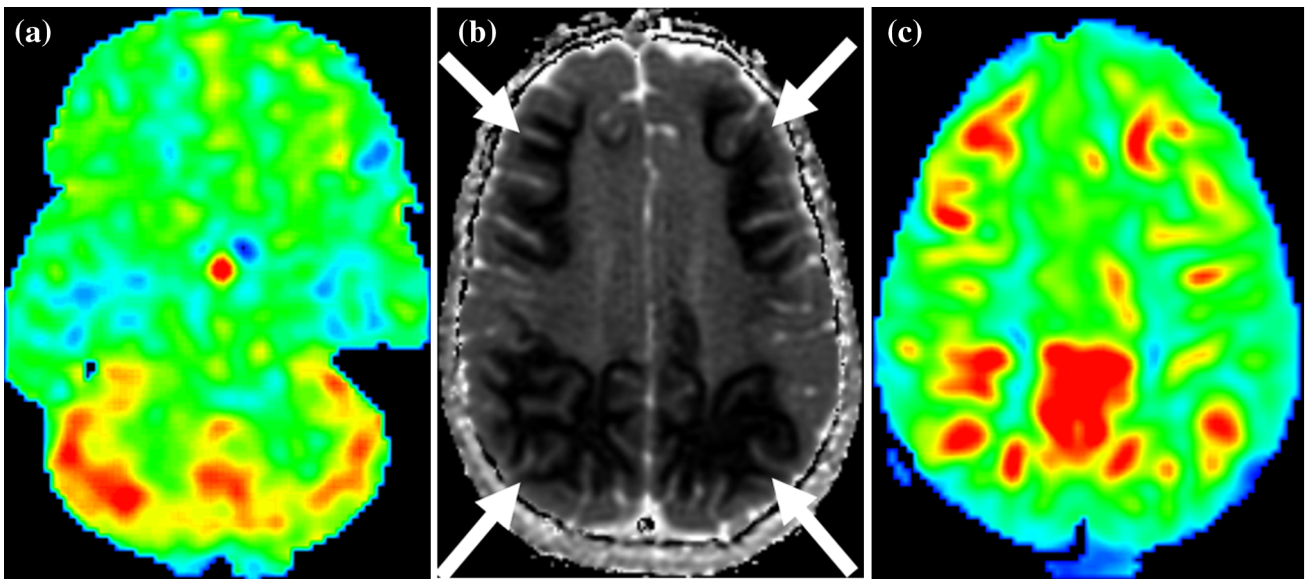


**Fig. 7** 10-year-old girl with vomiting, diarrhea, and loss of consciousness. Axial CBF map through the posterior fossa shows relatively high perfusion in the cerebellum (*red*) and reduced perfusion in both temporal and inferior frontal lobes (*green*). Reduced perfusion was seen throughout both cerebral hemispheres on higher slices, while anatomic and diffusion-weighted images were normal (not shown). Three days later, there is extensive cortical and subcortical ischemia displayed as dark signal (*arrows*) on apparent diffusion coefficient (ADC) map (**b**) with corresponding extensive cerebral hyperperfusion (*red*) on CBF map (**c**). Ischemia was also seen in the bilateral basal ganglia (not shown) (Color figure online)

Emergent MRI with ASL perfusion imaging can be key in diagnosing hemiplegic migraine, especially at the first presentation. If imaged early in the course, within the first 6–12 h of symptoms, ASL will show reduced perfusion in the area corresponding to the aura in the setting of normal anatomic and diffusion-weighted sequences. Susceptibility-weighted MR images may also show prominent low signal veins in the region of decreased perfusion,

postulated to represent venous stasis and increased deoxyhemoglobin secondary to increased oxygen extraction [27, 28]. If imaged later, usually more than 12 h after symptom onset, ASL will capture regional increased cerebral perfusion [29, 30•]. Follow-up examinations after resolution of migraine symptoms will show return of normal, symmetric brain perfusion (Fig. 6).

