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ORIGINAL COMMUNICATION

Strength and muscle structure preserved during long-term therapy in a patient with hypokalemic periodic paralysis (Cav1.1-R1239G)

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Abstract

We report a young wheelchair-dependent patient with an unclear proximal myopathy and a heterozygous, de-novo Cav1.1-R1239G mutation suggesting hypokalemic periodic paralysis (HypoPP). Sonography showed a loss of the pennate pattern indicative of an edema, whereas fatty degeneration was excluded. Within 7 days of therapy with spironolactone, potassium and physical therapy, muscle strength almost completely normalized, a normal pennate pattern appeared and the edema was markedly reduced. She learned to walk without aid and to do sports and has continued to do so for 11 years until now. Over the years, we tested serum potassium values, muscle strength, muscle edema and muscular sodium content by 1.5 T, 3 T and 7 T ^{1}H and ^{23}Na magnetic resonance imaging. No fatty muscle degeneration developed. Muscular edema-like changes only occurred when she was pregnant and was set to reduced therapy. Because of the ability to do sports again, her mobility was further increased. Our observational study on this single patient may suggest that: (1) muscle imaging and molecular genetics are important diagnostic tools, (2) weakness in periodic paralysis may be reversible, and (3) continued adequate therapy may preserve muscle structure and strength on a longterm, whereas weakness due to fatty degeneration could be considered progressive and irreversible. Although HypoPP is a rare disease, it should be included in differential diagnosis not only if there is paroxysmal weakness, but also in cases of myopathy of unknown origin.

Keywords Myopathy · Paralysis · Muscle edema · Precision medicine · Ion channel disorder

Introduction

Hypokalemic periodic paralysis (HypoPP) is an autosomal dominant neuromuscular disorder characterized by episodes of flaccid skeletal muscle weakness accompanied by a drop in serum potassium [1]. Weakness is most pronounced in muscles recently exercised. Whereas the weakness episodes usually last hours up to days, some patients develop a progressive proximal myopathy with seemingly permanent weakness [2–4]. A correlation between the frequency of weakness episodes and myopathy development has not been observed. In the majority of cases, HypoPP is caused by mutations in one of two genes, *CACNA1S* and *SCN4A*. Both encode voltage-gated ion channels of skeletal muscle, namely, Cav1.1, the tubular L-type calcium channel and Nav1.4, the sarcolemmal sodium channel. The mutations are situated in a transmembrane, helical S4 segment thought to act as voltage-sensor, and neutralize a positive amino acid such as arginine (R) (Cav1.1 [3, 5]; Nav1.4 [6, 7]). Substitution of the R residue with histidine (H) or glycine (G) leads to a pathologic

Dedicated to Eva Luise Köhler, former First Lady of Germany and patron of the ACHSE (Chronic Rare Disease Alliance) and our mentor, colleague and friend, Frank Lehmann-Horn, who initiated the study and sadly passed away in May 2018.

Frank Lehmann-Horn: Deceased.

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so-called gating pore current through the S4 segment that depolarizes the muscle presumably causing the weakness [4, 8–14]. Prophylaxis by carbonic anhydrase inhibitors (CAI), especially with acetazolamide, has been the most common treatment choice for HypoPP for nearly 50 years [1]. Used off-label, it reduced the frequency and severity of weakness episodes in 46% of HypoPP patients [15]. However, patients with an R-to-G mutation in either gene reacted adversely to acetazolamide [4, 15–18]. Diclofenamide, another CAI, reduced the median weekly attack rate of HypoPP patients to 0.3 vs. 2.4 in the placebo group [19]. Adverse effects of the CAI were paresthesia, cognitive disorder, confusion and dysgeusia. Spironolactone, an aldosterone antagonist (AA), was reported to be effective but less than acetazolamide [1], whereby the cited publication appeared in the pre-molecular era, i.e., at a time when the genotype of the treated patients was unclear. Therefore, very rare mutations with a potentially different response to certain drugs would have been neglected. A newer AA with higher affinity to the receptor is eplerenone [20].

In addition to genotyping and the response to drugs, magnetic resonance imaging (MRI) is another appropriate method to clarify what is causing muscle weakness [21]. Like computed tomography, T1-weighted sequences show the fatty degeneration and changes of the muscle volume; T2-weighted sequences indicate fatty degeneration and muscle water accumulation, and the short tau inversion recovery (STIR) sequence inhibits the fat signal and reveals water accumulation. Myoplasmic Na^+ concentration can be quantified using 1.5 T [4], 3 T [22, 23] and 7 T ^{23}Na-MRI [24]. Here, we tested whether reversal of chronic weakness with spironolactone plus K^+ was associated with reversibility for some image-based pathologic features (edema and intracellular Na^+ overload) and the absence of others (fatty degeneration or atrophy), and present the successful therapy for more than one decade in a young patient, who was wheelchair dependant for several years.

