NOTEWORTHY CASES

LEG MUSCLE MRI IN IDENTICAL TWIN BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

Significant variability in disease progression has been documented in patients with Duchenne muscular dystrophy (DMD).[1] This variability has been attributed to differences in the disease causing mutation[2] or in genetic modifiers.[3,4] and to differences in treatment, including corticosteroid regime.[5] Whereas female twins with dystrophin mutations have been shown to differ phenotypically due to differences in X-inactivation,[6] male twins with DMD have been reported to have identical ages at diagnosis, loss of ambulation, and death.[7–9]

The purpose of this study is to present a set of identical male twins with DMD whose lower limb muscles have been extensively characterized by MRI and MR spectroscopy (MRS) over a period of 12 months.

MATERIALS AND METHODS

Identical twin boys were recruited to participate in a larger study of magnetic resonance imaging and spectroscopy in boys with DMD. The boys were enrolled in a clinical trial (NCT01396239), and had completed 6 months of treatment with a phosphorodiamidate morpholino oligomer designed to restore the reading frame, increase dystrophin expression, and result in a delay in disease progression in DMD.[10]

The study was approved by the institutional ethics committee. Informed consent was obtained from the parents of the boys, and assent to participate was given by the boys. The study included MR data collection (approximately 90 min, in two segments) in a 3T MR scanner (Philips Achieva) for 4 visits over 12 months (baseline, 3 months, 6 months, and 1 year).

T_1-weighted 3D gradient echo images were acquired with a repetition time of 5 ms and echo time of 1.9 ms to allow for the visual evaluation of disease progression and to measure muscle size. We acquired 52 slices in the upper leg and 52 slices in the lower leg, with 2.8 mm slice thickness.[11] Chemical shift based imaging, often called Dixon imaging, was used to measure muscle fat fraction (FF).[12] Unipolar gradient echo images were acquired with a repetition time of 430 ms and echo times of 8.06, 9.21, and 10.36 ms. The slice thickness was 4 mm, interslice gap 1 mm, and a total of 16 slices were acquired, with a flip angle of 20°.[12] Water/fat separation was performed using a multipeak muscle model as previously described.[12] Pixelwise FF maps were calculated from the resulting water and fat images as FF = Fat/(Fat+Water). Individual muscle regions of interest were outlined on the water images and applied to the FF maps.

CASE REPORTS

At the first examination, the boys were 10.4 years old. They were similar in height (138 and 139 cm, respectively) and body mass (48.2 and 46.3 kg), with body mass indexes of 25.3 and 24.0 kg/m^2, respectively. Both boys were observed to have bilateral heel cord contractures. Functionally, both boys were in the late ambulatory stage of the disease; initially, Twin A was able to walk short distances (~10 m) unassisted, whereas Twin B was able to walk only with assistance. Both lost ambulation before the 3-month follow-up MRI visit (at or beyond week 24 of NCT01396239). Both boys were treated with 25 mg of prednisone daily.

Figure 1 shows the qualitative pattern of fatty infiltration, both between and within muscles, which is similar in the twins, and the accumulation of intramuscular fat over 12 months. The pattern of involvement is fairly typical for DMD. However, the extent of the similarities between twin A and twin B was remarkable. In Figures 2a and 2d, it can clearly be seen that the extent and rate of change in the soleus (Sol) and vastus lateralis (VL) FF are greater than the overall DMD population. Histograms from FF maps show the rapid and extensive replacement of the muscle compartment by fatty tissue in the Sol (Figs. 2b, 2c) and the VL (Figs. 2e, 2f).

DISCUSSION

At baseline and throughout the study, the pattern of fatty infiltration in the muscles of these twin boys was strikingly similar, with comparable patterns of fatty tissue infiltration both within and between muscles. It has previously been reported that identical twin boys with DMD reach disease milestones such as loss of ambulation at similar ages,[7–9] This high resolution MR study documents similar progression of the disease within different leg muscles.

