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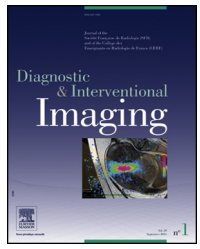

REVIEW /*Neuroradiology*

Arterial spin labeling in clinical pediatric imaging

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KEYWORDS
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Abstract Arterial spin labeling (ASL) perfusion-weighted magnetic resonance imaging is the only approach that enables direct and non-invasive quantitative measurement of cerebral blood flow in the brain regions without administration of contrast material and without radiation. ASL is thus a promising perfusion imaging method for assessing cerebral blood flow in the pediatric population. Concerning newborns, there are current limitations because of their smaller brain size and lower brain perfusion. This article reviews and illustrates the use of ASL in pediatric clinical practice and discusses emerging cerebral perfusion imaging applications for children due to the highly convenient implementation of the ASL sequence.

Many approaches exist to measure brain perfusion such as positron emission tomography (PET), dynamic susceptibility contrast magnetic resonance imaging (DSC MRI) and computed tomography perfusion (CTP). However, these techniques require administration of contrast material and/or exposure to ionizing radiation. Non-invasive and non-radiating

Abbreviations: AIS, Arterial ischemic stroke; ASL, Arterial spin labeling; CASL, continuous ASL; PASL, pulsed ASL; pCASL, pseudo-continuous ASL; ATT, Arterial transit time; AVM, Arteriovenous malformation; CBF, Cerebral blood flow; CTP, Computed tomography perfusion; DSC, Dynamic susceptibility contrast; DWI, Diffusion-weighted imaging; MRI, Magnetic resonance imaging; PC MRI, Phase contrast MRI; PET, Positron emission tomography; PLD, Post labeling delay; PRES, Posterior reversible encephalopathy syndrome; SNR, Signal-to-noise ratio; T1b, Relaxation time constant of arterial blood.

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methods such as Doppler ultrasonography and phase-contrast MRI (PC MRI) do not provide regional brain perfusion measurements, but only an overview based on cervical arterial flow. The emergence of arterial spin labeling (ASL) as a technique that provides both non-invasive and regional cerebral blood flow quantification offers new opportunities for assessing brain perfusion in neonates and children. ASL is currently moving from the field of research into that of routine clinical practice. A few studies have been conducted in pediatric patients and new clinical applications are emerging. These all make ASL a promising perfusion imaging method for assessing cerebral blood flow (CBF) in children [1].

The purpose of this article was to review and illustrate the use of ASL in pediatric clinical practice.

Technical principles

ASL is a non-invasive technique that uses endogenous blood water as a freely diffusible tracer. A previous article in this journal presents the principles of the technique [2]. The protons in arterial blood are magnetically labeled with a radiofrequency inversion pulse applied below the imaging slice in the neck vessels. Several labeling methods exist including continuous ASL (CASL), pulsed ASL (PASL) and pseudo-continuous ASL (pCASL). In CASL, a long flow-induced inversion pulse is applied. In PASL a short inversion pulse is applied to a larger region of the neck. pCASL is a hybrid method that utilizes a train of short RF pulses to mimic the effect of CASL. Because of several benefits the use of pCASL labeling is now recommended [3].

A labeled image is acquired after a minimum transit time for the labeled spins to reach the imaging slice, known as the inversion time or post labeling delay (PLD) (Fig. 1). A control image is acquired without prior labeling. Subtraction of the two images generates a perfusion-weighted image. Because the signal difference is only 0.5—1.5% of the full signal, multiple repetitions are needed to improve the signal-to-noise ratio (SNR). Subsequently, in order to obtain a quantitative perfusion map a quantitative model is required to calculate the ratio between the perfusion-weighted image signal and CBF. A number of parameters influence CBF quantification such as labeling efficiency, longitudinal magnetization of arterial blood, arterial blood and tissue relaxation time constant (T1b and T1t), arterial transit time (ATT), and blood-tissue partition coefficient. These parameters can be assumed or measured and may differ from adult literature values.

Initially proposed in 1996, CBF quantification using the ASL method has been improved with the addition of multiple parameters [4]. This method now has several research and clinical applications in adults [5,6]. However, a number of studies have demonstrated the challenges of optimizing ASL acquisition for subjects across a wide range of vascular and perfusion characteristics [3].

Given the non-invasiveness of the technique, which involves neither venous cannulation nor radiation, it is particularly suitable for children. In addition, ASL offers within-session repeatability and achieves absolute quantification of CBF.