Materials and methods

The patient gave her written informed consent to the genetic and all MRI studies, which were approved of by the Ethics Committee of both Ulm and Heidelberg University. Her relatives gave their written informed consent to the genetic studies. All studies were conducted according to the declaration of Helsinki in its present form. The exons and exon–intron boundaries of *CACNA1S, SCN4A, and KCNJ2* (methods in [4]) were amplified from genomic DNA and bidirectionally sequenced using an automated 373A sequencer (Applied Biosystems).

Molecular diagnosis

Sanger sequencing of all coding exons of the *CACNA1S* gene predicted a glycine substitution at arginine 1239 in Cav1.1. R1239G affects the second positive charge in the fourth domain S4 voltage sensor of the channel. No *SCN4A* or *KCNJ2* mutations were found in the coding regions [4].

Magnetic resonance imaging (1.5 and 7 T) examination and analysis

The patient underwent whole-body 1.5 T MR imaging in 2007 and 2017 (Magnetom Avanto, Siemens Healthineers, Germany). The sequence protocol comprised coronal standard T1-weighted (TR/TE = 623/8.1 ms) and STIR sequences (TR/TE = 3400/57 ms). In 2006 and 2007, we performed both ^{1}H MRI as well as ^{23}Na MRI of both calves on a clinical whole-body 1.5 T system (Magnetom Symphony, Siemens Healthineers, Germany), the protocol has been described before [4]. In 2017, we performed ^{23}Na MRI of both calves on a clinical whole-body 7 T system (Magnetom 7 T; Siemens Healthineers, Erlangen, Germany). Hardware specific for broadband spectroscopy and a CE-certified double-resonant (^{35}Cl/^{23}Na) birdcage coil (RAPID Biomedical, Rimpar, Germany) with the following frequencies (^{35}Cl: 29.1 MHz, ^{23}Na: 78.6 MHz) [24] were used for recording ^{23}Na signals.

For normalization of ^{23}Na signals, the values of samples from the soleus muscles were divided by the signal intensity of the agarose phantom in which NaCl was trapped. Principal features of the sequences used for Na^+ concentration measurements in the calf muscles had been previously described in detail [24, 25]. In short, we used a three-dimensional density-adapted projection reconstruction sequence for ^{23}Na MRI (TR/TE = 160/0.35 ms; slice thickness, 4 mm) with minimized T2* relaxation weighting. The 7 T ^{23}Na MRI was performed without repositioning the patient. Na^+ concentrations were quantified in the soleus muscle using three phantoms as reference containing 5% agarose gel and either 10, 20, or 30 mmol/l NaCl solutions. For exact positioning of ROIs within the soleus muscles, the 1.5 T whole-body ^{1}H MR images were used as reference. When distinct lipomatous degeneration of certain muscles was observed in ^{1}H MRI, the reader (M. A. W.) positioned ROIs in an area with more intact muscle. For normalization, supplementary ROIs were placed on the reference phantoms as described before [4, 20–24].

Muscle edema was assessed on STIR images. We defined areas of localized hyperintensity on STIR MR images as muscular edema-like changes according to

[26]. We evaluated the presence of this criterion with a four-point semi-quantitative visual scale, as has been described previously [27, 28]. Grade 1: homogeneous, hypointense signal, contrasting sharply with subcutaneous and intermuscular fat (normal muscle, no edema); grade 2: Slightly hyperintense, patchy intramuscular signal changes on STIR (< 50% of muscle cross-sectional area); grade 3: markedly hyperintense, patchy, but widespread intramuscular signal changes on STIR (> 50 of muscle cross-sectional area); grade 4: homogeneous hyperintense signal in whole muscle on STIR (100% of muscle cross-sectional area). Moreover, the reader also semi-quantitatively assessed edema-like changes of the soleus muscle on STIR images as has previously been described [4, 28] using a ROI analysis with background noise as reference ($ROI_{muscle}/ROI_{backround\ noise}$).

^{31}P-MR spectroscopy of the calf muscles was performed on a 1.5 T system as described previously [29]. Our patient demonstrated a normal muscular pH value of 7.07 in 2006 and 2007.

