Distinct neuromuscular phenotypes in myotonic dystrophy types 1 and 2
A whole body highfield MRI study

Abstract Myotonic Dystrophy Type 1 (DM1) and 2 (DM2) present with distinct though overlapping clinical phenotypes. Comparative

Introduction

Myotonic Dystrophy Type 1 (DM1) is the most common form of muscular dystrophy in adults. In Germany, Myotonic Dystrophy Type 2 (DM2) may be as common as DM1 [18]. Both disorders are autosomal dominantly inherited and caused by pathogenic repeat mutations [11]. DM1 and DM2 present with distinct but overlapping clinical phenotypes [4, 7, 9, 12]. The pattern of clinical skeletal muscle affection in DM1 usually differs from DM2. However, a profound general weakness may emerge in later stages of both disorders [4, 9].

Musculoskeletal magnetic resonance imaging (MRI) imaging data on skeletal muscle involvement are not at present available. We used the novel technique of whole body 3.0 Tesla (T) Magnetic Resonance Imaging (MRI) to further characterize musculoskeletal features in DM2 and compared the results with DM1.

MRI findings of 15 DM1 and 14 DM2 patients were evaluated with respect to patterns of skeletal muscle affection and clinical data using the Muscular Impairment Rating Scale (MIRS) and Medical Research Council scale (MRC).

All DM1 patients had pathological MRI compared with only 5 DM2 patients. In contrast to DM2, DM1 patients showed a characteristic distribution of muscle affection and clinical data using the Muscular Impairment Rating Scale (MIRS) and Medical Research Council scale (MRC).

All DM1 patients had pathological MRI compared with only 5 DM2 patients. In contrast to DM2, DM1 patients showed a characteristic distribution of muscle involvement with frequent and early degeneration of the medial heads of gastrocnemius muscles, and a perifemoral semilunar pattern of quadriceps muscle affection sparing the rectus femoris. The most frequently affected muscles in DM1 were the medial heads of gastrocnemius, soleus, and vastus medialis muscles. In DM2, however, the erector spinae and gluteus maximus muscles were most vulnerable to degeneration. MRI data were in line with the clinical grading in 12 DM1 and 3 DM2 patients. In 3 DM1 and 5 DM2 patients, MRI detected subclinical muscle involvement. 9 DM2 patients with mild to moderate proximal muscle weakness and/or myalgias had normal MRI. Pathological MRI changes in DM2 emerged with increasing age and were restricted to women.

Whole body 3.0T MRI is a sensitive imaging technique that demonstrated a characteristic skeletal muscle affection in DM1. In contrast, MRI was no reliable indicator for skeletal muscle involvement in mildly affected DM2 patients since myalgia and mild paresis were usually not reflected by MRI signal alterations.

Key words myotonic dystrophy · proximal myotonic myopathy · whole body highfield MRI · muscular impairment rating scale (MIRS)
has been previously performed in DM1 patients and was mostly restricted to the lower limbs, whereas systematic musculoskeletal imaging data on DM2 do not at present exist [1, 2, 6, 16, 21]. We applied the novel technique of whole body 3.0 Tesla (T) MRI in DM2 patients and compared the results with those from DM1. Our aims were to further characterize skeletal muscle affection and patterns of muscle involvement in both disease entities. MRI findings were additionally analysed in relation to clinical data thus evaluating the applicability and sensitivity of the whole body highfield technique with respect to subclinical skeletal muscle involvement.

Methods

■ Patients

15 DM1 patients (m/f: 5/10; mean age 45.8 ± 14.6 years, range 16–68) and 14 DM2 patients (m/f: 8/6; mean age 51.6 ± 11.8 years, range 37–70) from 10 families each were included in the study. Patients were consecutively recruited by the neurological outpatient clinic for neuromuscular disorders, University of Bonn, Germany, between 1 August 2004 and 31 May 2005. 11 DM1 and 9 DM2 patients were seen in Clinical routine follow-ups, whereas 4 DM1 and 5 DM2 patients were seen at first presentation subsequent to genetic testing. None of our patients had a past medical history of any other neuromuscular disorder or trauma.