Abbreviations: DMD, Duchenne muscular dystrophy; FF, fat fraction; MRS, MR spectroscopy; Sol, soleus; TP, tibialis posterior; VL, vastus lateralis

Key words: Dixon imaging; fat fraction; loss of ambulation; magnetic resonance spectroscopy; thigh muscles

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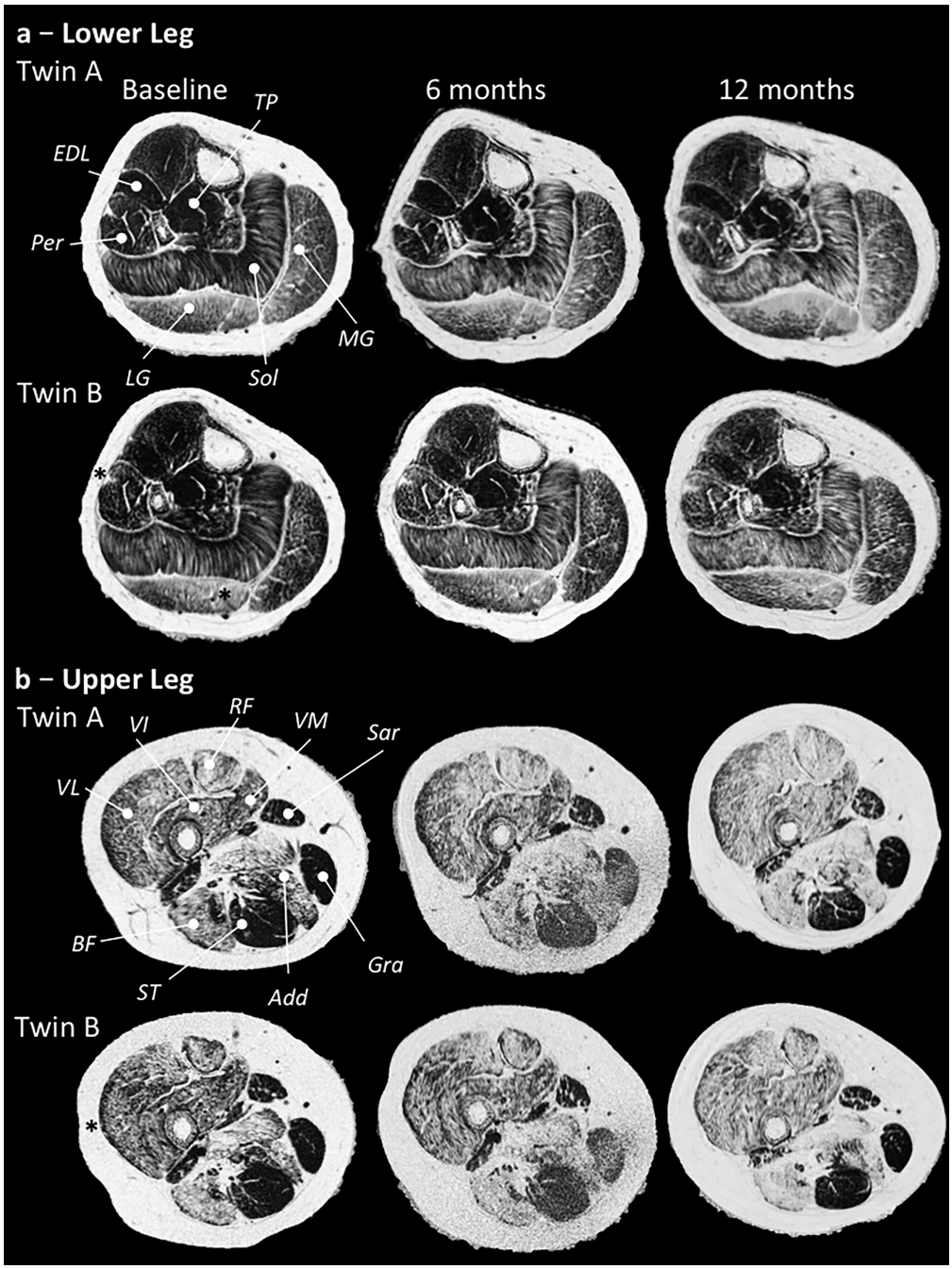
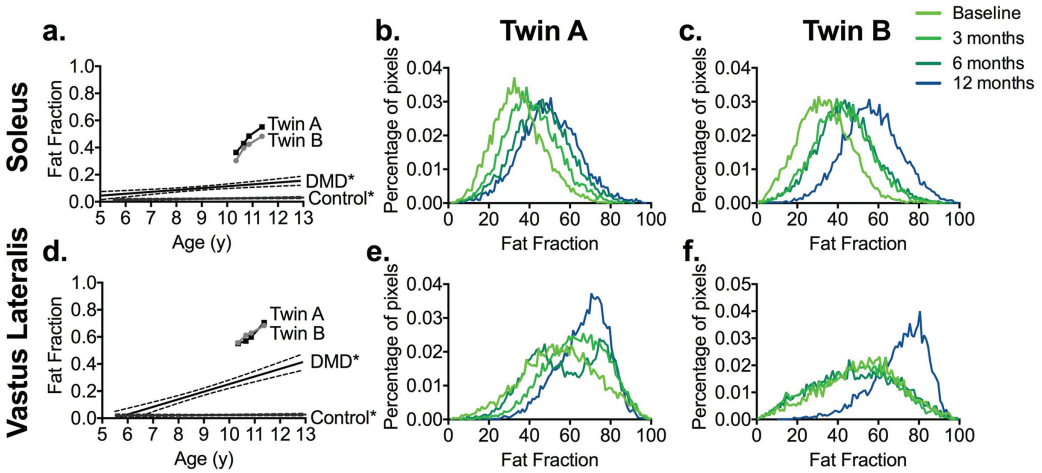


