ACTA MYOL 2025;XLIV:104-108;
DOI: 10.36185/2532-1900-1374

CASE REPORT

# The case of a highly trained TRPV4 related scapuloperoneal spinal muscular atrophy patient: a 5-year follow-up

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**Objectives.** This case report explores the feasibility and effects of long-term physical exercise (PE) in a patient with TRPV4-related scapuloperoneal spinal muscular atrophy (SPSMA).
**Methods.** We describe a 26-year-old male who regularly engaged in supervised PE since age 21. He underwent annual clinical evaluations and laboratory assessments every 25 months to monitor maximal oxygen consumption ($\dot{V}O_2$max), muscle strength, body composition, and emotional well-being.
**Results.** Over five years, the clinical condition remained stable. The patient showed $\dot{V}O_2$max and handgrip strength values comparable to athletic cohorts; body composition aligned with reference values for age- and sex-matched healthy individuals; and limb muscle strength was preserved over time. Additionally, he maintained an active working life and consistently reported positive emotional well-being throughout the follow-up period.
**Conclusions.** This report provides preliminary data supporting the feasibility and potential benefits of long-term PE in the management of TRPV4-related SPSMA.

**Key words:** physical exercise, scapuloperoneal spinal muscular atrophy, clinical disease progression, transient receptor potential cation channel, Member 4 (TRPV4)

Received: May 26, 2025
Accepted: July 17, 2025

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**How to cite this article:** Crisafulli O, Fortunati M, Quintiero V, et al. The case of a highly trained TRPV4 related scapuloperoneal spinal muscular atrophy patient: a 5-year follow-up. Acta Myol 2025;44:104-108. https://doi.org/10.36185/2532-1900-1374

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## Introduction

Missense mutations in the transient receptor potential cation channel, subfamily V, member 4 (TRPV4) gene, inherited in an autosomal dominant manner, have been associated with scapuloperoneal spinal muscular atrophy (SPSMA), along with other heterogeneous skeletal dysplasias and neuromuscular disorders (NMDs), such as Charcot-Marie-Tooth disease type 2C (CMT2C) and congenital distal spinal muscular atrophy [1]. Specifically, SPSMA exhibits marked variability in both disease severity and progression [2]. It is characterised by progressive muscle weakness and atrophy, at both higher and lower limbs, predominantly affecting the scapular and peroneal regions[3,4], often resulting in wheelchair use [2]. This leads to ongoing motor functional decline, compromising physical abilities and independence [3,4].
Physical exercise (PE), which has been reported as an effective countermeasure to such pathological consequences in several NMDs [5,6], may serve as a potential strategy to mitigate the long-term burden also of SPSMA patients. However, the rarity of the condition limits the availability of empirical data, leaving such consideration largely theoretical. Indeed, TRPV4 related SPSMA has an unknown prevalence and existing literature offering only

brief accounts of its long-term impact [3,4,7-10]. In this context, providing data on PE's long-term feasibility and effects could offer valuable insights to support and enhance patient care. Therefore, here, for the first time, we present data regarding physical efficiency, muscle strength, body composition, and self-reported emotional well-being of a young adult male patient with TRPV4 related SPSMA who underwent regular PE during the last 5 years.

## Case report

### *Patient*

The patient was a 26-year-old male affected by SPSMA, harbouring a heterozygous missense mutation in TRPV4 gene: c.281C > G/p.S94W. Investigation of the clinical history revealed that the onset of the pathological manifestations was at birth, with bilateral clubfoot, for which the patient underwent two surgical procedures during childhood. From early infancy, generalized ligamentous laxity and muscle weakness involving the shoulder girdle and neck flexors were consistently observed. Notably, head control was achieved late, around the age of 4 months. At 3 months of age, the patient underwent an evaluation at which the following diagnostic investigations were performed: serum creatine kinase and lactate dehydrogenase levels, brain and spinal magnetic resonance imaging, electromyography, and nerve conduction studies, all of which were within normal limits. Growth parameters remained consistently around the 10th percentile for both weight and height throughout development. Since age 20, the patient has been independently exercising at a local gym and, at the age of 21, following a recommendation from his neurologist, he sought guidance at our sports medicine centre to optimise his PE, tailoring it as an attempt to mitigate the manifestations of the disease. The patient underwent two types of periodic checks: a clinical evaluation, conducted annually to assess his general condition, and laboratory assessments, every 25 months, to investigate the effects of the PE protocol prescribed by our sports medicine centre. Informed consent was obtained in written form from the patient during the initial evaluation.

