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ScienceDirect

Neuromuscular Disorders ■■ (2018) ■■–■■

www.elsevier.com/locate/nmd

Muscle ultrasound elastography and MRI in preschool children with Duchenne muscular dystrophy

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Received 17 August 2017; received in revised form 12 February 2018; accepted 12 February 2018

Abstract

The aim of this study was to determine muscle tissue elasticity, measured with shear-wave elastography, in selected lower limb muscles of patients affected by Duchenne muscular dystrophy (DMD) and to correlate the values obtained with those recorded in healthy children and with muscle magnetic resonance imaging (MRI) data from the same DMD children, specifically the pattern on T1-weighted (w) and short-tau inversion recovery (STIR) sequences. Five preschool DMD children and five age-matched healthy children were studied with shear-wave elastography. In the DMD children, muscle stiffness was moderately higher compared with the muscle stiffness in HC, in the rectus femoris, vastus lateralis, adductor magnus and gluteus maximus muscles. On muscle MRI T1-w images showed fatty replacement in 3/5 patients at the level of the GM, while thigh and leg muscles were affected in 2/5; hyperintensity on STIR images was identified in 4/5 patients. No significant correlation was observed between stiffness values and MRI scoring. Our study demonstrated that lower limb muscles of preschool DMD patients show fatty replacement and patchy edema on muscle MRI and increased stiffness on shear-wave elastography. In conclusion, although further studies in larger cohorts are needed, shear-wave elastography could be considered a useful non-invasive tool to easily monitor muscle changes in early stages of the disease.

Keywords: Ultrasound elastography; Elastosonography; Muscle MRI; Muscle edema; Duchenne muscular dystrophy

1. Introduction

Duchenne muscular dystrophy (DMD) is a progressive muscle disease, affecting 1 in 3500 male births [1,2]. It is an X-linked, recessive, hereditary disease caused by defects in the gene encoding for the protein dystrophin, which is related to muscle fiber stability and cell signaling [3,4]. Early corticosteroid treatment is the mainstay of therapy for the condition [2,5,6]. While genetic testing and muscle biopsy remain the gold standard for diagnosis of DMD [7], the need to develop sensitive and reliable non-invasive methods to monitor disease progression and response to therapeutic strategies, particularly in young children, has increased over recent years. Indeed, a number of promising therapeutic approaches are considered to be more effective if administered in the early stages of the disease, namely from the first years of life [5].

Muscle magnetic resonance imaging (MRI) is a useful, well-established and validated non-invasive technique for assessing selective muscle involvement in neuromuscular disorders and it has found increasing use in clinical practice (mostly with a qualitative approach) as a method able to support the diagnosis of inherited and metabolic myopathies [8–10]. Compared to ultrasound and computed tomography, MRI is not operator-dependent and does not use ionizing radiations; moreover, by means of T1-weighted (T1-w) sequences, which reveal fatty replacement, and short tau inversion recovery (STIR) or T2-weighted fat-saturated sequences, which can highlight

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https://doi.org/10.1016/j.nmd.2018.02.007
0960-8966/

Please cite this article in press as: Anna Pichiecchio, et al., Muscle ultrasound elastography and MRI in preschool children with Duchenne muscular dystrophy, Neuromuscular Disorders (2018), doi: 10.1016/j.nmd.2018.02.007

muscle edema (e.g. in facio-scapulo-humeral dystrophy, and in dysferlin or inflammatory myopathies), it offers better tissue contrast for imaging deeper muscles compared to ultrasound [11–14].

Several studies have reported diffuse fibro-fatty changes on T1-w muscle MRI scans of DMD patients and a distinctive pattern of involvement at the level of the lower limbs has also been described [8,15,16]. Marden et al. were the first to detect muscular edematous alterations using STIR sequences and to demonstrate the importance of these changes, from the perspective of therapy management, as an index of the reversible inflammatory stage of the disease [17].

However, without sedation, MRI can be challenging in young children as it usually requires a high level of collaboration for prolonged periods of time. Other non-invasive imaging methods for assessing muscle involvement in DMD have therefore been proposed in recent years, including shear wave elastography (SWE) [18]. SWE is a non-invasive, ultrasound-based imaging technique that evaluates the deformation and compressibility of a tissue when an external force is applied, allowing quantitative assessment of tissue stiffness. Nonetheless, the clinical value of SWE in neuromuscular disease is limited, and few studies described quantitative ultrasound abnormalities in treatment-naïve DMD preschool children or explored the correlation with different or other non-invasive diagnostic techniques [18–20].

