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Research article

Measurement of pediatric regional cerebral blood flow from 6 months to 15 years of age in a clinical population

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ABSTRACT

Objectives: To investigate changes in cerebral blood flow (CBF) in gray matter (GM) between 6 months and 15 years of age and to provide CBF values for the brain, GM, white matter (WM), hemispheres and lobes.
Methods: Between 2013 and 2016, we retrospectively included all clinical MRI examinations with arterial spin labeling (ASL). We excluded subjects with a condition potentially affecting brain perfusion. For each subject, mean values of CBF in the brain, GM, WM, hemispheres and lobes were calculated. GM CBF was fitted using linear, quadratic and cubic polynomial regression against age. Regression models were compared with Akaike's information criterion (AIC), and Likelihood Ratio tests.
Results: 84 children were included (44 females/40 males). Mean CBF values were 64.2 ± 13.8 mL/100 g/min in GM, and 29.3 ± 10.0 mL/100 g/min in WM. The best-fit model of brain perfusion was the cubic polynomial function (AIC = 672.7, versus respectively AIC = 673.9 and AIC = 674.1 with the linear negative function and the quadratic polynomial function). A statistically significant difference between the tested models demonstrating the superiority of the quadratic ($p = 0.18$) or cubic polynomial model ($p = 0.06$), over the negative linear regression model was not found. No effect of general anesthesia ($p = 0.34$) or of gender ($p = 0.16$) was found.
Conclusion: we provided values for ASL CBF in the brain, GM, WM, hemispheres, and lobes over a wide pediatric age range, approximately showing inverted U-shaped changes in GM perfusion over the course of childhood.

1. Introduction

Arterial Spin Labeling (ASL), developed in the early 1990s, is an innovative magnetic resonance imaging (MRI) sequence that uses magnetically labeled protons of blood water as an endogenous contrast agent [1]. It enables imaging of brain perfusion and quantification of cerebral blood flow (CBF) without intravenous injection or irradiation, unlike nuclear medicine or MRI-based perfusion techniques involving injection of a paramagnetic contrast agent. Consequently, ASL is particularly well suited for investigating pediatric brain perfusion.

From birth to adulthood, the brain undergoes many overall and regional developmental changes. The ability to study these transformations would allow a better understanding of brain development. A possible way to do this could be the quantification of CBF using ASL due to its non-invasive nature and the close relationship between cerebral metabolism and perfusion [2]. ASL is also increasingly used in pathological contexts [3], particularly for newborn hypoxic-ischemic encephalopathy [4], cerebrovascular diseases [5], epilepsy, brain tumor grading and tumor identification [3,6].

ASL is not yet widely used as a routine perfusion method. One of the

Abbreviations: (p)ASL, (pulsed) arterial spin labeling; MRI, magnetic resonance imaging; CBF, cerebral blood flow; GM, gray matter; WM, white matter; CSF, cerebrospinal fluid; ROIs, regions of interest; AAL, automated anatomical labeling; AIC, Akaike's information criterion; LRT, likelihood ratio tests

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reasons for this is the incomplete knowledge of normal pediatric ASL CBF values and the potential changes in brain perfusion over the course of childhood. This knowledge is a prerequisite for the pertinent detection of CBF abnormalities. Several teams have studied CBF in pediatric populations using ASL but these studies were often limited to specific age groups, around birth [7,8] or after 4 years of age [9–12]. To our knowledge, there is only one study that reports CBF values using ASL in four subjects aged between 6 months and 4 years [13]. In this age group, sedation or general anesthesia is virtually mandatory to obtain the child's compliance, and this could have distorted the results of the investigation. Consequently, there is a real need to investigate normal CBF values in a wide range of ages in order to develop clinical use of ASL in the pediatric population and to better understand brain development.

The aim of this study was to investigate changes in brain perfusion in gray matter from 6 months to 15 years of age, using ASL sequences, and to provide reference values for the brain, gray matter (GM), white matter (WM), hemispheres, and lobes in this age range. A secondary objective was to study the effect of general anesthesia and gender on CBF values.

2. Material and methods

2.1. Study population

We retrospectively reviewed all consecutive routine brain MRIs performed in our pediatric radiology department between January 2013 and June 2016 for which ASL images had been acquired. The main inclusion criteria were age between 6 months and 15 years and normal morphological MRI images. The main exclusion criteria were all factors that could have affected CBF such as a history of stroke, brain tumor, metabolic diseases, seizure or headache in the previous 2 days, prematurity, brain malformations or neurosurgery. MRI indications were resumed in Table 1. We excluded scans with artifacts or significant patient movement. The study was approved by the local Institutional Review Board. According to national legislation, written consent is not necessary for such retrospective studies, however all the parents were informed about the study and could choose not to include their child.