Results

The patient was born with bilateral hip luxation. After immediate hospitalization, reposition, and treatment with a hip spica cast, spreader pants were employed. Normal motor development was observed in the first 3 years of life. Pronounced episodes of weakness of the lower extremities with inability to walk manifested at the age of 3 years. Those were triggered by moderate exertions and infections. During such an episode, a serum potassium of 2.7 mM and a slight CK elevation were the only pathologic serum findings, whereas thyroid parameters were normal. At the age of 8 years, she has been unable to walk unaided, showed positive Trendelenburg's sign, was unable to climb stairs without railing, could not get up from a chair or from a prone position and, therefore, became wheelchair-bound (Fig. 1). On premenstrual days, she was quadriplegic. Possibly due to the use of the wheelchair, a thoracic scoliosis developed with the result of a restrictive, moderate ventilatory dysfunction. At age of 15 years, muscle histology showed type1-fiber predominance, myopathy and normal immunohistochemistry. At age of 18 years, still wheelchair-bound, we saw the patient for the first time. She reported missing school often and frequent broncho-pulmonal infections due to impaired expectoration. Neurological examination revealed inability to stand up and a generalized muscle weakness. A thoracic scoliosis was marked (Fig. 2). An edema, pronounced in the upper legs, was obvious. We identified a heterozygous *CACN1AS* c.3715C > G transition predicting Cav1.1-R1239G. This very rare mutation is known to cause hypokalemic periodic paralysis associated with progressive

Fig. 1 Prior to therapy, the girl required a wheelchair to be mobile

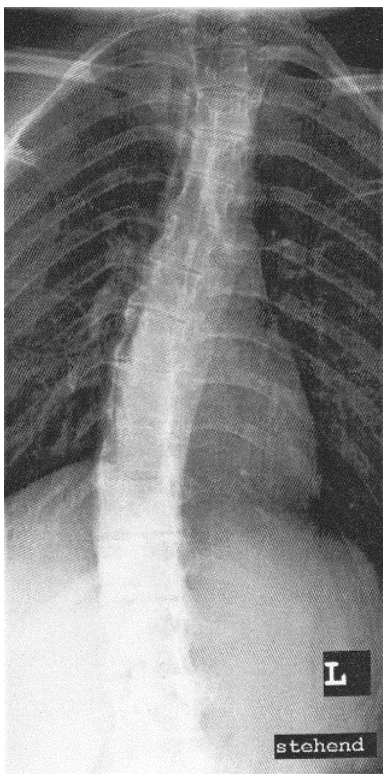

Fig. 2 X-ray of the thoracic spine in standing position ("stehend"). The convex bending of the thoracolumbar spine to the right side is visible. The degree of scoliosis slightly improved when lying down in comparison to the whole-body MRI examinations from September 2006, when she was 23 years old and August 2017, when she was 34 years old

weakness and respiratory insufficiency [4, 18]. R1239G was excluded in the parents and, later, in her son. We treated the muscular edema with intravenous spironolactone 100 mg/d, oral ingestion of potassium chloride (2/d KCl retard slow-K 600 mg-tablets), and physical therapy. The physiotherapist noted that passive extension of the hip and ankle dorsiflexion contributed to improved ambulation and that muscle strength increased from day to day. A plateau was reached at day seven (grip strength increased from 20 to 70 mbar). An ultrasonography of the gastrocnemius muscle revealed a loss of the pennate pattern. After 7 days, a normal pennate pattern re-appeared (Fig. 3). Changing spironolactone administration from intravenous to oral did not affect progress. Additionally, the mini pill desogestrel did not seem to impede recovery. Within 6 weeks, the patient became able to walk up to 12 km without aid and even to sometimes jog (Fig. 4). As a side effect, we observed that our patient, when she once increased the dose on her own, actually became weaker, developed cardiac arrhythmia, and suffered from hair loss. Reduction to the recommended dose stopped the adverse effects.

