Clinical Commentary

Whole-body high-field MRI shows no skeletal muscle degeneration in young patients with recessive myotonia congenita


Background – Muscle magnetic resonance imaging (MRI) is the most sensitive method in the detection of dystrophic and non-dystrophic abnormalities within striated muscles. We hypothesized that in severe myotonia congenita type Becker muscle stiffness, prolonged transient weakness and muscle hypertrophy might finally result in morphologic skeletal muscle alterations reflected by MRI signal changes. Aim of the study – To assess dystrophic and/or non-dystrophic alterations such as fatty or connective tissue replacement and muscle edema in patients with severe recessive myotonia congenita. Methods – We studied three seriously affected patients with myotonia congenita type Becker using multisequence whole-body high-field MRI. All patients had molecular genetic testing of the muscle chloride channel gene (CLCN1). Results – Molecular genetic analyses demonstrated recessive CLCN1 mutations in all patients. Two related patients were compound heterozygous for two novel CLCN1 mutations, Q160H and L657P. None of the patients showed skeletal muscle signal changes indicative of fatty muscle degeneration or edema. Two patients showed muscle bulk hypertrophy of thighs and calves in line with the clinical appearance. Conclusions – We conclude that (i) chloride channel dysfunction alone does not result in skeletal muscle morphologic changes even in advanced stages of myotonia congenita, and (ii) MRI skeletal muscle alterations in myotonic dystrophy must be clear consequences of the dystrophic disease process.

Introduction

Myotonia congenita type Becker is a non-dystrophic generalized myotonia caused by recessive mutations in the muscle chloride channel gene (CLCN1). Although the clinical presentation may be rather mild in general, muscle stiffness and transient weakness are frequently observed (1). In later disease courses, permanent muscle weakness may occur (1, 2). The clinical symptoms are usually more pronounced in recessive myotonia congenita (RMC) compared to the dominant type Thomsen.

In RMC, morphologic abnormalities have been occasionally described in skeletal muscle biopsies demonstrating a slight myopathy due to sustained muscle fiber activity and increased shear stress. However, fiber degeneration and fatty replacement occur infrequently and may signal permanent weakness (1). Muscle magnetic resonance imaging (MRI) is the most sensitive method in the detection of dystrophic and non-dystrophic abnormalities within striated muscle (3). However, most previous MRI applications were limited to certain body regions or to patients with dystrophic muscle
disorders, respectively (3–7). This study aimed to assess dystrophic and/or non-dystrophic alterations such as fatty or connective tissue replacement and muscle edema in patients with severe RMC using a whole-body high-field muscle MRI protocol. We hypothesized that in advanced disease courses, clinical skeletal muscle manifestations might finally result in morphologic skeletal muscle alterations as reflected by MRI signal changes.

Materials and methods

Three patients (m/f: 2/1; mean age 23 ± 9.5 years) with RMC underwent extensive clinical neurological, molecular genetic, and neurophysiological analyses. Molecular genetic analyses comprised testing for myotonic dystrophies as well as sequencing of CLCN1.

Muscle imaging studies included multi-sequence whole-body 3.0T MRI (Achieva; Philips Medical Systems, Best, The Netherlands) including axial slices of a T1-weighted Turbo Spin Echo (TSE), T2-weighted TSE, and a fat suppressed (spectrally selective attenuated inversion recovery) T2-weighted TSE. Detailed resolution and sequence parameters have been previously described (4). The muscles of the shoulder girdle, proximal upper limbs, hip girdle, thighs, lower legs and trunk were available for image analysis as formerly described (4). The muscles of the shoulder girdle, proximal upper limbs, hip girdle, thighs, lower legs and trunk were available for image analysis as formerly described (4). The image analysis was performed by two radiologists in consensus blinded to the clinical presentation and paraclinical data. The muscles were analyzed for appearance of muscle bulk, edema and fatty degeneration according to an established rating scale as previously described (4–7). The study was approved by the Local Ethics Committee, and written informed consent was obtained from all participants.

Results

Clinical presentation

All patients presented with serious disabling myotonia, warm-up phenomenon and a rapid loss of muscle strength following short-term exercise. Patients 1 (f, 17 years) and 2 (m, 18 years) were siblings. Both showed first symptoms in early childhood (3–4 years) that worsened with time. However, patient 2 was more severely affected in the later course of the disease and developed pronounced transient generalized muscle weakness that persisted up to several minutes following sustained muscle contraction. Upper arm muscles were prominent, whereas muscle bulks of lower legs were comparatively small. Patient 1 presented with disabling myalgias without permanent paralyses. Muscle bulks of upper arms and calves appeared hypertrophic. Patients 1 and 2 were dependent on a high mexiletine dosage of 900 mg/day and underwent regular cardiological controls. Patient 3 (m, 34 years) had first symptoms at the age of 10 years. Later, he developed generalized myalgias and mild prolonged transient paralyses of the lower legs following sustained voluntary muscle contraction. Calf muscles were hypertrophic. He was dependent on mexiletine 600 mg/day. All patients were able to stay in work by taking mexiletine which was of remarkable and continuing benefit.