The main drawback of the ASL method is a low SNR. However, there is a physiological improvement in SNR in children compared to healthy adults, mainly due to a higher

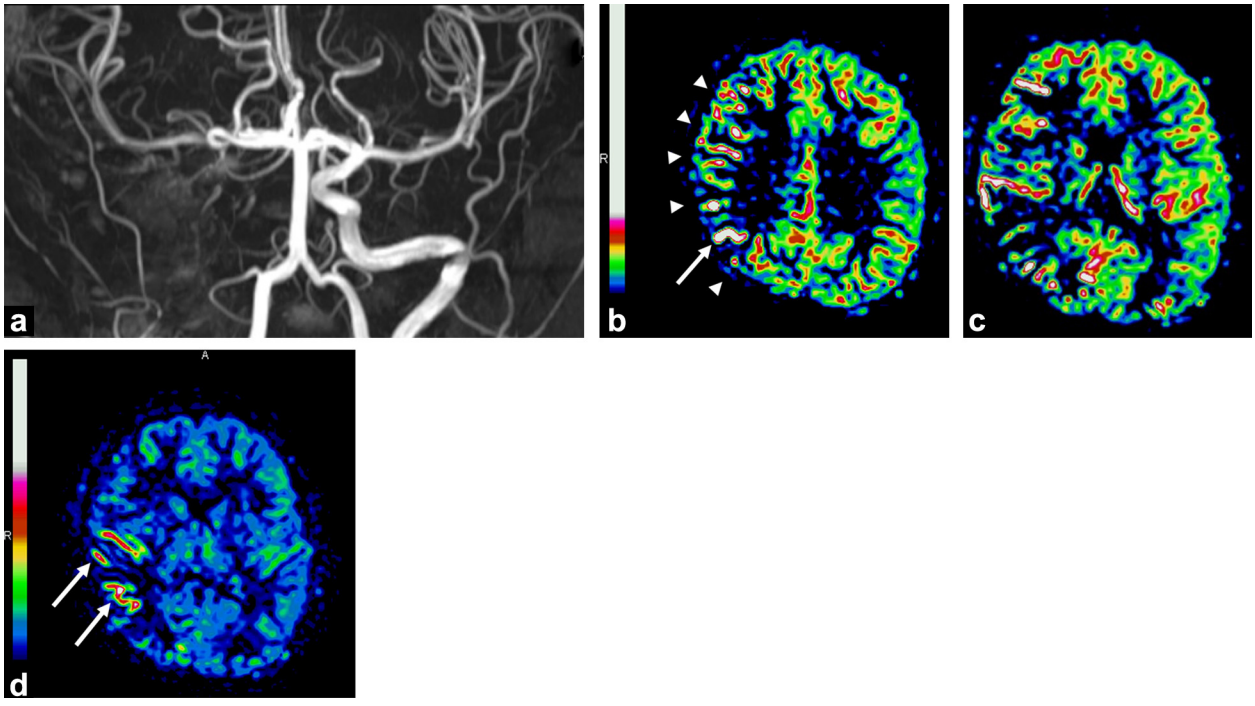

Figure 1. 11-year-old boy with recent surgical right internal carotid occlusion. MR angiogram shows right internal carotid occlusion (a). DWI shows no evidence of ischemia. ASL maps (b—d) show the transit time effect with pseudohypoperfusion of the right hemisphere (arrowheads) as well as linear high signal intensity representing slow flow in cortical vessels (arrows).

