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Quantitative Muscle MRI to Monitor Disease Progression in Hypokalemic Period Paralysis

Sonja Holm-Yildiz, MD, Thomas Krag, PhD, Tina Dysgaard, MD, DMSc, Britt Stævnsbo Pedersen, PT, Nanna Witting, MD, PhD, Louise Sloth Kodal, MD, Linda Kannuberg, MD, Jonas Jalili Pedersen, MD, Zhe Lyu, MD, Morten Müller Aagaard, MD, and John Vissing, MD, DMSc

Correspondence
Dr. Holm-Yildiz
sonja.desiree.holm-yildiz@regionh.dk

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Abstract

Background and Objectives

Primary hypokalemic periodic paralysis (HypoPP) is a muscle channelopathy that can cause periodic paralysis and permanent weakness. Currently, little is known about how progressive this myopathy is. Natural history data for HypoPP can potentially answer the question of progressiveness and form the basis for outcome measures to be used in follow-up and emerging treatment trials. We aimed to describe the natural history of HypoPP and assess whether quantitative fat imaging is a valuable biomarker to monitor disease progression.

Methods

In this prospective follow-up study, we examined disease progression using Dixon MRI to monitor changes in fat replacement of the muscle and stationary dynamometry to monitor changes in muscle strength.

Results

We included 37 persons (mean age 43 years, range 18–79 years) with HypoPP-causing variants in *CACNA1S*. Three participants were asymptomatic carriers, 22 had periodic paralysis, 3 had permanent weakness, and 9 had periodic paralysis in combination with permanent weakness. The median follow-up time was 20 months (range 12–25). We found that fat fraction increased in 10 of 21 examined muscles. An increase in the composite fat fraction of at least 1 muscle group was found in all symptomatic phenotypes. By contrast, we found no significant change in muscle strength.

Discussion

The results from this follow-up study support the use of quantitative muscle MRI to monitor subclinical disease progression in HypoPP in patients with and without attacks of paralysis.

Introduction

Primary hypokalemic periodic paralysis (HypoPP) is one of the rare skeletal muscle channelopathies causing period paralysis. The estimated prevalence of HypoPP is 1:100,000.[1-3] HypoPP is dominantly inherited and most commonly caused by pathogenic variants in the calcium channel gene *CACNA1S*.[1,3-5] HypoPP can present with periodic paralysis (PP) together with hypokalemia, progressive, permanent muscle weakness (PW) and mixed weakness (MW) with both periodic and permanent muscle weakness.[6-9] Attacks of paralysis most commonly occur on awakening and last from hours to days. Several trigger factors of attacks have been described, for example, high carbohydrate intake, alcohol consumption, cold exposure, and rest after heavy exercise.[7,10-12] The cause of permanent muscle weakness in HypoPP is unknown, and there is no known treatment for this part of the disease. The weakness

From the Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark.

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Glossary

HypoPP = hypokalemic periodic paralysis; **ICC** = intraclass correlation coefficients; **MRC** = Medical Research Council; **MW** = mixed weakness; **PA** = physical activity; **PP** = periodic paralysis; **PW** = permanent muscle weakness.

can develop in patients without clinical attacks of paralysis[6,8] and can progress in patients without attacks.[13] However, whether the attacks influence permanent weakness in some patients is still unknown.

In a previous study, we used qualitative scoring of T1-weighted muscle MRI and manual muscle strength testing to show that fat replacement of muscle and permanent muscle weakness are progressive in some patients with HypoPP.[13] Quantitative fat imaging using Dixon MRI is more sensitive than qualitative fat imaging using T1-weighted muscle MRI.[14] Furthermore, the method can be more sensitive than clinical outcome measures in detecting disease progression of myopathies over short periods.[14,15] Precise knowledge of the natural history of HypoPP and sensitive biomarkers of disease progression are essential in future clinical trials. In this follow-up study of persons with HypoPP-causing variants in *CACNA1S*, we used quantitative fat imaging using Dixon MRI and quantitative muscle strength assessment using stationary dynamometry in assessing disease progression. The aim was to gain further knowledge on the natural history of HypoPP and to identify whether quantitative fat imaging is a valuable biomarker to monitor disease progression in HypoPP, e.g., in future clinical trials investigating treatment effects on progressive, permanent muscle weakness.

