

MRI-based volume measurements demonstrate increased skull eccentricity and temporalis muscle hypertrophy in DMD patients compared with healthy age matched controls

Nathalie Doorenweerd^{1,2}, Chiara S.M. Straathof², Erik Niks³, Andrew Webb¹, Mark A. van Buchem¹, Jan J.G.M. Verschuuren³, and Hermien E. Kan¹

¹Radiology, Leiden University Medical Centre, Leiden, Zuid-Holland, Netherlands, ²Neurology, Leiden University Medical Centre, Leiden, Zuid-Holland, Netherlands,

³Neurology, Leiden University Medical Centre, Leiden, Zuid-Holland, Netherlands

Introduction. The X-linked disease Duchenne muscular dystrophy (DMD) is characterized by severe and progressive muscle weakness due to the absence of dystrophin. Isoforms of the mutated *DMD* gene are also expressed in the brain and about 30% of DMD boys' shows learning disabilities¹. The etiology is suggested to be a brain based process, but this mechanism remains to be clarified. With the development of new therapeutic strategies for DMD^{2,3}, lifespan will likely be increased significantly and cognitive impairment could then become an important factor limiting rehabilitation, behavioral functioning and social participation. Therefore, understanding the morphological background of cognitive and learning problems is necessary to guide therapeutic approaches. In this work, we present the first results of an ongoing study, planned to assess structural differences between brain morphology in boys with DMD compared with healthy age matched controls. Head circumference in children and adolescents, normally measured manually at regular consultations, was never reported to deviate from the norm in DMD. Our findings however, suggest that there is a difference in skull eccentricity and hence skull shape in DMD accompanied by severe temporal muscle hypertrophy. In addition, a trend was observed suggesting a smaller skull circumference in DMD boys.

Methods. 15 DMD (age 8-16 years) and 12 healthy age matched (age 9-16 years) Caucasian boys were recruited from a local database and schools. 3D T1w (TE 4.6ms, TR 9.8ms, FOV 224x168x177, res 192x192x140, 4:56min) T2w (TE 80ms, TR 3.9ms, FOV 224x144x180, res 448x392x40, 2:46min) and FLAIR (TE 120ms, TR 10s, FOV 224x144x180, res 224x224x40, 4:00min) images were obtained at 3T (Philips Achieva, Philips Healthcare, Best, The Netherlands) using an 8 channel headcoil. Images from DMD and age matched controls were assessed for gross structural and morphological changes by a neuroradiologist. In addition, a quantitative determination of eccentricity, skull circumference, and temporal muscle size was performed on transversal cross-sections of the 3D T1w scan from each boy from the anterior and posterior commissure (AC/PC) upwards (reconstructed to 10 slices, 1.5 mm thick, 2.0 mm slice gap). ROIs of the skull and temporal muscles were manually drawn in MIPAV⁴ and averaged for all 10 slices. Largest transversal head circumference was also manually tape-measured by an experienced neurologist. Differences between DMD and controls were assessed by t-tests and considered statistically significant at $p < 0.05$.

Results. In the visual assessment of the brain, no gross structural differences in brain morphology were detected in DMD compared to controls. However, morphological differences in skull and temporal muscle size between DMD and controls were apparent upon visual inspection (fig 1). Indeed, detailed quantitative analysis showed a significant difference between DMD and controls in skull eccentricity, accompanied by a trend ($p = 0.09$) in skull circumference in which DMD skulls are more circular and smaller in size (fig 2a/b). In contrast, the tape-measured outer head circumference did not differ between groups ($p = 0.84$). Finally, temporal muscle size was significantly larger and thus hypertrophic in DMD compared with controls, with on average a doubling in size (fig 2c).

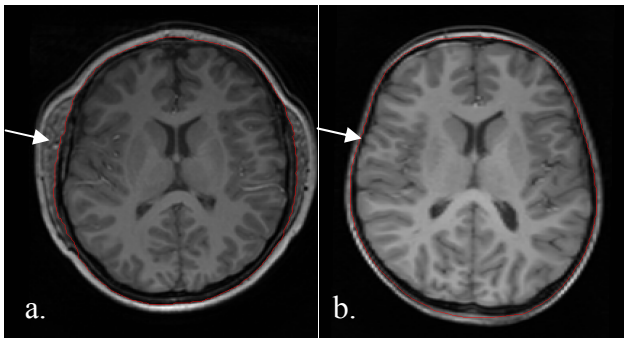


Fig. 1. Axial 3T T1w images of a 10 year old DMD patient (a) and an age matched healthy control (b)

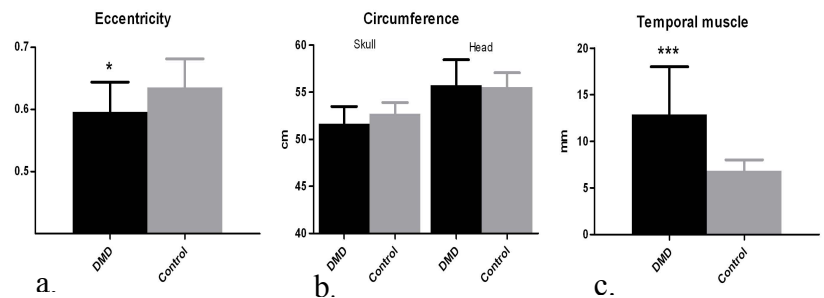


Fig. 2a-c. Skull eccentricity (a), circumference measured by MRI and tape-measured (b) and temporal muscle size (c) in DMD boys and healthy controls

Conclusions & clinical implications. Our results show a difference in skull shape between boys with DMD and controls, while no gross structural and morphological changes are present upon visual inspection of the brain which is consistent with recent findings⁵. The skull in boys with DMD was found to have a more circular form. This increased eccentricity has, to our knowledge, not been observed before although DMD patients have been shown to have different facial morphology^{6,7,8}. Secondly, the temporal muscles showed severe hypertrophy in almost all boys. Commonly muscle hypertrophy has mainly been observed in the calf muscles. The extra volume of temporal muscles could result in an increase of the outer tape-measured head circumference in DMD. However, the circumference assessed by tape-measure was not different between groups. The trend in the smaller skull size might have played role in this. The use of an average over 10 slices at the AC/PC angle in the MRI method could have resulted in an overestimation of the skull size compared with the angle used for tape-measures. However, due to different positioning in the coil it was imperative to maintain consistency between the subjects by using the angle through the AC/PC, and estimating the exact tape-measured angle in the 3D T1 images was unfeasible.

The implications of the different skull size and temporal muscle hypertrophy need to be studied further in order to determine if it 1) might hinder adequate measurements of skull circumference at young age, 2) might be useful to explain secondary symptoms like dental and feeding problems or 3) could even aid in early diagnosis of DMD.

References. [1] Anderson et al. Brain. 2002; 125:4-13 [2] Lancet Neurol. 2009 Oct;8(10):918-28 [3] Van Deutekom et al. N Engl J Med. 2007;357(26):2677-2686 [4] <http://mipav.cit.nih.gov> [5] Lv et al. AJNR Am J Neuroradiol. 2011 Sep 29. [Epub ahead of print] [6] Kiliaridis and Kälébo. J Dent Res. Sept 1991 70(9):1262-1265 [7] Eckardt and Harzer. Am J Orthod Dentofac Orthop. Aug 1996;110:185-90 [8] Matsuyuki et al. Eur J Orthod. Nov 2006;28:42-50 [9]