^{23}Na-MRI enabled depiction of an intracellular muscular sodium accumulation, which correlates well with the grade of muscular paresis. Ultrashort echo time of 0.2 ms allowed us to record signals containing predominantly the intracellular sodium [30]. Prior to therapy, 1.5 T ^{1}H-MRI showed hypotrophic and edematous muscular alterations in the lower legs (Fig. 5a). A specific 1.5 T ^{23}Na-coil measured the Na-content of the muscles, indicating a muscular sodium overload (Fig. 5b). The intensity of the ^{23}Na signal of the muscle was very high, namely as high as in the middle phantom that was filled with 51.3 mM Na^+ in 5% agarose to mimic Na^+ with restricted mobility as in myoplasm as described previously [4, 31]. The imaging protocol of the lower legs comprised axial T1-weighted turbo spin-echo for the detection of fatty muscle degeneration and axial STIR ^{1}H MRI sequences for the identification of muscular edema. The muscular signal intensity on STIR images was normalized to the background signal as described previously [4]. The left phantom contained NaCl solution to mimic Na^+ with unrestricted mobility as in the extracellular fluid. The third phantom contained 0.6% NaCl in H_2O. Altogether, the sodium overload may have been responsible for the muscle edema and sustaining the weakness, like previous reports suggested for HypoPP [4] and Duchenne muscle dystrophy [21]. Due to therapy, sodium accumulation was reduced, and the hypotrophic muscles became normotrophic (Fig. 5c). The particularly hypotrophic gastrocnemius and adductor muscles strikingly increased their mass. Additionally, the muscular edema was washed out, as observable in the fat-suppressed ^{1}H MRI (Fig. 5c). The ^{23}Na MRI of the lower leg muscles

Fig. 4 At age 19, due to the therapy, muscle strength markedly improved and the patient was able to walk long distances

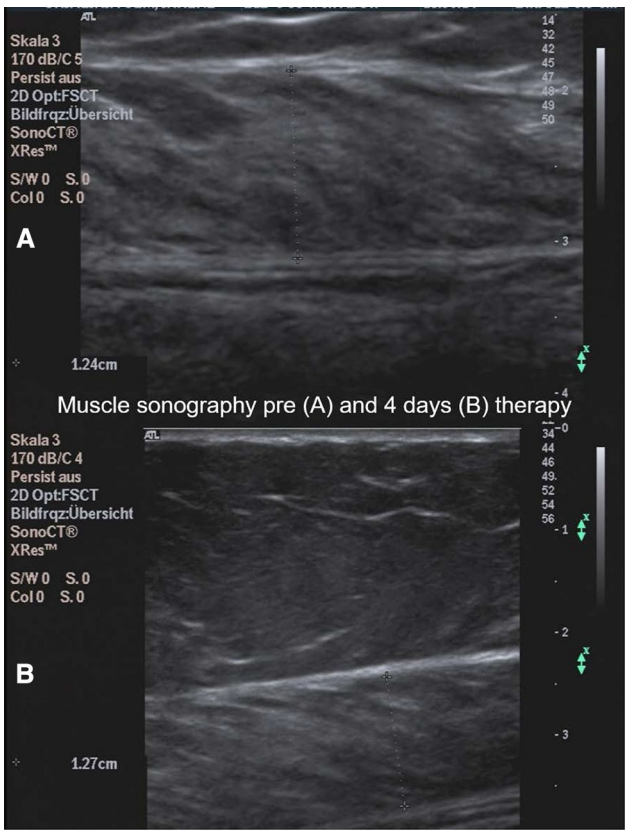

Fig. 3 Ultrasonography of the gastrocnemius muscle. **a** Loss of the pennate pattern before therapy. **b** After 7 days of therapy, a normal pennate pattern appeared and the muscular edema was reduced