Methods

Standard Protocol Approvals, Registrations, and Participant Consents

The research protocol was approved by the Danish National Committee on Health Research Ethics (approval number H-20057357). Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

Study Design

This prospective follow-up observational study was conducted between April 2021 and February 2024 at the Copenhagen Neuromuscular Center, Rigshospitalet, in Copenhagen, Denmark.

Participants

Inclusion criteria were age 18 years and older and a confirmed HypoPP-causing variant in *CACNA1S*. Exclusion criteria were contraindications for MRI or comorbidity that could affect muscle strength and/or fat replacement on MRI. Participants were recruited from the Copenhagen Neuromuscular Center. Some of the participants were enrolled in previously published MRI studies.[6,13]

Background Information

Clinical data were collected during an interview. The information included age, sex, Body Mass Index (BMI), age at symptom onset and diagnosis, history of periodic paralysis (and, if present, quantification of attacks during follow-up), muscle pain, and medication. Participants were encouraged to report not only full-blown attacks but also very mild attacks, defined as episodes with muscle weakness while still being able to perform all activities of daily living. Furthermore, information on leisure-time physical activity (PA) was collected using the Saltin Grimby Physical Activity Level Scale[16] modified by Schnohr et al.[17,18] PA was rated from 1 to 4 (1: sedentary or light activity less than 2 h/wk; 2: light physical activity 2–4 h/wk; 3: light physical activity >4 h/wk or vigorous activity 2–4 h/wk; 4: vigorous activity >4 h/wk or competitive sport several times a week).[17,18]

Muscle Strength

Muscle strength was assessed using a stationary dynamometer (Biodex System PRO 4 dynamometer, Biodex Medical Systems, NY) and by manual muscle strength testing. We used Biodex to assess the maximal isokinetic peak torque of knee flexion and extension and ankle plantarflexion and dorsiflexion. The tests consisted of 8 repeated muscle contractions with 15 seconds of rest between each contraction. All participants, except one who was tested on the left leg because of knee pain, were tested on the right leg. We used manual muscle strength testing (the Medical Research Council [MRC] scale) to assess the strength of shoulder abduction and adduction, elbow, wrist, finger, knee, and ankle flexion and extension. The MRC scale was also used to test hip flexion, extension, and abduction. Furthermore, trunk flexion and back extension strength were assessed manually and graded from 0 to 5 as described in "Musculoskeletal assessment: Joint range of motion and muscle strength".[19] However, testing of the back extension was slightly modified because no strap was used to stabilize the pelvis. The back extension was assessed in the prone lying position with a lift of the sternum from the plinth. Strength was graded with the degree of movement and resistance added through the position of the participant's upper limbs (0: no muscle contractions are visible/palpable to 5: the sternum is lifted from the plinth with hands behind the head).[19] Trunk flexion was evaluated in the supine position with a half curl-up starting with a posterior tilt of the pelvis. As for the assessment of back extension, strength was graded with the degree of movement and resistance added through the position of the participant's upper limbs (0: no movement of the pelvis posteriorly and no muscle contractions are palpable to 5: the head and scapula are lifted off the plinth with hands beside the ears).[19]

MRI

Fat replacement of muscle was assessed by whole-body muscle MRI, which was performed using a 3.0T scanner. The MRI protocol included axial T1-weighted and 2-point Dixon imaging, similar to the one described in a previous study on facioscapulohumeral dystrophy.[20] The thigh was assessed at 50% of the length of the femur, the calf at 33% of the length of the tibia (proximal-distal), and the lumbar muscles at the intervertebral disc level L4/L5. On visual inspection of the T1-weighted images, we found no significant side difference in the fat replacement of muscles and only analyzed 1 side (same side as muscle strength). We used the Dixon sequences to map the muscles and compartments manually using a viewer for MacOS (Horos V. 4.0). All the muscles of the thighs and the peroneus longus et brevis, the medial and lateral gastrocnemius, and the soleus of the calves were mapped individually. By contrast, the tibialis anterior, extensor digitorum longus, and extensor hallucis longus were mapped together in the anterior compartment, and the tibialis posterior, flexor digitorum longus, and flexor hallucis longus were mapped together in the deep posterior compartment. The anterior and deep posterior compartments are referred to as one of the examined muscles in the rest of the article. Psoas major, erector spinae, and multifidus were assessed at the lumbar level. They were all mapped individually and are referred to as muscles of the lumbar level in the article. All MRI scans were reviewed by the same investigator (S.H.-Y.) at baseline and follow-up. 10 scans were further reviewed by an extra investigator (Z.L.) to analyze for inter-rater reliability.