■ Clinical examination

Muscular strength was assessed according to the Medical Research Council scale (MRC) in DM1 and DM2 patients [13]. Symptomatic trunk muscle involvement was assessed according to clinical neurological examination reports and the resulted daily life activities (personal interview). Clinical muscular impairment in DM1 patients was categorised using the five-point Muscular Impairment Rating Scale (MIRS) for myotonic dystrophies [12]: 1, no muscular impairment; 2, minimal signs (myotonia, facial weakness, ptosis, nasal speech, jaw and temporal wasting, neck flexor weakness, no distal weakness except isolated digit flexor weakness); 3, distal weakness (no proximal weakness except isolated elbow extensor weakness); 4, mild to moderate proximal weakness (MRC between 3 and 4–); 5, severe proximal weakness (MRC < 3). Muscular strength in DM2 patients was evaluated according to the MRC as formerly described (detailed data not shown [5, 17]). Our DM2 patients were classified as follows: no weakness; mild proximal weakness (MRC between 4 and 4+); moderate proximal weakness (MRC between 3 and 4–); severe proximal weakness (MRC < 3) and trunk weakness. Since distal limb weakness was not present in our series of DM2 patients, only proximal pareses were considered for individual classification (Table 1). Musculoskeletal pain was described according to localisation (generalised, focal), temporal patterns (persistent, intermittent), and severity (mild, moderate, severe; personal interview).

■ MRI examination

Whole body MRI was performed on the same day of the clinical examination on a 3.0T whole body MR-system (Gyroscan Intera, Philips Medical Systems, Best, The Netherlands) using the implemented quadrature body coil and a flexible table top extension. The patients were placed in supine position with their arms beside the body. Examination areas ranged from the neck to the ankle. Because of exceeding the maximum field-of-view (FoV), the lateral parts of the upper limbs, especially the forearms, were not available for analysis. The MIRS sequence protocol included transversal slices of the following pulse sequences: T1 Turbo Spin Echo TSE (TR 500 ms, TE 12 ms), T2 TSE (TR 8393 ms, TE 80 ms), and spectral fat suppressed (SPAIR) T2 TSE (TR 6246 ms, TE 80 ms). For all sequences, the same geometric and slice parameters were used: slice thickness 9 mm, FoV 470 mm, matrix 245 × 512, slice gap 0.9 mm. The average scan time was 45 minutes per patient.

Image analysis: Image analysis was performed by two experienced radiologists in consensus, both blinded to clinical and genetic data. Skeletal muscles were analysed for fatty muscle degeneration and edematous changes. Quantitative assessment of muscle bulks (atrophy, hypertrophy) was not done. The degree of fatty degeneration was scored according to a modified scoring scheme as previously described [14]: 0, normal appearance; 1, discreet moth-eaten appearance with sporadic scattered T1 hyperintense areas; 2a, moderate moth-eaten appearance with numerous scattered T1 hyperintense areas; 2b, late moth-eaten appearance with numerous confluent areas of T1 hyperintensity; 3, complete fatty degeneration, replacement of muscle by connective tissue and fat.

The following muscles were evaluated: shoulder girdle and upper limbs (biceps, triceps, deltoid, supraspinatus, subscapularis), hip girdle (gluteus maximus, gluteus medius, gluteus minimus), thighs (vasti medialis, intermedius and lateralis, rectus femoris, gracilis, sartorius, adductor magnus, adductor brevis/longus, tensor fasciae latae, semimembranosus, semitendinosus, biceps femoris long head/short head), lower legs (tibialis anterior, tibialis posterior, soleus, popliteus, medial and lateral head of gastrocnemius, plantaris, peroneus longus), trunk (neck muscles, cervical/thoracic/lumbosacral erector spinae, latissimus dorsi, teres major, trapezius, pectoralis, serratus anterior, rectus abdominis, obliques internus abdominis, obliques externus abdominis, obtruratorius internus, obtruratorius externus, piriiformis, ilioposas).

For each patient, the number and the mean score of affected muscle groups in MRI were calculated. If a score range was given, the highest score was used for statistical analysis. An asymmetric affection of muscle groups is indicated in the tables irrespective of the more affected side.

For statistical analysis, the relationship between age of the patient, number and mean score of affected muscle groups was studied by the Spearman Rank Correlation (nonparametric rank statistic; software SPSS, version 12.0.1).

The study had been approved by the local university ethics committee (Lfd. Nr. 221/04) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all patients prior to the examinations.

Results

■ Clinical data (Table 1)

The diagnosis of myotonic dystrophy was confirmed by molecular genetic analysis in all patients. In DM1, repeat sizes were as follows: patient no. 2–4: 900–1000 CTG repeats, no. 4–8: 150–200 repeats, no. 5–9: 180 repeats, no. 6–10: 170 repeats, no. 7–11: 250–300 repeats, and no. 8–12: 1100–1200 repeats. In the remaining DM1 patients, the exact repeat length was not determined. A xXY-caryotype was detected in patient no. 11–17. 53.3% and 13.3% of our DM1 patients had a MIRS score of 4 and 5, respectively. 33.4% of our DM1 patients were assigned to lower scores 2 and 3. A total of 42.8% of our