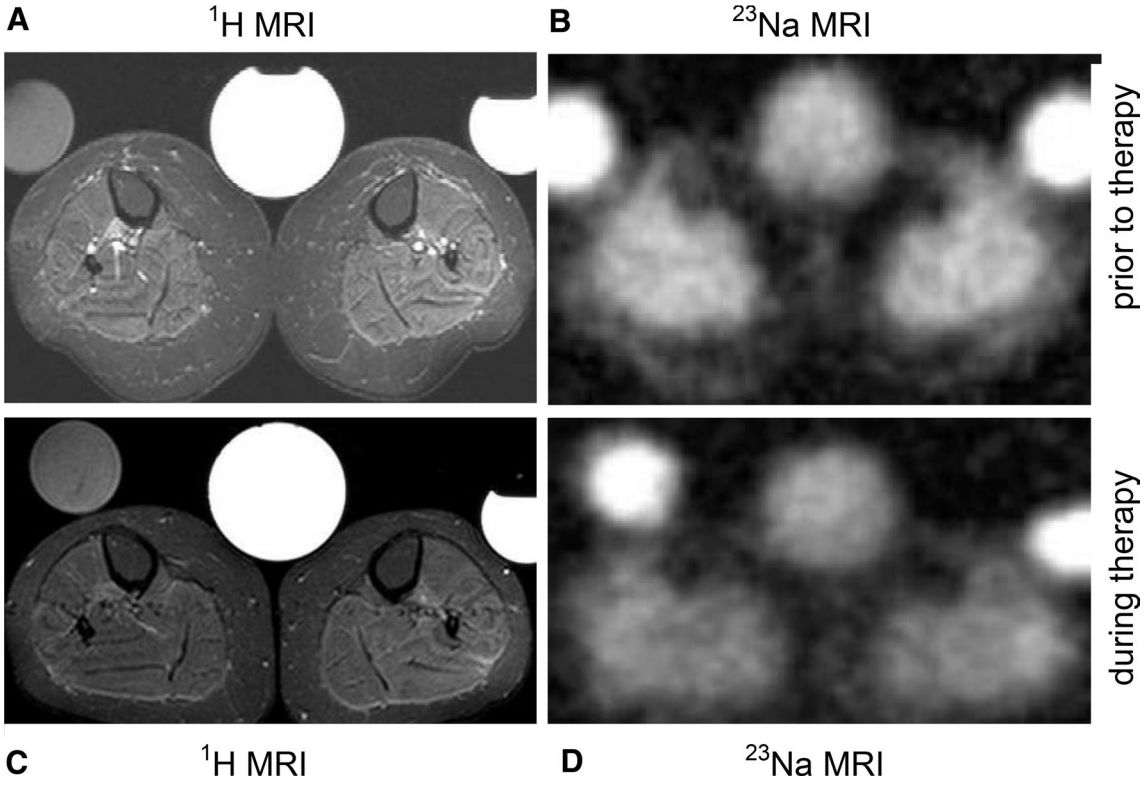

Fig. 5 Lower legs underwent a 1.5 T MRI before (**a**, **b**) and after six months of therapy (**c**, **d**). ^{1}H STIR MRI (left panels; **a**, **c**) and ^{23}Na MRI (right panels; **b**, **d**) were measured. **a** The tibial bones have low signal intensity on ^{23}Na-MRI. The edema is indicated by the bright signal in the fat-suppressed ^{1}H MRI. Due to therapy, sodium accumulation was reduced from 1.42 (24.65 mmol/l) initially via 1.09 (18.92 mmol/l) after initial therapy in 2006 to 0.90 (15.63 mmol/l) in 2007 after successful therapy (muscular ^{23}Na signal normalized to the 0.3% NaCl reference phantom). Reference phantoms filled with 0.3% NaCl (middle), 0.6 NaCl (left side of the patient) and 0.3% NaCl in agarose (right side of the patient) are visible and calculation of muscular sodium content was performed as described previously [4, 30]. Please note that at 1.5 T ^{23}Na MRI, the calculated mean muscular sodium concentration was 24.7 mmol/l in Cav1.1-R1239H/G and 15.0 mmol/l in healthy controls [4], while at 7 T ^{23}Na MRI it was 19.9 mmol/l in healthy volunteers and 35.3 mmol/l in patients with Cav1.1-R1239H [24]. Thus, the muscular sodium content of our patient is at the last visit only slightly increased, or in the upper normal range. Parallel to the decrease in muscular sodium accumulation, the muscle edema when assessed semiquantitatively using a ROI analysis decreased by 37% between 2006 and 2007 and this reduction persisted until 2017. Regarding the qualitative analysis, the calf muscles initially were scored as grade 3 for muscle edema in 2006 and were scored grade 1 in 2017 at the age of 34 years

showed a weaker sodium signal and a less severe edema (Fig. 5d). There was no fatty degeneration present.

Pregnancy led to deterioration and physical therapy alone was not sufficient to maintain strength. After prior consultation, we administered 50 mg/d spironolactone and potassium (KCl retard slow-K 600 mg-tablet/day) and instructed the patient on how to avoid triggers such as ingestion of carbohydrates and salt, rest after exercise, mental stress, cooling, and cortisone. Even so, general muscle weakness remained, but was tolerable for the patient. After birth of her healthy boy, her muscles required 2 months to recover under the original dose of 100 mg/day spironolactone and potassium chloride (2/day KCl retard slow-K 600 mg-tablets). Since then, she has again been able to ride, and to walk with her dog over long distances. Scoliosis has improved and the Trendelenburg's sign is now negative (Fig. 6). Hitherto, it was generally expected that the long term myopathy and the underlying alterations continuously progress despite therapy which was thought to only provide short-term effects limited by the time point in which side effects become intolerable. To question this assumption and to test the possibility of continuation of the improved status, we repeated the measurements 11 years after beginning the consequent therapy. In the meantime, the ^{23}Na MRI technique has improved and thus we used 7 T ^{23}Na MRI (Fig. 7) with improved signal-to-noise ratio [24] and again 1.5 T whole body ^{1}H MRI (^{1}H also for reasons of coregistration) at the same system like the measurements 10 and 11 years before to ensure comparability (Fig. 8). Indeed, the sodium muscle content of the calf muscles was 21.8 mmol/l. Measured with the identical protocol, the sodium content of healthy volunteers was in average 19.9 mmol/l (SD = ± 1.9 mmol/l) and for patients with Cav1.1-R1239H and Cav1.1-R528H in average 35.3 mmol/l and 33.0 mmol/l, respectively [24]. Compared to this study,