FIGURE 1. MR images (chemical shift-based FF maps) showing strikingly similar pattern of progression of fatty infiltration in the lower leg (top) and thigh (bottom) of twin boys with DMD. Increasing fatty infiltration is particularly noticeable in the biceps femoris (BF) and adductors (Add) in the posterior compartment of the upper leg, in all quadriceps muscles (VL, vastus medialis [VM], vastus intermedius [VI], and rectus femoris [RF]), and in the triceps surae (Sol, medial gastrocnemius [MG], lateral gastrocnemius [LG]) muscles. Sparing is noticeable in the gracilis (Gra), sartorius (Sar), and semitendinosus (ST) muscles of the upper leg and in the tibialis posterior (TP) and extensor digitorum longus (EDL) muscles of the lower leg. Near identical patterns of fatty infiltration were observed within each muscle, including specific patches of total replacement in the peroneal (Per) muscles, a rapidly progressing area in the medial portion of the LG, and a rim of less affected tissue on the superficial edge of the VL; each of these characteristics is marked with an asterisk.

The degree of similarity in these twin boys supports research into genetic modifiers of disease progression in DMD both to understand variability in clinical trial cohorts and to identify potential therapeutic targets.

Over the course of 12 months, the boys lost ambulation and experienced marked increases in intramuscular fat content. The rate of disease progression was more rapid than typical progression in DMD as described by Willcocks et al.[13] The unusually rapid disease progression in these boys compared with other boys with DMD has been described previously.[10] The rapid and progressive fatty tissue deposition in the lower and upper legs following loss of ambulation indicates that frequent loading is not necessary for continued disease progression in DMD.



*DMD and control lines are the linear regression with 95% confidence intervals for soleus and vastus lateralis, replotted from data collected in 97 ambulatory 5-14 year old boys with DMD and 42 unaffected control subjects published by Willcocks et al. using single voxel ^{1}H-MRS[15].

FIGURE 2. Quantitative measurement of FF over 12 months. The twins had considerably more intramuscular fat than similarly aged boys with DMD at baseline, and that the rate of fat accumulation was unusually rapid in these boys in both the Sol **(a)** and the VL **(d)**. Pixel by pixel histograms show broadening and rightward shift of the histogram over 12 months in the Sol **(b,c)** and a rightward shift accompanied by narrowing as more pixels contain high FFs in the VL **(e,f)**.

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