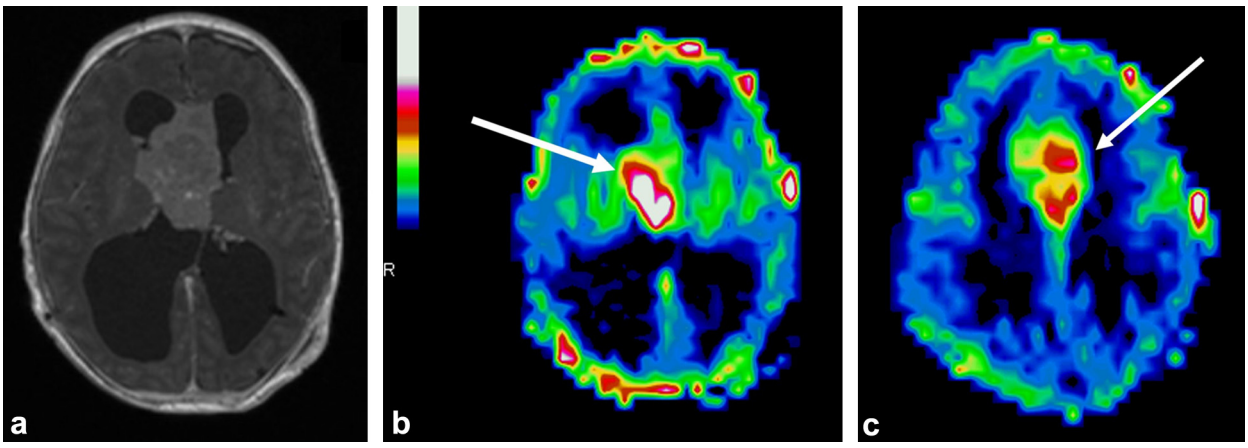

Figure 2. 3-day-old boy with hydrocephalus secondary to an interventricular tumor. T1-weighted MR image in the transverse plane after IV of gadolinium chelate shows an interventricular tumor (a). ASL perfusion maps (b and c) reveal hyperperfusion of the tumor with a ratio of 2.5 between the tumor and cortical perfusion. Tumor biopsy reveals high grade astrocytoma.

mean CBF and higher blood flow velocity in carotid arteries [6,7]. Indeed it results in reduced relaxation of the labeling effect and reduced transit effect in pediatric perfusion images. Moreover the higher water content of brain in children results in increased equilibrium MR signal and thereby improves pediatric ASL signal through increased tracer concentration and lifetime. Then pediatric perfusion images provides much stronger perfusion signal and provide much stronger delineation of cortical and subcortical structures compared with adult perfusion images [1].