Statistical Analysis

Statistical analysis was performed using R version 4.2.1. To compare changes in fat fraction and muscle strength from baseline to follow-up, we used the paired *t* test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Pearson correlation was used to test for linear relationships between variables (e.g., age and fat fraction). Intraclass correlation coefficients (ICCs) for the MRI analysis and their 95% CIs were calculated based on a single-rater, absolute-agreement, 2-way random-effects model.[21] A p value of ≤0.05 was considered statistically significant. To control for multiple comparisons when analyzing fat fractions of individual muscles, we adjusted p values using the Bonferroni correction.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Participants

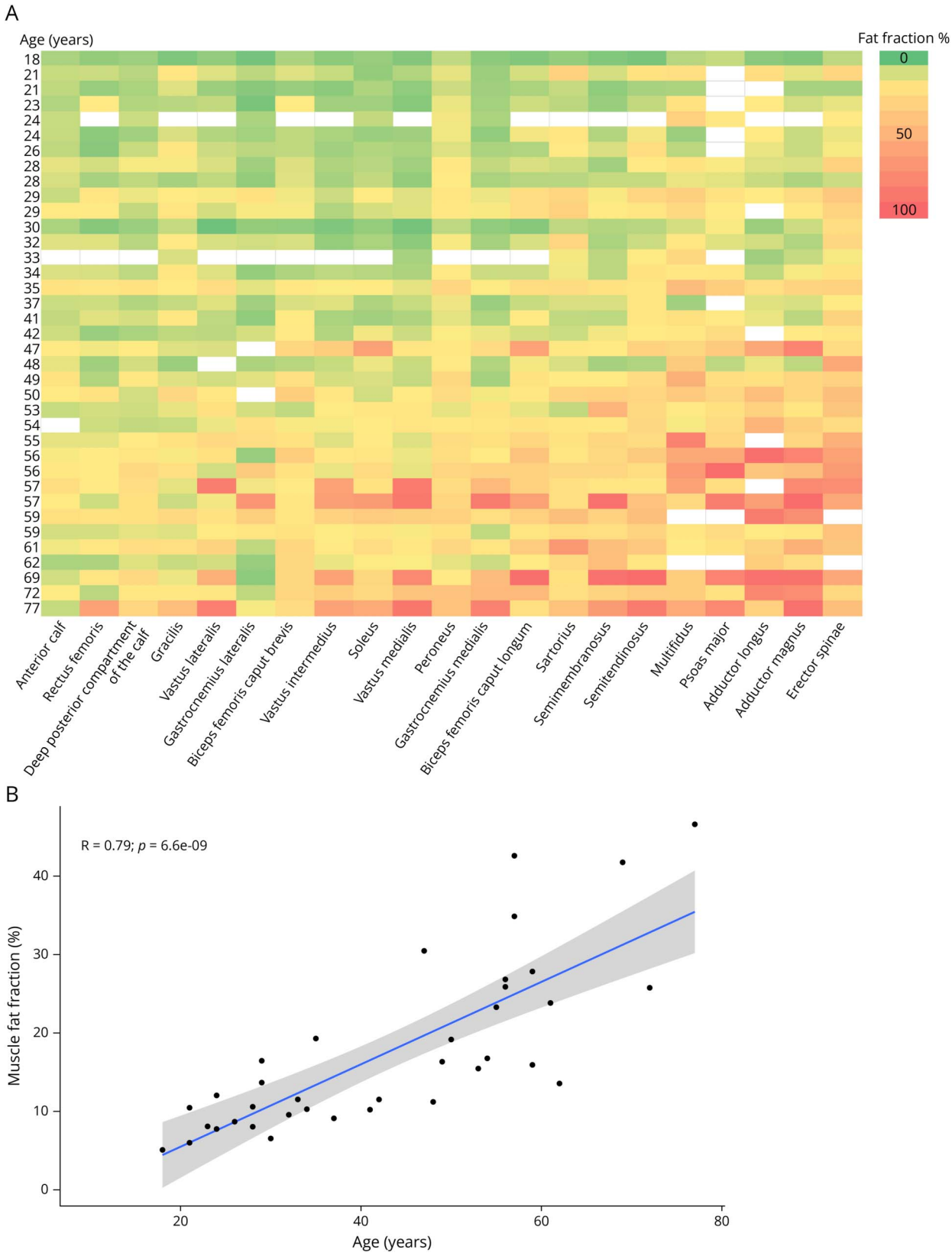
We initially included 43 participants. However, 3 participants declined to participate in follow-up visits, and 2 were lost to follow-up. Furthermore, 1 participant was excluded because of MRI artifacts. The excluded participants represented PP (n = 3) and MW (n = 3) phenotypes. 37 were included in the follow-up study: 12 women and 25 men (mean age 43 years, range 18–79 years; Table 1). All participants, except one who was heterozygous for the pathogenic variant p.R1239H (NM_000069.2: c.3716G>A), were heterozygous for the

