Temporal assessment of abnormal microvasculature in R6/2 transgenic mouse model of Huntington's disease by BOLD contrast microscopic MRA

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Introduction

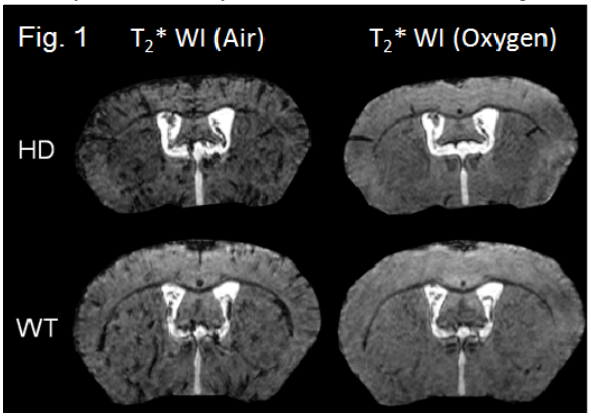
Cerebral microvascular aberrations are increasingly recognized as a major disturbance in the formation of brain pathologies. To appreciate the neurovascular abnormalities in brain disorders, approaches sensitive to the detection of small vessel changes are necessary. Previously, by using a technique called 3D ΔR_2 microscopic magnetic resonance angiography (3D ΔR_2 mMRA), it was discovered that mice with Huntington's disease (HD) (R6/2) exhibited a disorganized, arborous neurovasculature in the brain [1]. However, 3D ΔR_2 mMRA, despite a decent quality and resolution, is limited in clinical applications due to the use of the iron-oxide based contrast agents (CA). The iron-oxide based CA is associated with restricted availability, high costs, and potential adverse effects, which hinders further applications. To provide an equally useful 3D mMRA technique yet without the problems associated with the use of the CA, we proposed a newly developed method called 3D gas challenge ΔR_2* mMRA (3D gas ΔR_2* mMRA). This new approach requires no CA. The visualization of neurovasculature is based upon intrinsic blood oxygen level-dependent (BOLD) signal change from air inhaling to pure oxygen inhaling. By using 3D gas ΔR_2* mMRA, the structural, functional, and quantitative information (i.e. cerebral blood volume (CBV)) of small brain vessels can be obtained with equally high resolution and high quality. The major goal of the current study is to demonstrate the use of this new 3D mMRA technique in the visualization of small vessel abnormalities in HD. This new method is not only capable of showing exquisite neurovascular abnormalities but also useful for future clinical applications to characterize the spatiotemporal changes of cerebromicrovasculature in patients with brain disorders.

Materials and Methods

All experiments were performed on a 7T PharmaScan 70/16 MR scanner with an active shielding gradient. Male R6/2 mice and littermate controls (wildtype; WT) were used in this study. The mice were initially anesthetized with 5% isoflurane flowed in air at 2L/min. When fully anesthetized, the animal was placed in a prone position and fitted with a custom-designed head holder inside the magnet. 2% isoflurane was used to maintaine the anesthesia via a nose piece throughout the experiments. To determine ΔR_2*, T_2*-weighted images (T_2* WI) under the inhalation of air followed by oxygen were performed. The second T_2* WI was delayed by 15 minutes to allow complete gas exchange. T_2* WI was acquired using 3D gradient-echo with flow compensation (3D-GEFC) sequence with a TR of 100 ms, a TE of 35 ms, flip angle of 15^0 , FOV = 2×2×1 cm^3, acquisition matrix = 256×256×96 (zero-padded to 512×512×192). The image resolution in three directions was 39.06, 39.06, 52.08 μm^3. ΔR_2* map was calculated pixel-by-pixel by $(1/TE)\ln(S_{O2}/S_{Air})$ using MR Vision (MR Vision Co.). 3D view of microvasculature was constructed from the 3D ΔR_2* map using a volume-rendering utility of the Avizo software (TGS, Avizo, San Diego, CA).

Results and discussion

The T_2* WIs were acquired during air or oxygen inhalation on WT and HD mice and shown in Fig. 1. On T_2* WI from air inhalation, the hypointensities indicated the distribution of vessels, which were dominated by veins. HD showed more visible vessels as compared to WT. While inhaling oxygen, both HD and WT increased in signal intensities. The temporal changes of 3D gas ΔR_2* mMRA in WT and HD brains is shown in Fig. 2. In HD, vessels were increasingly seen at the older ages. By contrast, in WT, no significant changes were observed as a function of time. No significant increase of CBV was observed in WT cortex, while HD showed gradual increases in CBV as the disease progressed. The results demonstrate the sensitivity of 3D gas ΔR_2* mMRA to reveal small vessel aberrations in HD. This technique is potentially to be a clinically feasible method for characterizing cerebromicrovascular abnormalities in patients with brain disorders.



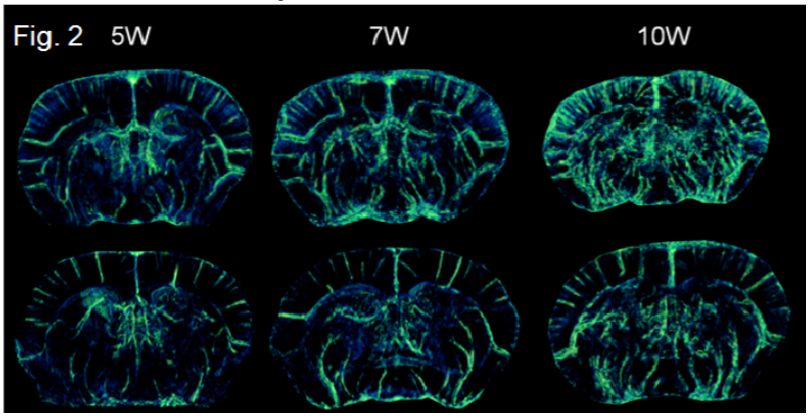


Fig. 1. T_2* WI of air and oxygen inhaling in 10-week-old HD and WT mice brains.

Fig. 2. Temporal change of 3D microangiography in HD and WT mice brains.

Reference: 1. Lin, C. Y. et al., *ISMRM 18*, 462, 2010.