2.2. MRI protocol

All scans were performed on a 1.5 T Magnetom Aera (Siemens Healthcare, Erlangen, Germany) with a 12-channel head coil. The complete imaging protocol varied according to clinical features but 3D T1-weighted and pulsed ASL (pASL) images were acquired in all cases. The parameters of both image types were standardized.

The parameters of 3D sagittal MPRAGE T1-weighted morphological images were as follows: TR = 2090 ms, TE = 4.92 ms, TI = 1100 ms, 256 × 256 matrix, 0.5 × 0.5 × 1 mm^3 voxel size, FOV = 26 cm^2, 160 slices, TA = 200 s.

Table 1
MRI indications for all children.

MRI indications	*n*
Headache	24
Seizure	12
Brief minor neurological deficit without sequelae	10
Psychomotor retardation	9
Autism	8
Facial Port-Wine Stain	8
Paresthesia	4
Behavioral disorders	3
Others[a]	6
Total	84

Note: All MRI images must be normal and were performed outside an acute context; *n* number of patients.

[a] Others: cervical bone malformation, drug intoxication, psychological problem, uveitis, weight loss, chronic fatigue.

The parameters of pASL axial images with the PICORE Q2TIPS labeling scheme [14] were as follows: TR = 3200 ms, TE = 12 ms, TI_1/TI_2 = 700/1800 ms, 64 × 64 matrix, 4 × 4 × 8 mm^3 voxel size, FOV = 256 mm^2, TA = 336 s, 9 slices, 8 mm slice thickness, 2.0 mm slice gap, 61 repetitions. One M_0 reference image (magnetization of brain tissue at the equilibrium used to normalize the difference perfusion map) and 30 control/label image pairs were acquired.

Depending on the age and behavior of children, sedation or general anesthesia was administered before performing the scan as required. A pediatrician performed sedation with permanent monitoring of oxygen saturation. The general anesthesia protocol was standardized using sevoflurane. A controlled ventilation system and an end-tidal carbon dioxide monitor were used to maintain normocapnia.

2.3. Data processing

Processing of both 3D-T1 and ASL images was performed using custom-built ASL processing tools based on SPM8 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College, London, UK) and MATLAB® 2014b (The MathWorks Inc., Natick, Massachusetts, USA).

2.3.1. Anatomical data processing

Brain data were extracted with the FSL Brain Extraction Tool (Analysis Group, FMRIB, Oxford, UK) [15]. A bias intensity correction of each T1-weighted sequence was performed using SPM. Then the sequence was segmented into GM, WM and cerebrospinal fluid (CSF) probability maps using NIHPD pediatric brain atlases [16]. Spatial normalization parameters, estimated by the same unified segmentation model SPM routine, were applied to register the 3D T1 volumes to the atlas space.

2.3.2. ASL data processing

The first step was a 6-parameter (rigid body) registration of the ASL volumes acquired from the same subject using a least-squares approach to reduce subject motion between repetitions [17]. Then the M0 image was separated from other ASL volumes; label and control volumes were pair-wise subtracted. The perfusion signal was usually obtained by averaging across the repetitions. However, a conventional mean is sensitive to outliers. To create a perfusion-weighted map, we replaced the conventional mean by a Huber-M-estimator, that minimizes the weight of a repetition far removed from the mean [18]. Then the perfusion-weighted map was co-registered to the 3D T1 gray matter map using a rigid transform and by maximizing Normalized Mutual Information. The averaged perfusion-weighted map was converted into a quantitative ASL CBF map by applying the following single compartment model [13,19]:

$$CBF = \frac{6000 \times \lambda \times \Delta M \times e^{\frac{(TI_2 + idx_{sl} \times TI_{sl})}{T_{1b}}}}{2 \times \alpha \times TI_1 \times M_{0b}} [mL/100g/min]$$

The factor of 6000 converts the unit from mL/g/s to mL/100 g/min. λ is the brain/blood partition coefficient in mL/g (0.9 mL/g) [20]. ΔM is the average difference in signal intensity between control and label acquisitions. TI_2, inversion time, is the time from the initial pulse to image acquisition (1800 ms) [20]. TI_2 is adjusted for each slice to take into consideration the time interval TI_{sl} (47 ms) between slice acquisitions in our 2D multislice ASL sequences. idx_{sl} is the slice index (0 for the first slice). Blood T1, T_{1b}, is the longitudinal relaxation time of blood in seconds (1350 ms). Alpha is labeling efficiency (98%) [20]. TI_1 is the duration between the inversion and saturation pulse (700 ms). M_{0b} is the longitudinal magnetization of blood at equilibrium and is estimated from the M0 map, the first volume of the ASL series.

Finally, the normalization step warped each individual quantitative