Table 1 Characteristics of Participants at Baseline

Participants with HypoPP	n = 37
Sex, n (%)	
Female	12 (32)
Male	25 (68)
BMI	25 ± 6
Age, y	43 ± 16
Age at symptom onset	21 ± 16
Age at diagnosis	24 ± 16
Disease duration, y	24 ± 16
Pathogenic variants in *CACNA1S*, n (%)	
p.R1239H (NM_000069.2: c.3716G>A)	36 (97)
p.R528H (NM_000069.2: c.1583G>A)	1 (3)
Phenotype, n (%)	
Asymptomatic	3 (8)
Periodic paralysis	22 (59)
Mixed weakness	9 (24)
Permanent weakness	3 (8)
Muscle pain, n (%)	
Constantly	1 (3)
Sometimes	4 (11)
Only after attacks of paralysis	17 (46)
No muscle pain	15 (41)
Medication, n (%)	
Potassium, periodic	22 (60)
Potassium, constant	16 (43)
Acetazolamide	3 (8)
No medication	11 (30)
Physical activity, n (%)	
Sedentary	2 (5)
Light physical activity	6 (16)
Moderate physical activity	22 (59)
Vigorous physical activity	7 (19)

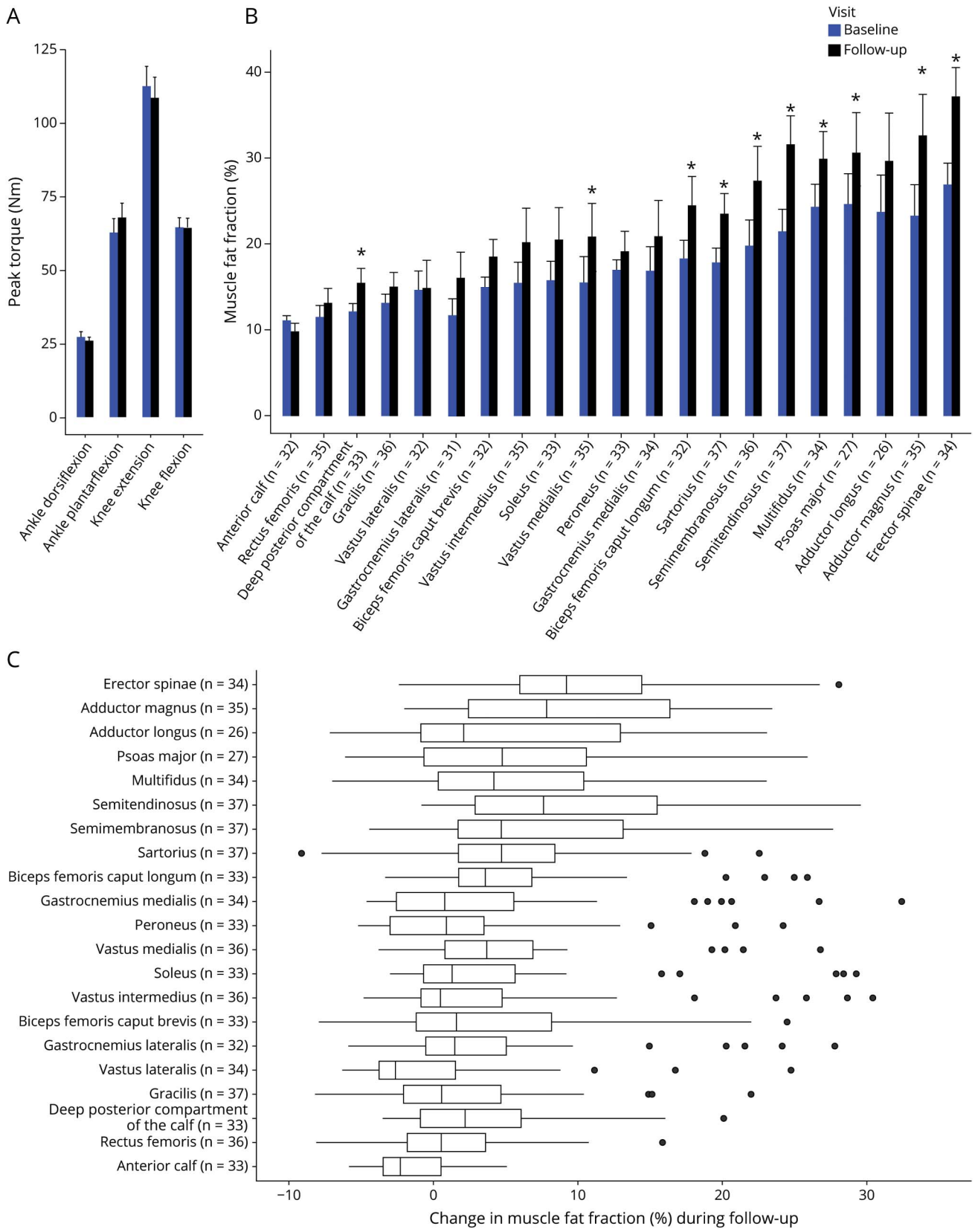
Participants could be treated with more than 1 medication.
Physical activity was rated as follows: 1: sedentary or light activity less than 2 h/wk; 2: light physical activity 2–4 h/wk; 3: light physical activity >4 h/wk or vigorous activity 2–4 h/wk; 4: vigorous activity >4 h/wk or competitive sport several times a week.

