Reduced cerebral blood flow in boys with Duchenne muscular dystrophy

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Target audience: Researchers and physicians in the field of neuroscience and neuromuscular diseases, as this research shows the cerebrovascular involvement of a neuromuscular disorder.

Background and purpose: Duchenne muscular dystrophy (DMD) is a neuromuscular disorder known to be associated with specific learning and behavioral disabilities[1-3]. It is caused by *DMD* gene mutations leading to absence of the dystrophin protein in various cell types including neurons, astrocytes, vascular endothelial and smooth muscle cells[4,5]. The role of dystrophin in the central nervous system is not completely understood, and the pathophysiology of the learning and behavioral problems remains elusive. We previously reported reduced grey matter (GM) volume and altered white matter microstructure in DMD compared with healthy age-matched controls[6]. As dystrophin is associated with vasculature as well, we now aimed to assess whether there are changes in cerebral blood flow (CBF) in these DMD patients.

Methods: T1-weighted (TE/TR 4.6 ms/9.8 ms, res 1x1x1 mm) and pseudo-continuous arterial spin labeling (pCASL)[7] (TE/TR 14 ms/4020 ms, post-label delay 1.525 ms, label duration 1650 ms, background suppression pulses (BGS) at 1680 and 2760ms, voxel-size 3x3x7 mm) scans were obtained at 3T from 30 DMD patients and 22 age-matched controls (8-18 years). A customized analysis pipeline was employed that included subtraction of label and control conditions and registration of the CBF maps to T1 and MNI space (FSLv5). Quantification of CBF was performed as described before[7,8], slightly adapted to correct for the finite labeling duration (T_1 of blood 1664 ms[9], T_2^* of arterial blood 50ms, ρ 1.05 g/mL, labeling efficiency 0.85 and loss of label due to BGS 0.83). Quantification was performed on the mean GM CBF signal and on the CBF maps. Group statistics were performed using a T-test and AVONA for the mean GM CBF; voxel-based group analyses were performed with a GLM and age as covariate.

Results: Representative perfusion maps are shown in figure 1A. DMD patients had lower CBF at 41.1 mL/100g/min +/- 7.8 versus 49.9 +/- 8.7 in controls (p=0.002) (Fig 1B). The reduced CBF was found throughout the brain irrespective of age. The differences remained significant after correcting for grey matter volume, which was also reduced in these patients. The biggest difference with controls was found in patients predicted to miss both the full length and Dp140 isoforms of dystrophin (DMD_Dp140-) (fig.1C bottom). Patients predicted to miss only the full length dystrophin (DMD_Dp140+) also had reduced CBF but to a lesser extent (fig. 1C top).

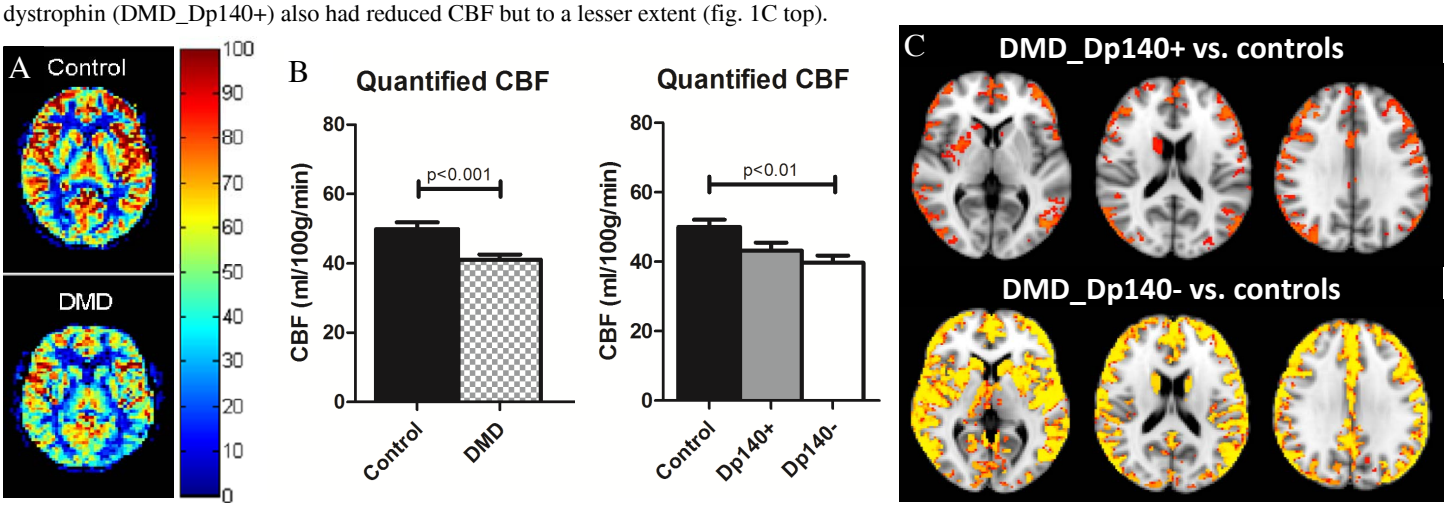

*Figure 1. **A)** Representative cerebral blood flow maps of a healthy 10y old control (top) and a 9y old boy with DMD (bottom). Color coded values are in ml/min/100g. **B)** The quantified CBF showing significant CBF reduction in the whole patient group versus controls (left) and in DMD_Dp140- versus controls specifically (right). **C)** Localization of the reduced perfusion in statistical maps ranging from p<0.05 (red) to p<0.001 (yellow) showing differences throughout the grey matter in both DMD_Dp140+ and DMD_Dp140 versus controls.*

Discussion and conclusions: Boys with DMD have a 17.6% reduced cerebral blood flow compared to age-matched controls. Patients predicted to miss both full length dystrophin and isoform Dp140 show the lowest CBF compared with controls. However, voxel-based analysis show that the group missing only full length dystrophin also has significantly reduced CBF throughout the brain compared with controls. A recent study in *mdx* mice, an animal model for DMD, also showed reduced CBF (15%) in addition to leaky blood-brain-barrier permeability and increased arteriogenesis[10]. That study proposed increased intracranial pressure as underlying cause for the reduced CBF. However, as the greatest differences here reported are in patients missing both full length and Dp140, whereas *mdx* mice only miss full length dystrophin, more research is required to further assess the vascular involvement in the brain pathophysiology in DMD.

References: [1]Cotton S *et al* Dev Med Child Neurol. 2007;[2]Hendriksen JG *et al* J Child Neurol 2008;[3]D'Angelo MG *et al* Pediatr Neurol 2011;[4]Waite A *et al* Trends Neurosci. 2012;[5]Loufrani L *et al* 2008 Circulation 2001;[6]Doorenweerd *et al* Ann Neurol 2014;[7]Alsop DC *et al* Magn Res Med 2014; [8]Chalela JA *et al* Stroke. 2000; [9]Lu H *et al* Reson Med. 2004;[10]Goodnough CL *et al* Neuroimage 2014 .