Fig. 6 The patient was asked to lift her left leg. She performs it without the Trendelenburg's sign

the muscular sodium content of our patient is at the last visit only slightly increased, or in the upper normal range. The muscle strength for foot dorsi-/plantar flexion of the right and left leg ameliorated from 1/5 and 2/5 (13 September 2006), over 4/5 and 4/5 (17 October 2006 as well as 02 November 2007) to 4–5/5, 4-5/5 (02 August 2017), all muscle tests were performed by the same senior physician according to the MRC grading scheme. No electromyography has been carried out.

Discussion

The previously published families with mutation Cav1.1-R1239G have in common that the motor and intellectual development was normal [4, 16–18]. Family history was either meaningful for the occurrence of HypoPP or the mutation occurred de-novo like in the patient reported here. Most patients developed permanent weakness between three and 14 years of life before periodic paralysis occurred. Generalized weakness spells occurred after physical exercise or intake of carbohydrate rich meals or alcohol. Some days, getting up in the morning was impaired. Leg cramps were often reported. Worse attacks happened before menstruation mainly at night and during pregnancy.

Although CAI have been the most common treatment choice for HypoPP, the patients with the very rare R-to-G mutations in both Cav1.1 and Nav1.4 reacted adversely to the CAI acetazolamide [4, 15, 17, 18]. Therefore, we chose a different group of diuretics, AA, and administered spironolactone. In HypoPP, muscle weakness is caused by membrane depolarization to values at which action potentials cannot be elicited and, therefore, muscle fibers are not activated [4, 32]. Weakness and sodium accumulation were well correlated, as has been described for sodium channelopathies [31], HypoPP [4], and Duchenne muscular dystrophy [21]. The sodium ions accumulate in the intracellular space, and by virtue of osmotic forces, this overload will cause accumulation of intracellular water (edema). This disequilibrium plus the electrical inexcitability leads to histological alterations that are not specific. Therefore, 7 T ^{23}Na signals indicate that the weakness is associated with an intracellular sodium overload, but not with fatty muscle degeneration, suggesting that muscle weakness due to edema and depolarization may be reversible as long as muscles have not undergone fatty degeneration. In agreement with this theory, MRI in our patient showed quite normal appearing muscles, similar to endplate disorders [27].

Muscle weakness can be caused by edema or permanent disruption of the muscle tissue such as fatty muscle degeneration or muscle atrophy. Since the therapy is different for these cases, muscle ultrasound and ^{1}H-MRI are highly useful for determining pathogenesis, therapy, and prognosis. Even though no treatment is currently available to stop or reverse the fatty degeneration, i.e., the replacement of muscle mass by fat and connective tissue, muscle edema can be washed out by diuretics and aldosterone antagonists. These drugs also lead to a repolarization of muscle fiber and an increase in their strength [4]. Based on our data, we conclude that muscle weakness due to edema (or better due to membrane inexcitability which is due to sodium influx that results in edema) can be reversed and progression avoided or at least delayed by continuous therapy, whereas weakness due to fatty degeneration is considered to be progressive and irreversible. Although HypoPP is a rare disease it should be included in differential diagnosis not only if there is paroxysmal weakness but in all cases of myopathy of unknown origin.

In summary, our observational study of an individual with hypokalemic periodic paralysis (HypoPP) over a period of 11 years reveals a chance to recover from permanent muscle