During the first clinical evaluation, a visual inspection highlighted left-convex dorsal scoliosis and bilateral cavus. The neurological examination revealed that osteotendinous reflexes were barely elicitable in the upper limbs and absent in the lower limbs and that there was no presence of tremors, ataxia, involuntary movements, or Beevor's sign. Local strength was assessed using the Medical Research Council (MRC) scale, reporting muscle weakness following a scapuloperoneal distribution. From a functional standpoint, the patient was autonomous in ambulation, including walking on toes, but not on heels, and maintained independence in postural transitions, with the ability to jump preserved. Regarding the upper limbs, the patient presented with bilateral winging scapula and an inability to abduct bilaterally beyond 45° (Fig. 1B), with tremor during exertion. Conversely, unilateral abduction occurred with compensatory mechanisms, mainly on the right side (Fig. 1C-D). No symptoms of cardiological or respiratory impairment were observed.

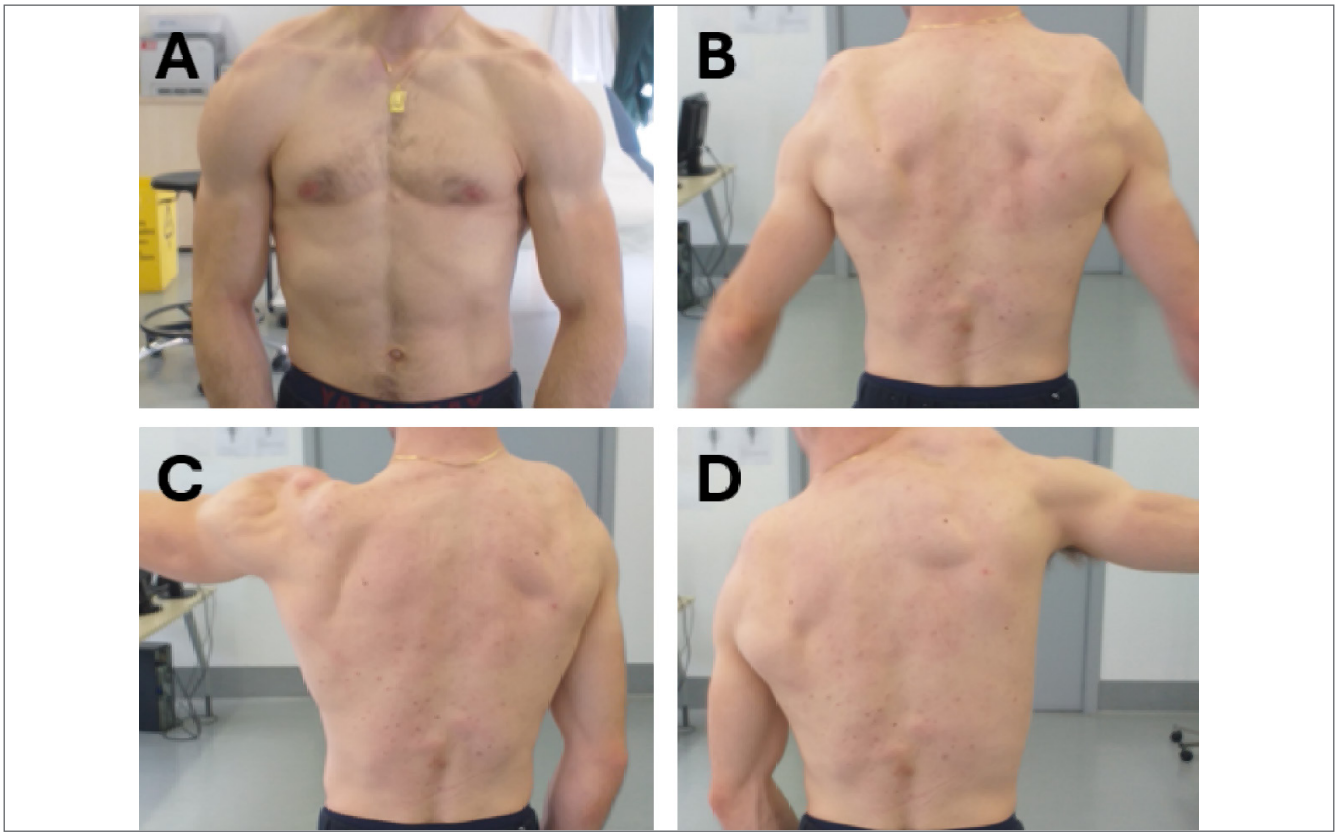



**Figure 1.** Patient at first evaluation. (A) Anterior view of the upper body; (B) posterior view during bilateral arm abduction; (C) left arm abduction; (D) right arm abduction. Written permission to publish the photos was obtained from the patient.

## Materials and methods

### *Performance evaluations*

#### Cardiopulmonary exercise test

To evaluate maximal oxygen consumption ($\dot{V}O_2$max), an incremental cardiopulmonary exercise test (CPET) was conducted on a calibrated cycle ergometer (E100, Cosmed, Italy). The patient began pedalling at 20W for 3 minutes, with power output (PO) increasing by 15W every 3 minutes until exhaustion. Carbon dioxide production ($\dot{V}CO_2$), and oxygen consumption ($\dot{V}O_2$) were measured breath-by-breath using a two-way respiratory mask covering the nose and mouth (V2 Mask, Hans Rudolph Inc., USA) connected to a gas analyser (Quark PFT, Cosmed, Italy). The test was considered maximal when it met these criteria: Respiratory exchange ratio ($\dot{V}CO2/\dot{V}O_2$, RER) ≥ 1.1, ratio of perceived exertion (RPE) ≥8, and $\dot{V}O_2$ at plateau for at least 30s. Notably, RER was derived from raw values, while $\dot{V}O_2$max was calculated as the average of the 30s following achievement of RER≥ 1.1 and RPE≥ 8.

#### Handgrip strength test

Handgrip strength test (HST) was assessed using a Baseline dynamometer (Fabrication Enterprises Inc., USA). The participant sat comfortably with the elbow flexed at 90° and performed three maximal isometric contractions for both the dominant and non-dominant hand, with the highest value recorded for each[11].