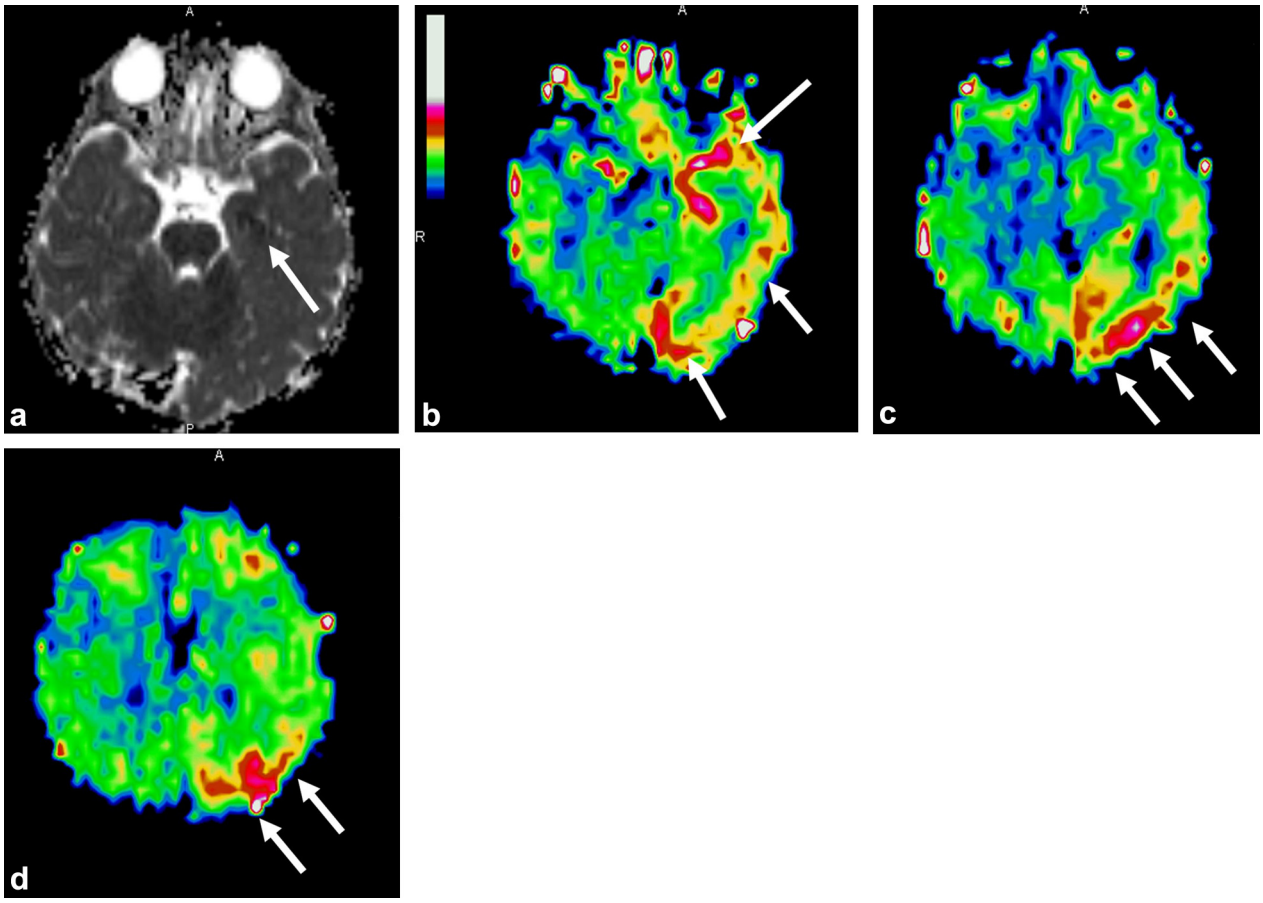

Figure 3. 14-month-old boy presenting with fever, right unilateral clonic seizures and ipsilateral hemiplegia that lasted for more than 1 hour. Postictal EEG showed slow focal and persistent left cerebral hemisphere activity 24 hours after the seizure. MRI performed during the postictal state shows no abnormality on conventional imaging. Apparent diffusion coefficient map (a) reveals restricted focal left hippocampal diffusion (*arrow*). ASL perfusion map (b–d) reveals a larger abnormal area of hyperperfusion in the left temporal and parieto-occipital lobes (*arrows*).

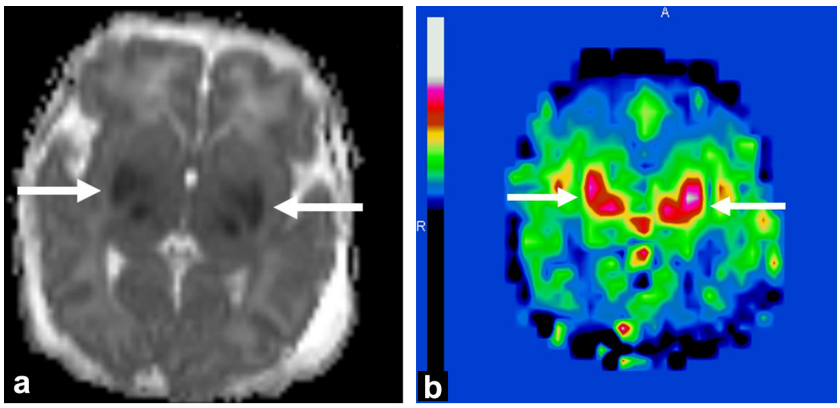

Figure 4. Asphyxiated neonate treated with hypothermia showing basal ganglia injury on MRI obtained on day 3 of life. ADC map (a) shows restricted diffusion in the bilateral thalami and lentiform nuclei (*arrows*). ASL perfusion map (b) reveals higher perfusion within the same areas (*arrows*).

Technical issues in pediatric imaging

Interpretation of perfusion data in children is further complicated by age-related changes (Table 1) and sedation-related changes in CBF. Indeed there is a need for perfusion map templates for healthy children to determine a normal perfusion map with regard to normal age-related changes in cerebral perfusion. CBF has been shown to be very low in neonates and then to rapidly increase during the first 6 month of life [8] and to continue slightly increase to be maximal between 5 and 10 years, according to study and cerebral perfusion imaging techniques [7,9,10] and depending on the cortical region [11]. Then CBF shows a negative correlation with age decreasing rapidly during adolescence

