MRI measurements following chronic bilateral common carotid occlusion in newborn and adult rats: a model for moyamoya syndrome?

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Introduction Moyamoya syndrome (MMS) is an occlusive cerebral arteriopathy angiographically characterised in humans by bilateral stenosis of the terminal internal carotid arteries and the presence of basal collateral vessels. The most common clinical presentation is with cerebral ischaemic symptoms in childhood. Aetiology is not understood at present and, in particular, it is not known whether the collateralisation is part of the vascular pathology or whether it represents the response of the developing brain to arterial occlusion. Presently, invasive revascularisation surgery is the only treatment available. Chronic abnormalities of tissue perfusion (i.e. hypoperfusion) have been identified in children with MMS using MRI[1]. However the relationship between long term hypoperfusion and clinical outcome has not been clarified. Currently there is no animal model specific for MMS. Development of a model would be useful for study of the consequences of chronic hypoperfusion in the maturing brain as well as for development of novel therapeutic interventions. Previous animal studies have demonstrated that bilateral common carotid artery occlusion (BCCAO) led to blood flow decline to less than 35% of controls[2]. Permanent BCCAO induced morphological abnormalities in hippocampal cells and quantifiable cell loss within 7 months of blood flow reduction in aged rats but were resolved in young rats [3,4,5,6]. Collateral vessel development in response to BCCAO has been reported in animal models[7,8]. The aim of this study was to develop a model of MMS using BCCAO and to follow the subsequent vascular and morphological changes using magnetic resonance imaging (MRI).

Methods Four adult Sprague-Dawley (SD) rats were studied in experiments where CBF was measured before and immediately after BCCAO surgery. For chronic experiments 8 adult (3-months old) SD rats and 8 newborn pups (3-day old) SD rats were randomly divided into equal groups for BCCAO or sham control surgery. Animals were anaesthetised with 2.5% halothane and maintained on 1.75% halothane with 70/30% N_2O/O_2. Coronal images were obtained approximately 3.3mm from bregma on a 2.35T horizontal bore SMIS system. CASL[9]: 128 x 64pixels, 2mm slice thickness, 44 averages and T1 fits using 8 different TI times with 22 averages. T2: MASAGE-IEPI[10], 128 x 64pixels, 2mm slice thickness, 16 averages. DWI: 128 x 64 pixels, 2mm slice thickness, 48 averages. High resolution spin-echo: 128 x 128pixels, 1mm slice thickness, 17 slices, FOV 30 x 30mm, 10 averages. CO_2 Reactivity- T2*: 128 x 64pixels, 2mm slice thickness, FOV 40 x 20mm, 40 averages. Six baseline acquisitions before a 5 minute challenge with 15% CO_2 with continuous MRI. MR angiography (MRA): 128 x 128 x 128pixels, FOV 25 x 25 x 30mm, visualisation by maximal intensity projection (MIP) software.

Results & Discussion

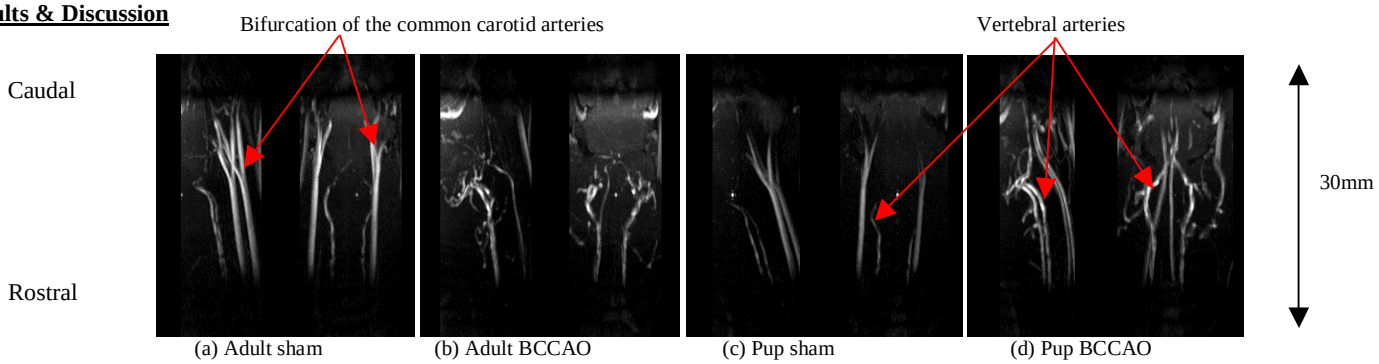

Figure 1: Sagittal (left in each frame) and axial (right) MRA MIPs of the neck 6 months following surgery in control (a & c) and BCCAO animals (b & d). Note the presence of the characteristic bifurcation of the common carotid arteries in the sham-operated rats.

There were significant reductions in CBF after BCCAO surgery in the cortices and hippocampi (~50%) and a 20% decrease in the thalami. However, 6 months following surgery CBF was restored in both adult and pups (sham controls: 116 ± 27ml/100g/min, 78-160 ml/100g/min; operated: 124 ± 30 ml/100g/min, 74-176 ml/100g/min *(mean ± sd, range)*). No changes were observed in the apparent diffusion coefficient (ADC), T1 or T2 values 6 months post-surgery. A 5 min 15% CO_2 challenge did not yield any differences in T2* change between groups. No structural changes were observed using high resolution spin echo MRI. These results were surprising in light of the literature cited which suggests anatomical change. To investigate the underlying mechanism for the return of CBF to control values, we performed MRA of the neck. As expected, signal from the common carotid arteries was present in the sham-operated rats, but was absent in the BCCAO animals. Interestingly, signal from the vertebral arteries appeared to be enhanced and the presence of collateral formation was evident (fig.1). Two observers blinded to the groupings of the animals evaluated the MRA images and reported more tortuous vertebral arteries in the BCCAO adults and more midline collaterals in the BCCAO pups indicating different modes of adaptation dependent on the age at onset of the insult. Our studies suggest that this model, in the developing and mature animal, will be useful for investigating vascular events in response to vaso-occlusive disease.

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Acknowledgements We thank the Wellcome Trust and BBSRC for financial support of this project