### *Body composition evaluation*

Body composition analysis was performed using a bioelectrical impedance analysis (BIA EFG, Akern, Italy) following the manufacturer's instructions. BIA's raw bioelectrical parameters (resistance [R], Reactance [Xc], and phase angle [PhA]) were considered. Specifically, R represents the body's opposition to the flow of an alternating electrical current, Xc is related to the capacitance properties of the cell membrane, while PhA indicates the relationship between R and Xc through the following formula[12]:

$$PhA = arctang \frac{Reactance}{Resistance} x\ 180°/\pi$$

PhA is proposed as a proxy indicator of skeletal muscle mass and quality, with higher values reflecting better muscle condition[13]. Measures were obtained with the Bodygram PRO v.3.0 software.

### *Self-reported measure evaluation*

The self-reported physical, social, emotional, functional well-being, and fatigue were assessed with the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).

## Physical exercise training

Following the initial assessment, the patient followed the training programs provided by our team, which were carried out at a gym of his choice under the supervision of dedicated personnel. Overall, the PE consisted of resistance training (RT) three times/week and endurance training (ET) for two sessions/week. RT sessions, of ≈60 minutes each, comprised one primary exercise along with at least one secondary exercise targeting every major muscle group, with adjustments in weight, sets, and repetitions to ensure progressive overload. Specifically, thanks to the ability of the patient to autoregulate himself using the resistance exercise-specific rating of perceived exertion (RPE) [14], we asked him to maintain an effort level of approximately 7.5 on the RPE scale. This value reflects a capacity for completing 2 to 3 more repetitions. Whenever the exertion was perceived to be below this threshold, we asked him to increase either the load, the number of sets or repetitions to maintain the target level of RPE. ET sessions, lasting between 45 to 60 minutes, were conducted on a cycle ergometer, alternating moderate intensity (i.e. ≈70% of the maximal heart rate (HRmax) as determined during CPET) and high intensity (i.e. ≈85% HRmax). Moreover, prior to each ET session, approximately 15 minutes were allocated to specific strengthening exercises targeting the scapular and lower limb muscles, aiming to counteract the pathological scapuloperoneal muscle weakness. For the scapular and shoulder girdle muscles, free-weight exercises included scapular retraction, elevation and depression, as well as shoulder extension performed in the prone position. To enhance distal lower limb function, the protocol involved ankle dorsiflexion and plantarflexion, alongside heel and toe raises. All exercises were performed with a 3-second isometric hold at the peak of the concentric phase. These exercises were scheduled before ET, rather than before RT, to avoid pre-fatigue that could have compromised RT performance.