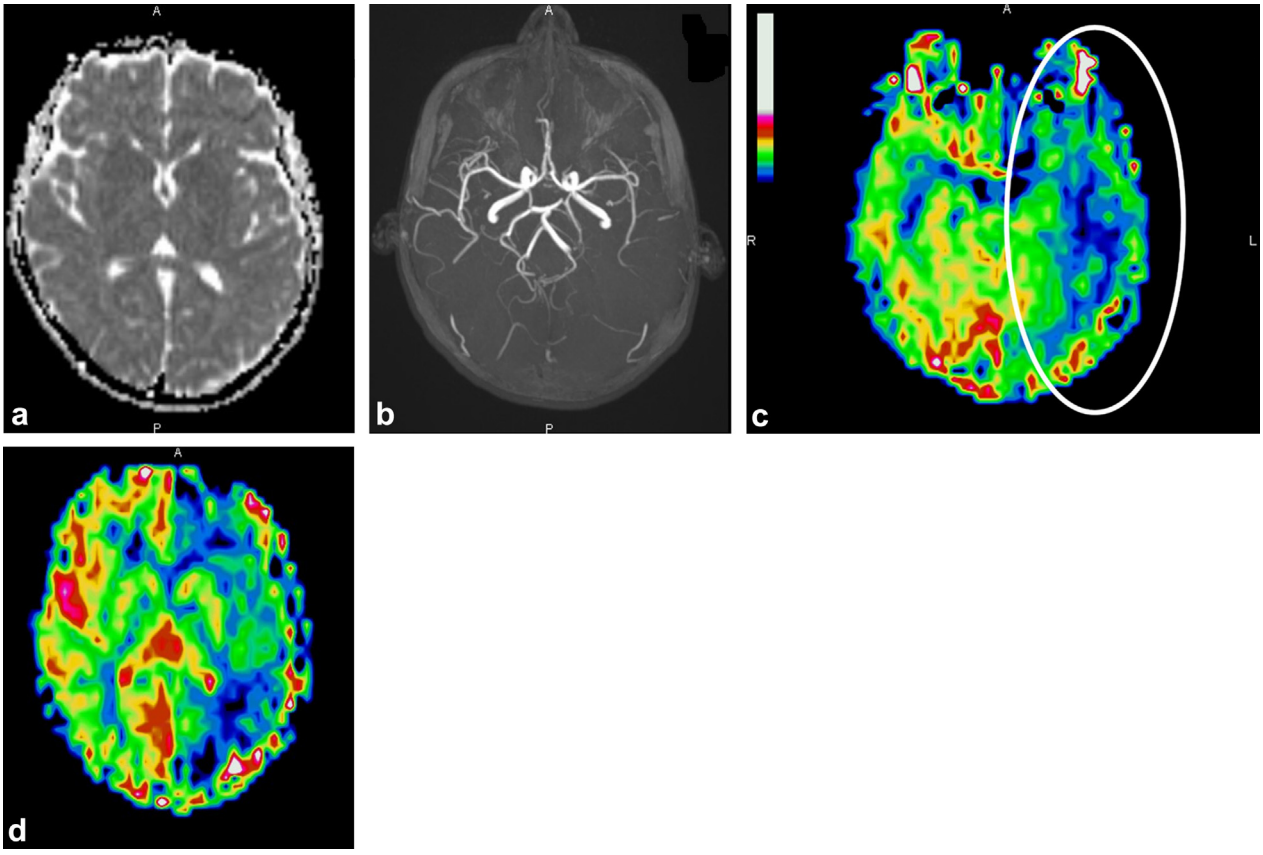

Figure 5. 12-year-old boy with no prior history of cephalalgia presenting a visual impairment followed by acute left temporal cephalalgia. Neurological examination reveals distal right arm deficit and paraesthesia and aphasia. Conventional MRI performed 10 hours after the onset of symptoms was normal with no restricted diffusion on the ADC map (a) and MR angiography was also normal (b). ASL perfusion map (c and d) was the single abnormal sequence, and showed hypoperfusion in the left temporal and parietal cerebral areas (*circle*). A diagnosis of first migraine attack with aura was made with total resolution of symptoms after ibuprofen administration.