In patients 1 and 2, genetic analysis identified a novel G-to-C base change at position 480 in CLCN1 exon 4 which resulted in a p.Gln160His change in CLCN1 protein (Q160H). This mutation was not present in 100 control samples (200 chromosomes), but recurred in an unrelated patient who carried p.Arg894X on the other allele, supporting the recessive nature and putative disease-causality of this amino acid substitution. A second novel heterozygous missense mutation was identified in patients 1 and 2 which resulted in a T-to-C base change at position 1970 in CLCN1 exon 17 leading to a p.Leu657Pro change in CLCN1 protein (L657P). To our knowledge, this mutation has not been described before, however, affects a highly conserved region of the CLCN1 protein. The patients’ father carried the latter heterozygous mutation, whereas the patients’ mother harbored the c.480G>C mutation in a heterozygous state thus demonstrating compound heterozygosity in both patients (Fig. 1). Both parents were clinically asymptomatic and showed no myotonic discharges in electromyography of vastus lateralis, biceps brachii and abductor digit minimi muscles compatible with a recessive mode.

Figure 1. Pedigree showing genotyping data of patients 1 and 2 and their clinically unaffected parents. Wt, wild-type; Q160H, L657P, recessive CLCN1 mutations; white circle/square, heterozygote and clinically unaffected; black circle/square, compound heterozygote and clinically affected.
of inheritance. In patient 3, a homozygous nonsense mutation was detected in exon 23 of \textit{CLCN1} (c.2680C>T coding for p.Arg894X). Unfortunately, the parents of patient 3 were not available for genetic testing to verify the patients’ homozygous state and to exclude a deletion on the second allele. Myotonic dystrophy types 1 and 2 were excluded in all patients by molecular genetic analyses.

Whole-body MRI findings

None of the patients showed signs of muscle degeneration or edema. Patients 1 and 3 demonstrated with mild hypertrophy of thigh and calf muscles when compared to a healthy control subject. Complete results are summarized in Figs 2 and 3.

Discussion

Muscle MRI is the most important imaging tool for \textit{in vivo} assessment of patients with neuromuscular disorders (3–6). Most of the previously applied protocols mainly focused on certain anatomic regions (5, 8–10). Although the implementation of a whole-body protocol might be difficult in terms of artifacts in the abdominal and chest region, the diagnostic advantage of a time-sparing and high-quality ‘whole-body’ scanning of the musculoskeletal system is obvious (4, 11, 12). We herein report first results in RMC using a whole-body high-field MRI protocol. Moreover, we identified two novel \textit{CLCN1} mutations underlying Becker myotonia in a sibling pair. The recessive effects of the mutations were clearly shown by the family study (Fig. 1). Amino acid L657 is situated in the alpha-2 helix of the cystathionine-beta-synthase 1 (CBS1) domain of the \textit{CLCN1} protein (13). Chloride channels have two such domains named after cystathionine-beta-synthase in the carboxy terminus of the channel. The CBS domains consist of three beta-sheets and two alpha-helices, and interact with each other through the beta-sheets whereby the alpha-helices enable the proximity required for interaction (14). The interaction influences the function of the common anion gate. As proline is considered to interrupt helices, the subsequently altered conformation of the alpha-2 helix of CBS1 may reduce interaction of the beta-sheets and disturb function of the common gate of the chloride channel.

The clinical findings of prominent leg muscles were mirrored by MRI results in patients 1 and 3 demonstrating mild skeletal muscle bulk hypertrophy of proximal thighs and calves without fatty or connective tissue replacement (arrows).

Figure 2. Whole-body MRI findings in patients 1–3. Axial sections of T1 weighted TSE sequences at the level of the shoulder girdle (top row), pelvis (second row), thighs (third row) and calves (bottom row). In all patients, shoulder girdle and trunk muscles showed no trophic changes. In line with the clinical manifestation, patients 1 and 3 had hypertrophy of thigh and calf muscles (arrows). Particularly note patient 3 with significant calf hypertrophy and no signs of fatty or connective tissue replacement indicating genuine muscle hypertrophy and no pseudohypertrophy. Lower leg muscles of patient 2 were comparatively hypotrophic in line with the clinical appearance. Fatty degeneration or skeletal muscle edema were not observed in our patients.
We conclude that even in severe RMC significant morphologic skeletal muscle changes are not present or not strong enough to be visualized on 3.0T MRI which suggests an isolated functional neuromuscular defect. However, one has to keep in mind potential limitations of currently available MRI techniques in the interpretation of up-to-date muscle imaging data. Recent 3.0T muscle MRI investigations in Duchenne muscular dystrophy tracking disease progression over a period of 9 and 18 months suggested that some dystrophic changes, possibly defined by a certain ratio of fat and connective tissue, might escape detection by MRI (15). It would be tempting to compare our MRI findings with skeletal muscle biopsy results, however, biopsies could not be performed in our patients for ethical reasons. Our findings are in contrast to previous whole-body MRI studies in myotonic dystrophies that characterized distinct patterns of skeletal muscle damage particularly in myotonic dystrophy type 1 (4). Our results thus underline that (i) chloride channel myotonia and even serious and prolonged transient weakness alone do not result in MRI skeletal muscle signal changes, and (ii) MRI fatty skeletal muscle changes and edema seen in myotonic dystrophy type 1 are not the result of chloride channel dysfunction but clearly consequences of the dystrophic disease process. Furthermore, we could demonstrate that prominent muscle bulks in myotonia congenita are due to genuine muscle hypertrophy and not to pseudohypertrophy as frequently seen in muscular dystrophies.

Muscle MRI might be helpful to distinguish between dystrophic and non-dystrophic myotonic disorders. This could be useful in rare clinically unclear or monosymptomatic cases of myotonic disorders and might help to choose the right genetic test. However, muscle MRI is certainly not intended to become a diagnostic routine tool in myotonia in the clinical practice: more important beyond potential diagnostic implications, our MRI data gave first imaging insights into skeletal muscle tissue integrity in RMC.

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