Figure 1 Fat Fraction of Individual Muscles of Patients With HypoPP at Baseline



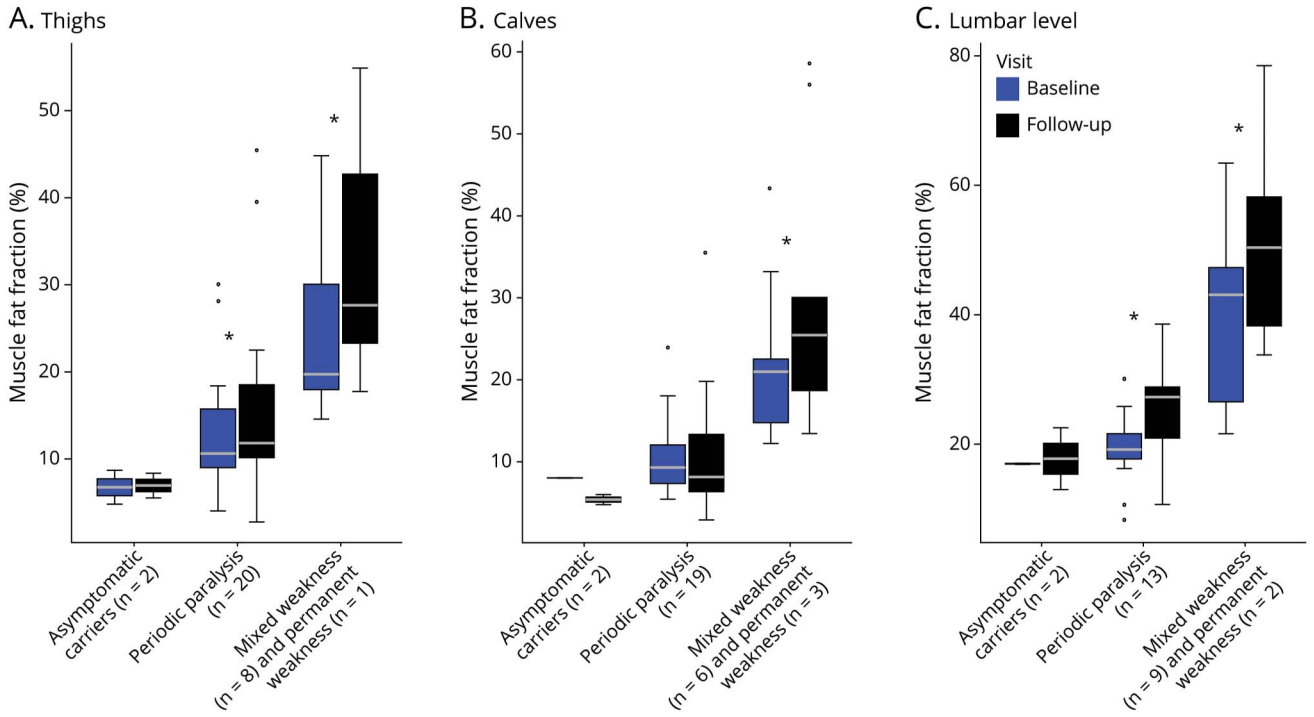
(A) The map is ordered by age at baseline. Every patient represents a row. The color visualizes the severity of fat replacement by fat fraction (%). White bar: muscle excluded because of poor quality of MRI. (B) Relationship between the composite fat fraction (%) of all examined muscles and age at baseline.

Figure 2 Muscle Strength and Fat Replacement of Individual Muscles



Muscle strength (A) and muscle fat fraction (B) at baseline and follow-up. Values are mean ± SD. An asterisk * indicates a significant difference. Boxplots of change in muscle fat fraction (%) in individual muscles during follow-up (C).

Figure 3 Change of Muscle Fat Fraction in Different Phenotypes



The boxplot shows the composite fat fraction of the thighs (A), calves (B), and lumbar level (C) of asymptomatic carriers, participants with periodic paralysis, and participants with permanent weakness with or without period paralysis. An asterisk * indicates a significant difference.

pathogenic variant p.R528H (NM_000069.2:c.1583G>A). The participants represented all phenotypes: AS (n = 3), PP (n = 22), MW (n = 9), and PW (n = 3). The participants with the phenotype AS were 1 woman and 2 men. The mean age was 29 years (range 26–32). Twenty-three participants had attacks of paralysis during follow-up (median 25, range 1–500). Eight participants (26%) with previous attacks of paralysis did not have attacks during follow-up. The median follow-up time was 20 months (range 12–25).

Baseline Muscle MRI

In total, 777 muscles were examined in the 37 participants. However, because of MRI artifacts, only 732 muscles were included in the baseline analysis. The fat fraction in the analyzed muscles at baseline ranged from 2% to 79% (Figure 1A). The most severely affected muscles were the erector spinae, with a median fat fraction of 25 (6–62), and the adductor magnus, with a median fat fraction of 16 (4–78). The composite fat fraction of examined muscle increased with age (R = 0.79, $p < 0.001$) (Figure 1B). The composite fat fraction was calculated as the mean fat fraction of analyzed muscles weighted for cross-sectional area. This relationship was not found for disease duration and fat fraction (R = 0.18, $p = 0.290$). The ICC was 0.97 (95% CI 0.96–0.98), $p < 0.001$, indicating an excellent inter-rater reliability.