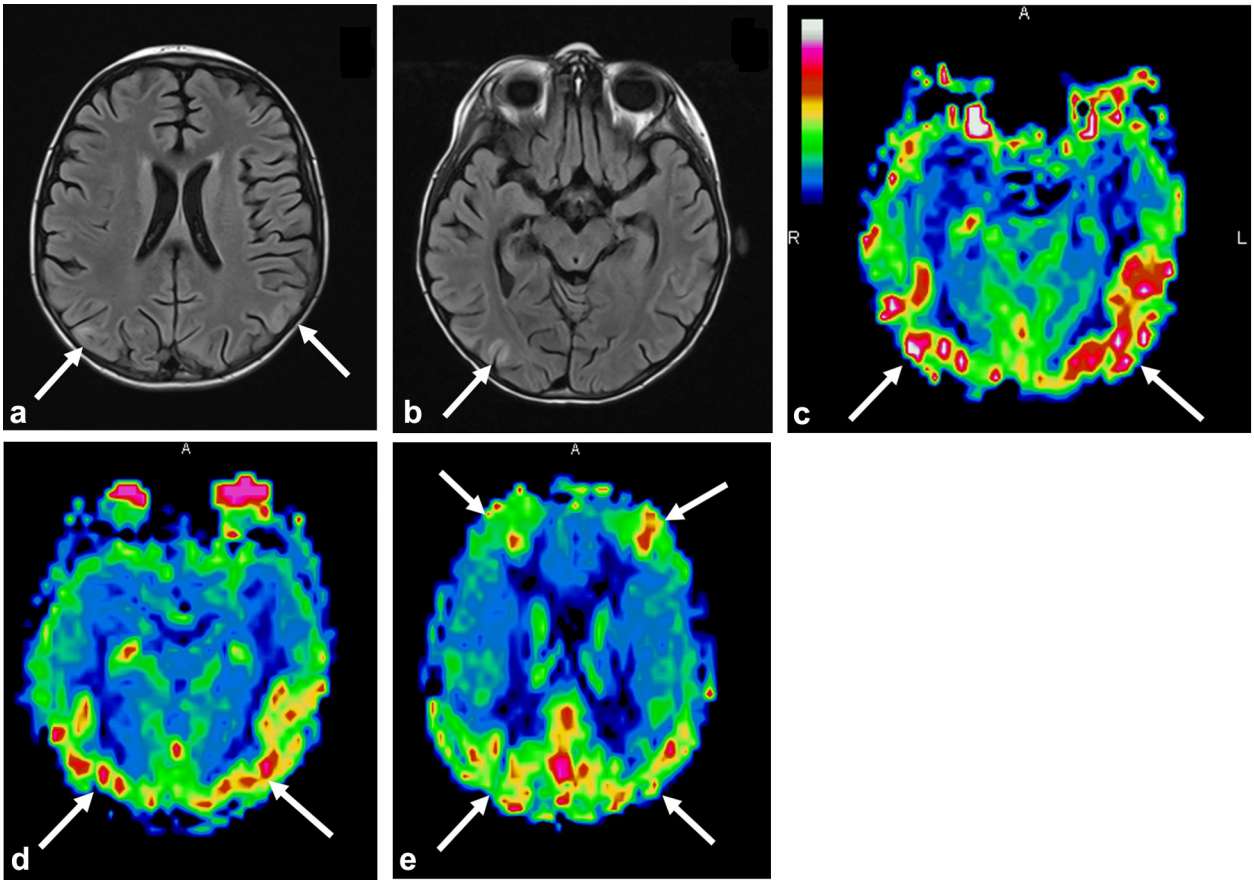

Figure 6. 9-year-old boy with a history of undetermined severe vascularitis presenting with seizures and hypertension: a and b: FLAIR images in the transverse plane demonstrate typical posterior involvement of posterior reversible encephalopathy syndrome with focal areas of high cortical signal intensity (*arrows*); c—e: ASL perfusion map shows more extensive hyperperfusion within the same areas (*arrows*).

until a plateau is reached around 25 to 30 years [7,12,13]. However, to our knowledge, there are no studies that have reported ASL CBF measurement in children with a specific age range of 5 month to 6 years.

A substantial proportion of pediatric patients receive anesthesia or sedation for MRI, which may have impact on cerebral perfusion [14]. Given general unknown effects of sedatives on ASL imaging, sedation status remains an important consideration in pediatric imaging.

Another point is the lack of standardization of acquisition parameters and image processing methods. Standardization of acquisition and post-processing methods is paramount to enable ASL to mature from a experimental method to a widespread clinical tool [15]. In clinical practice, CBF maps are automatically generated by the manufacturer workstation with assumed or measured quantification parameters. However, it is not clear whether values estimated in adults and applied to a neonatal and pediatric population allow

Table 1 Age-related evolution of CBF values in grey and white matter using ASL technique.

Age range	Global CBF	Mean GM CBF	Mean WM CBF	Labelling method	References
Healthy term neonate	13—27	16 (cortex) 30 (basal ganglia)	10	PASL pCASL pCASL	Miranda et al., 2006 [9], Pienaar et al., 2012 [10], Massaro et al., 2013 [11]
3—5 months	24—56	25—60	15—30	PASL PASL	Duncan et al., 2014 [12], Varela et al., 2015 [13]
4—12 years		97 ± 5	26 ± 1	CASL	Biagi et al., 2007 [7]
7—17 years	74	82.4	41.5	pCASL	Jain et al., 2012 [14]
13—19 years		79 ± 3	22 ± 1	CASL	Biagi et al., 2007 [7]
Up to 20 years		58 ± 4	20 ± 1	CASL	Biagi et al., 2007 [7]