## Hypoxic Ischemic Injury

Hypoxic ischemic injury (HII) to the brain is seen in children of all ages, from those suffering perinatal asphyxia to older children with near-drowning, cardiac arrest, or other acute global insult. Several studies in asphyxiated newborns, including those undergoing therapeutic

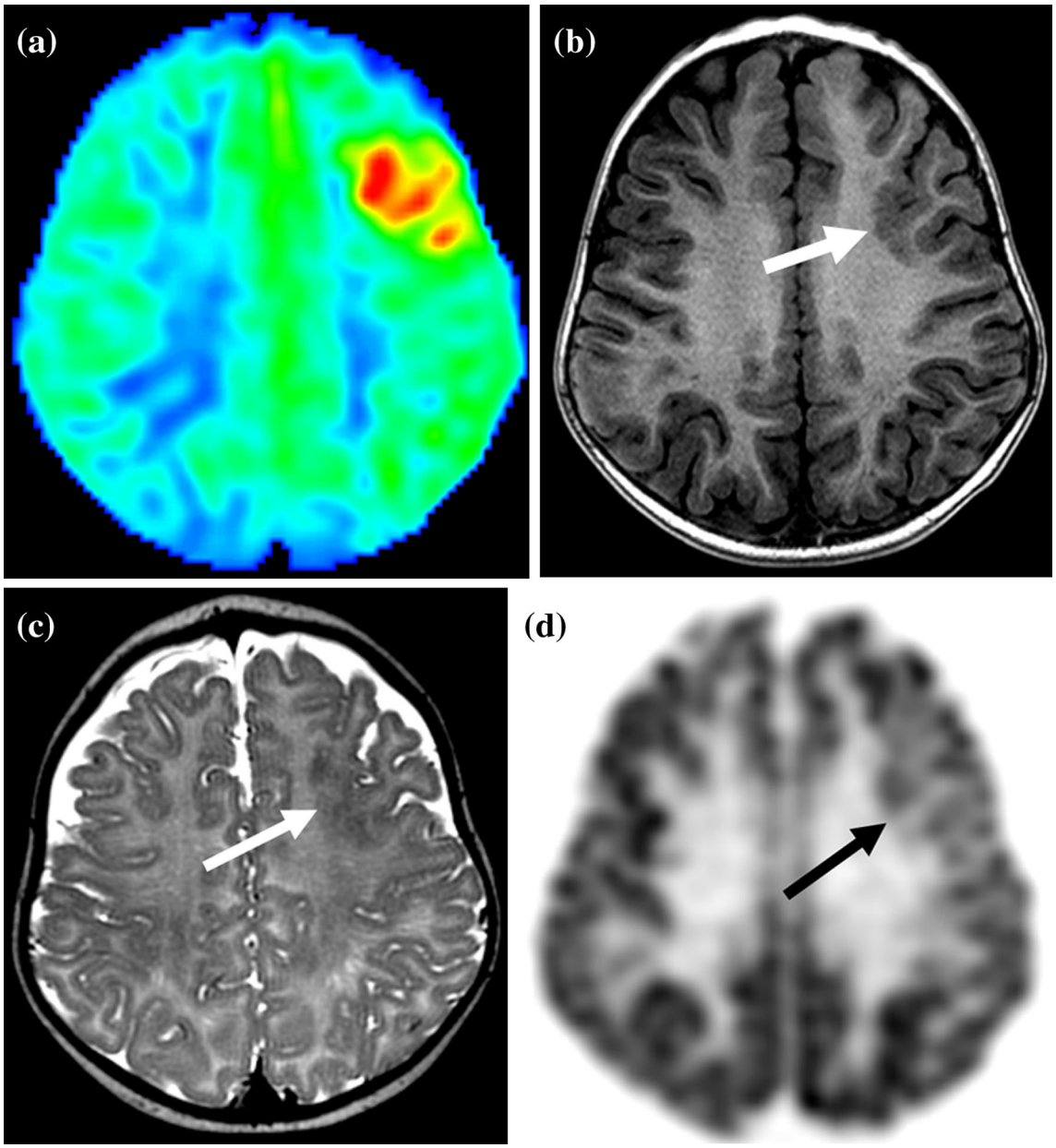


**Fig. 8** 15-month-old girl presenting in status epilepticus. MRI was obtained from the emergency department, with CBF map from ASL **a** showing markedly increased perfusion in the left frontal lobe (*red*) corresponding to the area of abnormality on EEG. Axial T1-weighted image **b** shows subtle thickening of left frontal gyri and irregularity of the gray-white junction (*arrow*), only perceived on focused second review informed by the ASL hyperperfusion. In retrospect, cortical dysplasia with gray-white blurring and abnormally low white matter signal (*arrow*) is better seen on an axial T2-weighted image (**c**) from an exam performed at 4 months of age, highlighting the variable appearance of cortical dysplasia depending on the degree of myelination. Subsequently, interictal $^{18}$F-FDG PET (**d**) showed hypometabolism in the left frontal lobe (*arrow*) and the patient underwent frontal lobectomy for seizure control (Color figure online)