Fat Fraction From Baseline to Follow-Up

Thirty-nine muscles at follow-up MRI were excluded because of artifacts, which is why 693 muscles in total were included in the progression analysis. The fat fraction increased in 10 of 21 examined muscles (Figure 2B). The most considerable progression was found in erector spinae with a median change of 9 (-2 to 28) and adductor magnus with a median change of 8 (-2 to 23) (Figure 2C). The composite fat fraction of the thigh and the muscles at the lumbar level increased in all symptomatic phenotypes (Figure 3, A and C). Furthermore, the composite fat fraction of the calves increased in patients with permanent weakness (Figure 3B). The number of asymptomatic carriers was too small (n = 2) to apply statistics (Figure 3). The composite fat fraction was calculated as the mean fat fraction of the muscles in the assessed level weighted for cross-sectional area, and only participants with an acceptable MRI quality of all analyzed muscles of the assessed level were included in the composite analysis (Figure 3). There was no correlation between increase in composite fat fraction in the muscles of the thighs, calves, or lumbar level and the number of attacks of paralysis in participants with attacks during follow-up.

Baseline Muscle Strength

Manual muscle strength testing at baseline showed that 11 patients had reduced muscle strength. The reduced strength was observed at trunk flexion (n = 8), back extension (n = 1), hip flexion (n = 10), hip abduction (n = 5), hip extension (n = 3), knee flexion (n = 5), and knee extension (n = 4).

Muscle Strength From Baseline to Follow-Up

During follow-up, muscle strength assessed by manual muscle strength testing declined (with a 1-point decrease) in 7

patients with reduced muscle strength at baseline and in 1 with normal strength at baseline. The reduction in muscle strength was observed at trunk flexion (n = 1), back extension (n = 1), hip flexion (n = 4), hip extension (n = 1), hip abduction (n = 5), and knee extension (n = 2). However, the median muscle strength grade did not differ from baseline to follow-up. Furthermore, the mean peak torque of knee extension and flexion and ankle plantarflexion and dorsiflexion did not differ from baseline to follow-up (Figure 2). 1 participant was too weak to test in the stationary dynamometer at follow-up and was excluded from the follow-up analysis of mean peak torque.

Discussion

In this study we examined disease progression in persons with HypoPP-causing variants in *CACNA1S* using quantitative muscle MRI and quantitative muscle strength assessment with stationary dynamometry. We found a significant increase in muscle fat fraction in half of the examined muscles from baseline to follow-up. A significant increase in muscle fat fraction was found in both phenotypes with and without permanent muscle weakness. However, we found no significant changes in muscle strength from baseline to follow-up. The study demonstrates that quantitative MRI can detect subclinical disease progression in HypoPP, providing new information on the natural history of disease progression in individual muscles.

The finding that quantitative MRI can detect subclinical disease progression is in line with findings in other muscular dystrophies such as limb-girdle muscular dystrophy 2I,[14] Becker muscular dystrophy,[22] Duchenne muscular dystrophy,[23] and late-onset Pompe disease.[15]

For quantitative MRI to be a good biomarker in HypoPP, the change in fat replacement needs to relate to clinical outcomes. We did not find a statistically significant decrease in muscle strength. However, 7 participants had a decline in muscle strength assessed with manual muscle strength testing during follow-up, indicating that a longer follow-up period may show significant changes. Furthermore, muscle strength of hip flexion was affected in most of the participants with permanent weakness at baseline when assessed by manual muscle strength testing, and almost half of them had a decline in strength in hip movements at follow-up. Manual muscle strength testing has some limitations because of variability and the fact that a change in MRC requires a relatively large change in strength to be detected,[24] so it could be very interesting to monitor the muscle strength of the hip with quantitative strength assessment. It is possible that we would have found a significant change in muscle strength if we had added quantitative muscle strength assessment with stationary dynamometry to the muscles of the hip. However, the relationship between the progression of fat replacement of muscle in persons with HypoPP and decline in muscle strength requires further investigation, and we, therefore, suggest a study with a longer follow-up time, including quantitative muscle strength assessment of the hip.