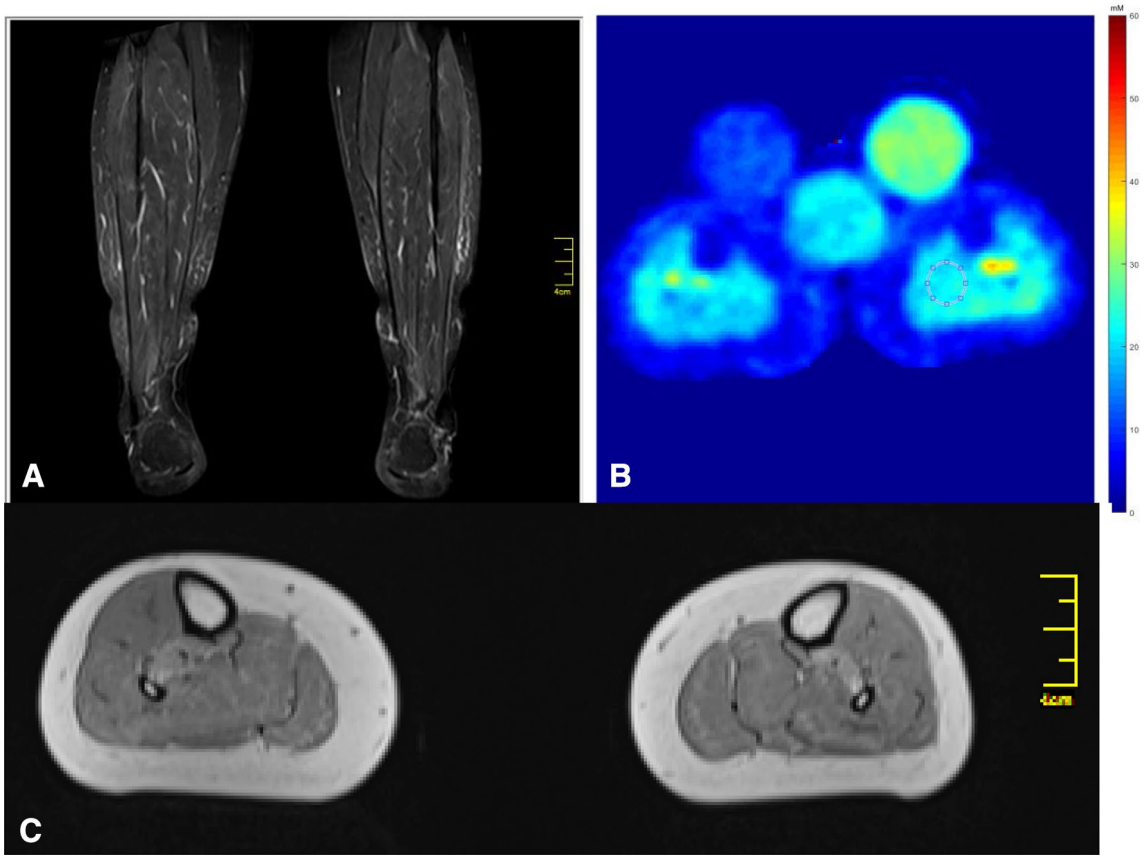

Fig. 7 Coronal ^{1}H STIR MR image shows no muscle edema within both calves (**a**). 7 T ^{23}Na-MRI of the lower legs, 11 years after beginning the therapy (**b**). Note, Na^{+} concentrations were quantified in the soleus muscle using three phantoms as reference containing 5% agarose gel with either 10, 20, or 30 mmol/l NaCl solutions (from right to left side of the patient). Axial T1-weighted ^{1}H MR image at the lower leg level (**c**) shows no fatty infiltration

weakness by therapy with spironolactone plus K^{+}. Therapeutic response can be monitored with several image-based metrics of muscle status (ultrasonography, ^{1}H-MRI and ^{23}Na-MRI). The individual is confirmed to have an ultra-rare cause of HypoPP (de novo *CACNA1S* R1239G) which in her and others has a severe phenotype with early onset myopathic weakness, respiratory compromise, and also the transient exacerbations that are typical of HypoPP. The proband was wheelchair-dependent at age 8, and yet remarkably regained ambulation when placed on sprinolactone plus K^{+} at age 18 and has retained near normal strength over the intervening 11 years. Ultrasonography and ^{1}H-MRI showed muscle edema before initiation of therapy, which then resolved when the strength improved over the first month. There was no fatty degeneration or atrophy. ^{23}Na-MRI revealed a hyperintense signal compatible with intracellular Na overload that was initially very severe (approximately 50 mM, normal about 20 mM) but then resolved and did not recur while on pharmacotherapy. This longitudinal study of a single patient illustrates several interesting features of HypoPP. First, the diagnosis can be delayed for more than a decade when the presentation is atypical with "permanent" myopathic features rather than episodic attacks of weakness, especially when there is no family history for a de novo mutation. Second, moderate to severe weakness that has persisted for a decade in HypoPP