CBF: Cerebral Blood Flow values in mL/100 g/minute; GM: grey matter; WM: white matter.

population-specific rather than subject-specific values to be used. Then pediatric specific standardization is needed to provide reproducible and comparable quantitative measurements of cerebral perfusion. As an example Varela et al. have shown that the accuracy of ASL CBF measurements in infants is improved with the use of infant-specific auxiliary parameters, particularly blood and tissue T1, which are much more variable in the imaged infants than in adults [16]. Another study demonstrated the accuracy and longitudinal repeatability of pCASL sequence in a sample of 22 children aged from 7 to 17 years with particular attention paid to incorporating developmental changes in blood T1 [17].

Clinical applications

Pediatric neurovascular diseases

Arterial ischemic stroke

Brain infarct may show both hyperperfusion and hypoperfusion during the acute stage in children. In 10 children with arterial ischemic stroke during the acute stage, Chen et al. have reported that CBF maps showed 5 lesions with hypoperfusion, 2 with hyperperfusion, 2 with normal perfusion and a complex lesion in one patient [18]. Perfusion-diffusion mismatch is a central concept in the imaging of ischemic stroke in adults [19]. However, post-ischemic hyperperfusion in stroke is well known. Moreover, the etiology of arterial ischemic stroke differs between adults and children and clots are less frequent in children than in adults. Other causes of focal autoregulatory dysfunction include posterior reversible encephalopathy syndrome (PRES) with initial vasoconstriction and hypoperfusion followed by rebound hyperperfusion [6].

Moyamoya disease

A good correlation between ASL perfusion-weighted MRI and $H_2[^{15}O]$-PET [20] and DSC MRI [21] has been shown in children with Moyamoya disease. However, one of the main limitations of the ASL technique is that the time between labeling in the feeding arteries and the arrival of labeled blood in tissue (i.e., ATT) can have a significant effect on the ASL signal. In cerebrovascular disorders such as Moyamoya disease, the ATT may be prolonged leading to focal intravascular signal artifacts. Moreover, CBF may be underestimated in regions with delayed arterial transit time. Multi-delay ASL can improve CBF quantification and could be used as a prognostic imaging biomarker in patients with Moyamoya disease. By incorporating delayed ATT into the calculation of CBF, multi-delay ASL is able to provide imaging consistent with CT perfusion in Moyamoya disease [22]. Yet artefacts may be useful as they can predict the presence and intensity of the collateral arterial network in Moyamoya disease [23].

Sickle cell disease

Several studies have investigated the value of ASL for measuring regional CBF in children with sickle cell disease in order to identify the existence of altered CBF in areas unaffected on conventional images [24]. There is a need for a reliable screening method to identify patients at risk of silent infarct. However, it is important to be aware of the difficulties involved in interpreting CBF asymmetries as reported in several studies. There are technical issues with ASL in children with sickle cell disease. For example, chronic anemia and compensatory increases in blood velocity and flow reduce the arterial transit time and labeling efficiency. Moreover, hematocrit levels affect the longitudinal relaxation time of arterial blood and this affects quantification. Gevers et al. took these technical aspects into account and did not find any correlation between CBF asymmetries and silent infarct in 12 children [25]. Care should be taken in interpreting ASL-CBF measurements in sickle cell disease patients.

Vascular malformations

One study demonstrates nidus location and patency in a cohort of 21 pediatric patients with brain arteriovenous malformation. This paper shows that the mean CBF in the arteriovenous malformation is twice those of normal contralateral cortical CBF [26]. Moreover quantification of nidal CBF may enable objective monitoring of arteriovenous malformation obliteration after treatment. Another related technique is unenhanced time-resolved spin-labeled MR angiographic imaging that has been shown to be a reliable clinical tool for cerebral arteriovenous malformation characterization in adult population [27,28].

Pediatric brain tumors

A few studies have addressed the issue of perfusion of brain tumors in pediatric patients (Fig. 2). Tumor evaluation with ASL has been studied, and correlations between flow and tumor grade have been established. ASL may play a complementary role to DSC MRI for investigation of pediatric brain tumors given that it can provide information on capillary perfusion [29]. Yeom et al. have studied the main ASL perfusion patterns among various pathologic types of brain tumors in a series of 54 children [30]. As found in adults, the maximum relative tumor blood flow (rTBF) of high-grade tumors was significantly higher than that of low-grade tumors. However, rTBF cannot separate high-grade from low-grade tumor at the individual level. There was no correlation between rTBF values and patterns of contrast enhancement. Moreover, posterior fossa tumors should be interpreted with caution due to posterior fossa susceptibility artifacts.