In addition, this study did not include functional outcome measures such as 6-minute walk distance and 10-minute walk test or patient-reported outcomes such as the Individualized Neuromuscular Quality of Life questionnaire.[25] It could also be interesting to include such measures in future, more extended follow-up studies to assess the relationship between changes in clinical outcome and quality of life and changes in quantitative MRI to ensure that MRI changes are clinically relevant. Correlations between change in quantitative MRI and clinical outcome measures have been investigated for other muscular dystrophies such as facioscapulohumeral muscular dystrophy[26] and limb-girdle muscular dystrophy autosomal recessive type 12,[27] indicating that this could also be the case in HypoPP. However, this requires further studies.

The frequency and severity of attacks of paralysis can, in some patients, be reduced by minimizing triggers, by potassium supplements, and by treatment with the carbonic anhydrase inhibitors acetazolamide and dichlorphenamide.[7,10-12] In this study, we found no correlation between the progression of fat replacement and attacks of paralysis during follow-up, indicating that frequent attacks of paralysis are not necessary for the progression of myopathy.

This is in line with previous studies showing that permanent weakness and fat replacement of muscle can develop and progress in patients without periodic paralysis.[6,8,13] However, data in this and previous studies are limited and should be interpreted cautiously. Furthermore, in a model (K+-depleted rats) of HypoPP, acetazolamide has been shown to prevent the development of myopathy.[28] Only 3 participants in this study were treated with acetazolamide, so we cannot conclude the influence of acetazolamide on progressive myopathy, and it would be very interesting to have a randomized controlled trial to assess the possible effect of acetazolamide and dichlorphenamide on progressive myopathy in persons with HypoPP. In a previous study, we have shown that autophagy is negatively affected in patients with HypoPP and suggest that this dysfunctional autophagy could contribute to the progressive nature of the myopathy.[29]

In approximately 60% of cases, HypoPP is caused by pathogenic variants in *CACNA1S*, which encodes the alpha-1 subunit of the L-type calcium channel, and 10%–20% of cases are caused by pathogenic variants in *SCN4A,* which encodes the skeletal muscle sodium channel alpha subunit.[3,4] All the study participants, except one, carried the most common variant in CACNA1S, and the result cannot be generalized to the broader population of persons with HypoPP-causing variants. Investigating persons with other variants and comparing the result with that of this study could be interesting.

A limitation of our study is the limited number and heterogeneity of participants regarding disease severity, medical treatment, and physical activity. Subgroup analysis in more extensive studies could be interesting as to why multicenter studies are warranted. Another limitation is that only one MRI slide of each level was analyzed. A recent study of persons with pathogenic variants in *SCN4A* variants also used Dixon MRI to study fat replacement. They found that the amount of fat varied in different parts of the leg muscle.[30] Fat replacement of muscle in HypoPP is also not always homogeneous through the muscle, and it can be very focal.[6] Therefore, the slices measured in our study may not be representative of the entire muscle progression. Another limitation is the variation of the follow-up period from 12 to 25 months. Participants with the shortest follow-up period would likely have developed more fat replacement of the muscle if the follow-up period was precisely 18 months, and participants with the longest follow-up period would likely have developed less fat replacement if the follow-up was precisely 18 months. Therefore, estimating the yearly disease progression is not possible in this study. Finally, a limitation of the study is the lack of healthy controls. Mild fat replacement of the muscle can be part of normal aging,[20] and a comparison of progression with that of healthy age-matched controls could be relevant to ensure that this has not affected the results. However, a significant progression in half of the examined muscles during the short follow-up in a cohort with both young and old participants is more than we would expect because of age.

In conclusion, the results from this follow-up study support the use of quantitative muscle MRI to monitor subclinical disease progression in HypoPP in patients with and without attacks of paralysis.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Sonja Holm-Yildiz, MD	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Thomas Krag, PhD	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Tina Dysgaard, MD, DMSc	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Britt Stævnsbo Pedersen, PT	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Nanna Witting, MD, PhD	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Louise Sloth Kodal, MD	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Linda Kannuberg, MD	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jonas Jalili Pedersen, MD	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Zhe Lyu, MD	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Morten Müller Aagaard, MD	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
John Vissing, MD, DMSc	Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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