## Results

Annual clinical evaluations did not reveal any additional deficits compared to the initial assessment, indicating a stable clinical condition. Moreover, at the ages of 21, 23, and 26 years (rounded to the nearest year), he underwent three laboratory assessments (25 months apart). His body mass remained nearly the same (59.7 kg, 59.9 kg, and 60.4 kg), and his height did not change (164.0 cm). Data regarding $\dot{V}O_2$max, HST, body composition, and self-reported measures are presented in Table I. It is worth noting that, although assessed also during clinical evaluations, only the MRC test values collected concurrently with the three laboratory assessments are reported, to ensure consistency in data presentation. These data are presented in Table I.

## Discussion

This is the first study reporting data regarding $\dot{V}O_2$max, muscle strength, body composition, and perceived emotional well-being during a 5-year follow-up of a young male patient diagnosed with TRPV4 related SPSMA who regularly engaged in PE. This NMD is an extremely rare condition, with only case reports described to date, exhibiting high phenotypic variability [2-4,7-10], with unclear progression over time, apart from single reports as was the case of a young man with very slow clinical disease course[3] for which; however, the need for walking orthoses when patients got their middle age has been emphasized [4,8]. Even though there is insufficient clinical information

**Table I**. Results of the three laboratory assessments.

| **Performance evaluation** | | | |
|---|---|---|---|
| **Cardiopulmonary exercise test** | | | |
| | 1st assessment | 2nd assessment | 3rd assessment |
| $\dot{V}O_2$max (mL/min) | 2986 | 3110 | 2652 |
| $\dot{V}O_2$max (mL/min/kg) | 50.0 | 51.9 | 43.8 |
| **Strength evaluation** | | | |
| | 1st assessment | 2nd assessment | 3rd assessment |
| Handgrip strength D (kg) | 57.3 | 58.8 | 55.7 |
| Handgrip strength ND (kg) | 53.6 | 56.1 | 52.5 |
| **Medical Research Council Scale** | | | |
| | 1st assessment | 2nd assessment | 3rd assessment |
| Total score (point) | 45 | 52 | 52 |
| **Body composition evaluation** | | | |
| | 1st assessment | 2nd assessment | 3rd assessment |
| Phase angle (°) | 5.9 | 5.8 | 6.5 |
| **Self-reported measures evaluation** | | | |
| | 1st assessment | 2nd assessment | 3rd assessment |
| Physical well-being | 25 | 26 | 28 |
| Social/Family well-being | 21 | 21 | 23 |
| Emotional well-being | 22 | 22 | 23 |
| Functional well-being | 16 | 19 | 24 |
| Fatigue subscale | 43 | 45 | 49 |

D: dominant hand; ND: nondominant hand; L: left side of the body; R: right side of the body; mL/min: millilitre/minute; ml/min/kg: millilitre/minute/kilogram; W: watt; bpm beats per minute; °: degree; L: litre; cm: centimetres, kg: kilograms, m: meters, VO2max: maximal oxygen consumption. MRC total strength values (0-60 points) were obtained by adding the score (0-5 points) of the shoulder abductors, the elbow flexors, and the wrist extensors of both the left and right arm, along with the the score (0-5 points) of the hip flexors, the knee extensors, and the foot dorsiflexors of the left and right leg.

to establish a clear trend in SPSMA progression, the few available data suggest that by mid-ageing, limb atrophy and weakness become so pronounced that ambulation and upper-arm movements are severely limited[4,8]. In the present case, the patient exhibited muscle weakness with a scapuloperoneal distribution, a finding consistent with previous reports in the literature[2,3,6-9]. Reduced strength in the tibialis anterior is reported as a cause of the typical steppage gait pattern and inability to walk on heels[3], while the shoulder girdle and scapula muscle weakness determine the upper limb abduction limitation[4,8].