Another study focused on choroid plexus neoplasms in 13 children (7 papillomas and 6 carcinomas) [31]. This study shows that relative CBF values were significantly higher in carcinomas than in papillomas when using ASL. ASL is therefore a promising technique to discriminate between choroid plexus carcinomas and papillomas, which is difficult with conventional imaging techniques.

Epilepsy

Localized areas of decreased CBF have been found in children with focal cortical dysplasia during the interictal period [32]. This hypoperfusion was associated with structural MRI abnormalities and PET hypometabolism in 5/6 cases. CBF was significantly lower in the lesion than in the normal cortex [32]. One paper reported multiple hypo perfused areas

correlating with MRI tubers and ^{18}FDG hypometabolic areas in three patients with tuberous sclerosis [33]. On the other hand, ictal cortical hyperperfusion is believed to be a useful marker for identifying epileptogenic areas and has been observed with ASL imaging [34]. ASL imaging in a 25-year-old man with partial epilepsy status showed strong focal hyperperfusion of the region corresponding to the anatomical and physiological epileptic focus and also provided a clear contrast with the relative hypoperfusion in the interictal state [34]. The ASL sequence could be added at the end of the morphological MRI for epilepsy investigation and this would provide non-invasive functional information and help to detect the pathological area (Fig. 3).

Hydrocephalus

The distinction between ventriculomegaly and hydrocephalus with increased intracranial pressure is important. Yeom et al. were the first to assess cerebral perfusion using ASL in children with hydrocephalus [35]. Patients with symptomatic hydrocephalus had lower CBF than healthy controls for all brain regions. The median CBF increased after alleviation of obstructive hydrocephalus in all subjects. The results were consistent with another study reported using nuclear medicine methods [36]. Thus ASL measurement of CBF may be used as a potential non-invasive method to assess intracranial pressure, although additional data are needed.

Neonatal perfusion imaging

Brain perfusion plays a key role in the pathogenesis of brain damage in high-risk neonates (both preterm and full-term asphyxiated infants) (Fig. 4). It is challenging to perform ASL MRI in neonates due both to their low physiological baseline CBF compared to older children and adults and the method's low SNR. Technical adjustments to imaging parameters are needed to address the fundamental differences between pediatric and adult populations. Moreover, ASL is highly sensitive to motion. Yet some studies have been conducted in asphyxiated neonates, showing an early hyperperfusion in brain regions subsequently exhibiting injury [37]. Regions with low ADC values are highly correlated with increased co-located regions of increased ASL CBF intensity in 9 newborns aged between 0 and 3 days presenting with ischemia [38]. Moreover, ASL may be used as a spectroscopy biomarker to predict neurodevelopmental outcome. De Vis et al. have shown that a higher ASL perfusion value in 28 neonates with hypoxic ischemic encephalopathy was associated with a worse neurodevelopmental outcome at 9 or 18 months of age [39]. Technical and image processing improvements are needed to extend the use of ASL to neonates.

Emerging applications

ASL imaging can easily be performed during conventional MRI procedures without any side effects at the penalty of a longer examination time of approximately 5 minutes. Cerebral perfusion may therefore be assessed in numerous clinical applications (Figs. 5 and 6). By way of example, the use of ASL MRI can not only rule out differential diagnosis but also provide evidence for positive diagnosis of migraine by showing focal CBF abnormalities whereas conventional MRI is normal [40]. Another example is the use of ASL in metabolic disorders such as in stroke-like episodes of MELAS, showing hyperperfusion in the acute phase [41]. Another field of research is the investigation of cerebral perfusion before and after surgery in neurosurgical pathologies such as craniosynostosis and arachnoid cyst, as a better understanding of the physiopathology of these diseases and the functional impact of surgery can be gained.

Conclusion

The main advantage of ASL perfusion-weighted MR sequences in pediatric practice is their radiation-free and non-invasive nature. Moreover, there is a physiological improvement in SNR in children compared to healthy adults owing to a greater mean cerebral blood flow. Concerning newborns, there are current limitations because of their smaller brain size and lower brain perfusion. There are many emerging cerebral perfusion imaging applications for children due to the highly convenient implementation of the ASL sequence.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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