hypothermia, have shown concordant results with ASL perfusion imaging. Infants who went on to develop HII show reduced perfusion in injured brain areas on day 1 of life, followed by hyperperfusion which peaked on days 2 and 3 [31–33]. These early perfusion abnormalities detected with ASL precede changes on T2-weighted and diffusion-weighted imaging, allowing an early window into the severity of injury. In newborns already showing decreased apparent diffusion coefficient (ADC) with diffusion-weighted imaging in the first few days of life, corresponding elevated CBF is seen with ASL imaging, often encompassing a larger area [34]. How these findings relate to reperfusion injury, neurologic outcomes and possible interventions are under investigation.

Similar post-anoxic perfusion disturbances have been seen with older children and adults (Fig. 7) [35, 36, 37•]. The hyperperfusion seen in vulnerable tissue such the basal ganglia, perirolandic cortex, and hippocampi is hypothesized to be due to loss of cerebrovascular autoregulation [35]. Depending on the degree and duration of hypoxia, watershed areas including the centrum semiovale or the entire cortex and white matter may be affected. After cardiac arrest and resuscitation, restricted diffusion and elevated perfusion usually co-localize, especially in children with poor outcomes [36]. In the most severe cases, global cerebral hyperperfusion in the first week after HII portends poor outcome, with one study showing only 4 of 16 such patients surviving at 4-month follow-up [35]. A recently described pattern of marked bilateral medial occipital lobe hyperperfusion in the first week after HII has also been associated with high mortality [37•]. Despite challenges in imaging neonates, we have found ASL in the setting of HII to be valuable across the pediatric age spectrum, often predicting a greater degree of injury than shown on conventional imaging when performed early in the course.

## Epilepsy

High-resolution anatomic brain MRI is a cornerstone in the evaluation of epilepsy, helping to identify children with a potentially treatable or surgically resectable cause of seizures. Ictal and interictal SPECT and, more recently, interictal [$^{18}$F]-fluoro-deoxy-D-glucose ($^{18}$F-FDG) PET have been used to identify the seizure focus by detecting its abnormally high perfusion during the seizure and decreased perfusion or glucose metabolism at baseline. ASL does not provide the same degree of anatomic detail as $^{18}$F-FDG PET, but nonetheless can also show similar findings [38, 39•, 40–42]. One recent study of surgical candidates with refractory epilepsy showed hemispheric concordance of hypometabolism with $^{18}$F-FDG PET and hypoperfusion with ASL in 18 of 20 cases, with complete agreement for localization in 14 patients [39•]. In another recent study performed in the ictal or immediately postictal state, ASL perfusion abnormality was identified in 39% of seizure patients and was concordant with electroencephalogram (EEG) in 77% of those having foci detected with both modalities [40]. In our experience, focal cortical hyperperfusion in the acute setting is much easier to detect with ASL than hypoperfusion in an outpatient exam. Ictal hyperperfusion may, in fact, be the first indication of status epilepticus in a critically ill patient undergoing MRI and help direct further evaluation [3]. It may also direct the radiologist to perform a second search of an area of the brain in which subtle cortical dysplasia may have been overlooked (Fig. 8).

## Conclusions

Arterial spin labeling perfusion MRI is a useful adjunct to conventional MR imaging in children, and can be successfully performed in all age groups from neonates to adolescents. Compared to other perfusion imaging techniques, ASL performs well in head-to-head studies and is especially well suited for use in children, lacking ionizing radiation or need for intravenous injection. At our tertiary care pediatric hospital, we incorporate ASL into routine protocols for a wide variety of indications, including all emergency or inpatient exams. ASL is especially useful in the work-up of brain tumors, moyamoya, migraine, hypoxic ischemic injury, and seizures.

#### Compliance with Ethical Standards

**Conflict of interest** Lauren W. Averill is a section editor for *Current Radiology Reports*. Vinay V. R. Kandula declares no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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