The proposed regular PE program may have exerted a positive effect on affected muscles, as suggested by the absence of any decline in MRC scores over the five-year period (Table 1). However, the limited available evidence regarding the natural progression of the disease prevents definitive conclusions from being drawn on this aspect, including for mechanisms of adaptation to exercise of trained skeletal muscle. Interestingly, HST, commonly used indicator for overall strength, was maintained aligned with several sports populations[11], and between the 75th and the 90th percentile of reference values for age and sex-matched healthy subjects[15]. Noteworthy, $\dot{V}O_2$max reflects physical efficiency for patients in a clinical setting[16]; thus, a high value is desirable. His relative $\dot{V}O_2$max, which peaked above 50.0ml/min/kg on two occasions, aligns with a large cohort of athletic populations[17] and is clearly superior to other patients affected by NMD[18], reflecting an exceptional physical efficiency. Noteworthy, the decrease in $\dot{V}O_2$max during his last follow-up would be due to short-term training cessation of two months prior the evaluation session, due to increased work commitments. This reduction in $\dot{V}O_2$max aligns with those observed in athletes with comparable values during a similar short-term training cessation[19]. This observation is relevant because, although speculative in nature, would suggest that such decrease is physiological and does not appear to be mediated by disease progression. Nevertheless, the last $\dot{V}O_2$max value registered is still comparable to age- and sex-matched physically active healthy individuals[20]. On the contrary, no data exist on the impact of short-term training cessation on HST, which may plausibly account for the slight reduction observed in the last laboratory assessment. Regarding PhA, which is commonly used as a proxy for muscle mass[12], its increase from baseline suggests an improvement in body composition. Notably, even PhA was within the reference value in a substantial age- and sex-matched cohort of healthy subjects[12]. This result seems in line with previous studies in which PE practice, especially RT, has been associated with PhA increment[21]. Of note, patients' diet also may have contributed to the observed PhA modifications[22]. Such an aspect has not been investigated in the present work and may represent an interesting perspective for future research regarding physical efficiency maintenance in these patients.

Additionally, the patient improved self-reported physical, social, emotional, and functional well-being from baselines, with the fatigue scale (indicating an overall absence of daily fatigue) that aligned with healthy subjects instead of individuals with NMDs[23].

In summary, a patient with TRPV4 related SPSMA, who initially engaged in self-managed PE and later received guidance and supervision from a sports medicine team, was able to maintain $\dot{V}O_2$max and muscle strength over 5-yr follow up, and to improve body composition, achieving outcomes comparable to those of healthy individuals and even athletic populations. This may have contributed to preserved autonomy and self-reported positive emotional well-being. Additionally, the patient did not report any new limitations beyond those previously noted, nor any adverse effects, which supports the safety of the proposed long-term training. More generally speaking, these findings align with increasing evidence supporting the beneficial effects of PE in NMDs [4] and should be regarded as preliminary data endorsing the potential utility of PE in TRPV4-related SPSMA.

## Conclusion

This study has shown the long-term feasibility and effectiveness of regular PE in a patient affected by TRPV4 related SPSMA, showing that, despite the NMDs, the subject achieved $\dot{V}O_2$max, alongside muscle strength, and body composition, comparable to a healthy and/or athletic population. Our preliminary results encourage further

studies implementing PE in a wider sample of patients.

## Conflict of interest statement

The authors declare no conflicts of interest.


## Funding

This research received no external funding.


## Authors contributions

O.C and G.D.: study conceptualization. O.C, M.F, V.Q., A.B. and G.D.: collection of data and manuscript writing. O.C., A.B. and G.D.: scientific review.

## Ethical consideration

This case report was conducted following ethical standards to ensure respect for the dignity and the rights of the patient involved. Written informed consent was obtained from the patient for the collection and publication of clinical data and images. The patient was informed about the nature of the study, its purposes, and the use of personal information. Measures were taken to ensure anonymity of the patient.

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