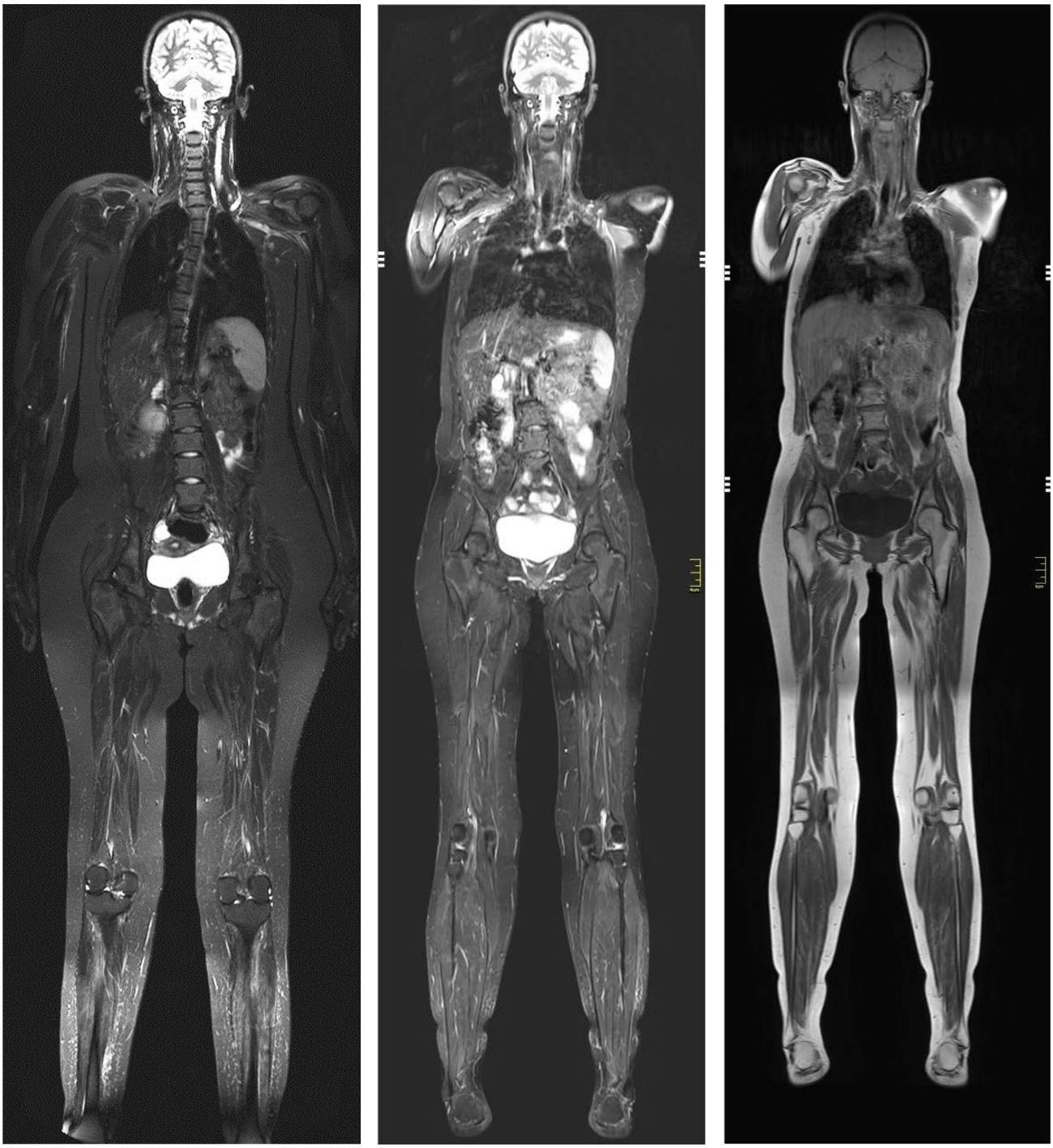

Fig. 8 Coronal whole body 1.5 T ^{1}H MR images in 2006 (STIR sequence, left) and 2017 [STIR sequence (middle) and T1-weighted sequence (right)]. Notably, because of the ability to do sports again, the subcutaneous fat has decreased. In 2017, there are no relevant muscular edema-like changes and no fatty muscle degeneration present

can be reversed with appropriate therapy. However, we have to acknowledge that the observations here were made for a single patient. Thus, clearly more data from other patients are warranted to confirm our results.

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Compliance with ethical standards

Conflicts of interest The authors report no conflicts of interest.

Ethical approval All human studies have been approved by the appropriate local ethics committee and have been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consent was obtained prior to inclusion in the study.

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