In an attempt to shed new light on DMD muscle pathology and find a potential marker for use in the follow-up of these patients, in particular for determining the optimal timing of therapeutic interventions, we investigated muscle SWE and MRI abnormalities in treatment-naïve DMD preschool children. First, we determined resting muscle tissue elasticity measured with SWE in selected lower limb muscles and compared the values obtained with those of age-matched HC; second, we correlated muscle stiffness (SWE) values with MRI (T1-w and STIR) findings.

2. Materials and methods

2.1. Subjects

Between June 2015 and September 2016, we performed muscle MRI in all DMD patients followed at our institution and not under treatment at the time of the study. On the same day as the MRI examination, they also underwent SWE. The C. Mondino National Neurological Institute Ethics Committee approved this study and informed consent was obtained from the patients' caregivers. DMD diagnosis was based on physical examination, elevated creatine kinase levels and genetic or biopsy confirmation of dystrophin mutation or absence of dystrophin, respectively. Boys were excluded if they had previously been included in clinical trials, taken nutritional supplements, or used corticosteroids for other medical conditions. The HC submitted to SWE were matched for age and BMI with the patients, and were also selected according to the following exclusion criteria: 1) recent (<1 week) muscle trauma or intense physical activity involving the lower limbs; 2) acute pathology that can lead to rhabdomyolysis (e.g. *Salmonella* infection); 3) recent intake of drugs which can cause rhabdomyolysis.

2.2. SWE

SWE was performed using an ultrasound scanner equipped with a shear wave module (Toshiba Aplio 500; Toshiba Medical, Japan) able to obtain quantitative, real-time and compression-independent measurements. Elastosonographic evaluation was performed using a multifrequency linear probe with a frequency range of between 4 and 15 MHz. Two musculoskeletal radiologists (C.B., F.C.), each with five years experience in musculoskeletal ultrasound, performed the measurements blinded to the subjects' characteristics. The dominant lower limb was evaluated. Patients were first evaluated in a supine position (lying on the examination bed or in their mother's arms) and then in a prone position, with their muscles relaxed. The following muscle bellies were studied: gluteus maximus (GM), rectus femoris (RF), vastus medialis (VM), vastus lateralis (VL) and adductor magnus (AM) for the thigh; tibialis anterior (TA) and medial gastrocnemius (MG) for the lower leg. All muscles were examined on a transverse scan between the proximal and intermediate third, specifically considering for VM, VL, RF and AM the axis between the superior aspect of the patella and the anterior superior iliac spine, and for TA the axis from the inferior aspect of the patella to the lateral malleolus, similarly to Jansen et al [21]. The correct measurement level was lightly marked with a dermographic pen. The only muscle evaluated on a longitudinal scan (for both anatomical and practical reasons) was the GM. Indeed, transverse scans of this muscle can be difficult to evaluate and suboptimal in terms of image quality. A generous amount of gel was used to minimize the required pressure of the transducer on the skin and special care was taken to avoid inducing pressure on each muscle while preserving optimal probe coupling during each measurement. Every evaluation started with a B-mode acquisition of the anatomical region in order to correctly identify the different muscles and to determine the optimal transducer locations for each muscle to maximize the alignment between the transducer, parallel to the skin plane, and the directions of the muscle fibers [22]. Subsequently the B-mode image was superimposed on the elastography box. When the elastography box yielded homogeneous stiffness values, a 5-mm round region of interest was positioned on each of the aforementioned muscles avoiding tendons, aponeuroses and fascial tissue, with the transducer in a fixed position; the scanner automatically provide the corresponding stiffness value. No changes in any SWE parameters (including frequency of the probe) were performed in our study protocol between DMD children and healthy controls.

2.3. MRI protocol and MRI scoring/analysis

A 1.5T MRI scanner was used (Philips Gyroscan 1.5 T, Koninklijke, The Netherlands). Sequential, axial T1-w images (representative parameters: slice thickness, 5 mm; interslice gap, 10 mm; repetition time (TR), 500 msec; echo time (TE),

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