Altered brain morphology in boys with Duchenne Muscular Dystrophy compared to healthy age matched controls

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Target audience: Researchers and physicians working on Duchenne Muscular Dystrophy (DMD) or similar neuromuscular disorders, with a focus on brain involvement.

Purpose: To study brain morphology in boys with DMD compared to healthy age-matched boys.

Methods: 23 DMD patients (age 8-17 years) and 19 healthy age-matched boys were recruited from a nationwide database and local schools. 3D T1weighted (TE/TR 4.6 ms/9.8 ms, resolution 1x1x1 mm, 4:55min) and DTI (TE/TR 56 ms/9440 ms , resolution 2x2x2 mm, 32 directions, 6:40min) images were obtained at 3T (Philips Achieva) using an 8 channel head coil. Scans were visually assessed by an experienced neuroradiologist. FSL[1] version 4 was used for all quantitative analyses. ExploreDTI[2] was used for motion/distortion correction. Intracranial volume (ICV), total brain volume (TBV), and volumes for grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) were determined[3]. For each parameter the volume relative to ICV was calculated. GM volume was subdivided into cortical GM and subcortical GM. The subcortical GM was further segmented into individual structures of the amygdala, hippocampus, nucleus accumbens, caudate nucleus, putamen, pallidum and thalamus[5]. Fractional anisotropy (FA) and mean diffusivity (MD) of the whole brain were measured and WM skeleton FA/MD maps were created with tract-based spatial statistics (TBSS)[6].

Results: Visual assessment did not reveal gross structural brain abnormalities in patients and controls. Quantitative analysis showed smaller ICV and TBV in DMD patients ($p<0.01$). Absolute GM volume was also significantly smaller in DMD and remained so after correcting for ICV. Absolute volumes of the thalamus and caudate nucleus were smaller in DMD, but these differences were not statistically significant after correction for ICV. Relative CSF volume was increased in DMD. Relative WM volume did not differ. In DMD FA was lower and MD was higher, both in whole brain and specifically in the WM. The TBSS analysis showed mean FA tract skeleton regions in which DMD differed significantly from controls (Fig.1).

Table 1. Intracranial volumes in DMD and controls.

	Control			DMD			p=
n=	19			23			
Age	13.01	+/-	1.92	12.53	+/-	2.8	0.526
Intracranial volume (cc)	1664	+/-	104	1566	+/-	131	0.014
Total Brain volume (cc)	1650	+/-	99	1560	+/-	124	0.003
GM volume (cc)	813	+/-	43	749	+/-	55	<0.001
WM volume (cc)	619	+/-	47	586	+/-	62	0.072
CSF volume (cc)	213	+/-	28	225	+/-	30	0.528
GM % of ICV	49.3	+/-	1.7	48.1	+/-	1.8	0.034
WM % of ICV	37.5	+/-	1.1	37.5	+/-	1.5	0.868
CSF% of ICV	13.2	+/-	1.2	14.4	+/-	1.7	0.016
Whole Brain FA (0-1)	0.269	+/-	0.01	0.256	+/-	0.01	0.004
Whole brain MD ($x10^{-3}$)	0.882	+/-	0.02	0.923	+/-	0.05	0.008

Absolute ICV, TBV, GM, WM and CSF volumes are given in ccs. GM, WM and CSF volume relative to ICV are given in %. Whole brain FA is a value between 0-1 and whole brain MD is in mm^2/s.

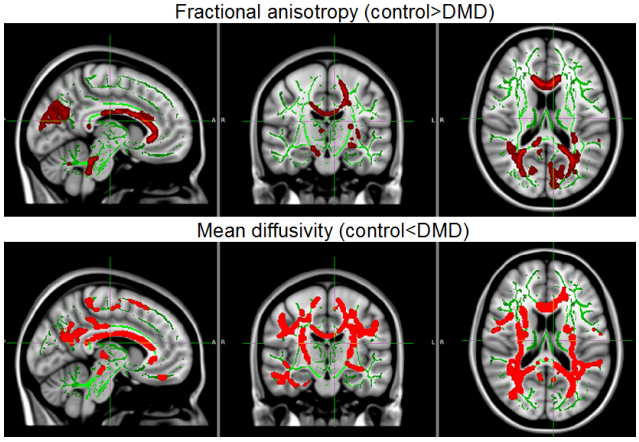

Figure 1 Tract based spatial statistics of the white matter skeleton (green). Top: fractional anisotropy with in red; control>DMD, $p<0.05$ Bottom: mean diffusivity with in red; control<DMD, $p<0.001$.

Discussion: Our results show widespread differences in brain morphology between boys with DMD and healthy age matched controls. Absolute TBV and ICV are smaller in DMD. Additionally, GM volume, both absolute and relative to ICV, is smaller in DMD which may indicate that fewer neuronal cell bodies are present. This GM volume difference is more pronounced in the cortex compared to subcortical GM structures. Regions with increased MD show increased tissue water content in the WM skeleton. Regions with decreased FA indicate either reduced fiber density or increased membrane permeability. Increased membrane permeability seems more likely since a reduced fiber density would presumably be accompanied with reduced WM volume which was not found. Dystrophin isoforms are normally localized throughout the brain[7] and the expression of one or more of these isoforms is affected depending on the location of the mutation. The global spread of morphological differences in DMD may therefore prove vital for understanding the etiology of the learning and behavioral problems known to be associated with this disease[8].

Conclusion: Quantitative analysis of brain MRI in Duchenne muscular dystrophy shows lower grey matter volume and higher white matter tissue water content compatible with increased membrane permeability or reduced fiber density. These data provides clues to understanding the etiology of the higher incidence of learning and behavioral problems in Duchenne.

References: [1] M. Jenkinson et al. 2012, NeuroImage, 62:782-90 [2] A. Leemans et al. 2009, proc ISMRM 17 3537 [3] M. Jenkinson et al 2005, proc OHBM 11 [4] Y. Zhang et al 2001, IEEE Trans Med Imag, 20(1):45-57 [5] B. Patenaude et al 2011, NeuroImage, 56(3):907-922 [6] S.M. Smith et al 2006, NeuroImage, 31:1487-1505 [7] H.G.W. Lidov et al 1996 Brain Pathology 6: 63-77 [8] J.L. Anderson et al 2002, Brain 125:4-13