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Definition of malnutrition and body composition in patients with Crisponi/Cold-Induced Sweating Syndrome type 1

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Abstract

Background

Crisponi/Cold-Induced Sweating Syndrome type 1 (CS/CISS1) is an ultra-rare CRLF1-related disorder marked by neonatal feeding difficulties, recurrent hyperthermia and long-term autonomic dysfunction. Although nutritional impairment is recognized as a persistent clinical feature, energy metabolism and body composition have never been evaluated. This study provides the first integrated assessment of resting energy expenditure (REE), dietary intake, and bioelectrical impedance analysis (BIA) in individuals with CS/CISS1.

Methods

Over a 12-month period, we prospectively enrolled 14 genetically confirmed CS/CISS1 patients and 14 age-matched healthy controls. Participants underwent anthropometric assessment, 3-day food diary evaluation, indirect calorimetry to measure REE, and BIA to assess body composition. Measured REE was compared with predictive equations (Schofield and Harris–Benedict). Non-parametric tests were used, with significance at $p < 0.05$.

Results

CS/CISS1 patients exhibited significantly altered BIA profiles, including higher resistance and lower phase angle, suggesting reduced fat-free mass quality and suboptimal hydration. Compared with controls, total energy intake was markedly lower in CS/CISS1 (1475 vs 2295 kcal/day, $p < 0.001$), with lower lipid and higher carbohydrate percentages. Measured REE in CS/CISS1 was comparable to values estimated by predictive equations, but lower than in controls. A trend toward differences in REE across genetic subgroups was observed.

Conclusion

Individuals with CS/CISS1 exhibit reduced caloric intake, lower REE compared to controls and the Italian population, and measurable deficits in body composition consistent with chronic undernutrition. These results emphasise the importance of incorporating nutritional assessment as a standard part of care in such patients. We recommend tailoring the intervention to boost dietary energy density and help preserve fat-free mass.

Introduction

Crisponi syndrome/Cold-Induced Sweating type 1 (CS/CISS1, MIM#272430) is an ultra-rare autosomal recessive disorder characterized by life-threatening symptoms such as hyperthermic episodes,

respiratory distress, and feeding failure in infancy that shift towards cold-induced sweating, scoliosis, and thermoregulatory instability in early childhood. Crisponi and Cold-Induced Sweating syndromes were originally described as separate conditions because of their different progression patterns phenotype. The neonatal presentation with congenital onset is called Crisponi syndrome, first described in a cohort of 17 newborn patients of Sardinian origin.[1] The later childhood/adolescent presentation is called cold-induced sweating syndrome and was[1] initially reported in two Israeli sisters [2], and subsequently confirmed in two Norwegian brothers.[3] CS/CISS1 is currently recognized as a single genetic disorder caused by pathogenic variants in *CRLF1* (*cytokine receptor-like factor 1*).[3–7] Genotype-phenotype analysis by Herholz et al. (2011) demonstrated that CS and CISS are variable expression of a single disease entity.[8] Phenotypic severity is linked to the amount of residual protein function encoded by *CRLF1*, which, along with CLCF1, forms a complex that signals through the CNTF receptor, a pathway critical for the development, survival, and functional maturation of autonomic neurons. This pathway contributes to the proper differentiation and cholinergic programming of sympathetic neurons innervating sweat glands. Impairment of this signaling leads to abnormal sweat gland innervation and dysregulated autonomic output, ultimately causing the thermoregulatory abnormalities characteristic of the syndrome.[5, 7, 8] CS/CISS1 presents at birth in individuals with typical facial dysmorphisms including a round and large face, chubby cheeks, depressed nasal bridge and anteverted nares, long philtrum, micrognathia and hands' bilateral camptodactyly. During the neonatal period, affected infants exhibit stimulus or crying-induced contraction of facial and oropharyngeal muscles, which subside during sleep or quiet states. Episodes of overstimulation may further trigger opisthotonos-like posturing characterized by extended neck, raised and flexed arms. The clinical course is marked by recurrent febrile episodes (approximately 38°C), with hyperthermic peaks at 42°C, occurring in the absence of identifiable infection. Supplemental oxygen is frequently required during episodes of laryngospasm or cyanosis. When associated with respiratory dysfunction, this constellation of symptoms may progress to seizures and, in severe cases, sudden death.[1,5,6]

Generalized hypotonia, associated with impaired sucking reflex and micrognathia, causes feeding difficulties, often requiring enteral nutritional support with a nasogastric or gastrostomy tube. During the first decade, dysphagia and gastroesophageal reflux may occur and feeding impairment is now recognized as a persistent and clinically relevant feature across patients' lifespan.[6] Despite the severity of early symptoms, some children survive beyond infancy and show spontaneous improvement in feeding challenges and episodes of hyperthermia. However, during early childhood, they may develop scoliosis, experience mild psychomotor delay, and exhibit cold-induced sweating accompanied by markedly elevated plasma noradrenaline levels.[6,9] Although the neurological and dysmorphic phenotype of CS/CISS1 has been well documented[6], the spectrum of nutritional and feeding difficulties needs to be clarified. Onesimo et al. (2024) showed that feeding difficulties are a distinctive clinical feature of CS/CISS1 and often persist from infancy to adulthood. During the neonatal period, 100% of patients required enteral feeding due to immature suckling abilities, while 14% had gastrostomy tubes.[10] During

adulthood, 67% of patients reported episodes of dysphagia, particularly with liquids, while 100% of adults experienced occasional drooling, although to a milder extent compared to childhood.[10]

Although families consistently report nutritional difficulties from the neonatal period through adulthood, the energy metabolism or body composition in CS/CISS1 have not been systematically evaluated to date. This constitutes a significant knowledge gap, as chronic feeding impairment, recurrent hyperthermia episodes, reduced physical activity, and potential alterations in hydration status may collectively contribute to distinct metabolic profiles or alterations in lean mass quality. To investigate these gaps, our aim was to expand current knowledge of nutritional issues in CS/CISS1 by providing, to our knowledge, the first integrated description of resting energy expenditure and body composition in this population.

Patients and Methods

Fourteen Italian patients with a confirmed molecular diagnosis of CS/CISS1 syndrome and fourteen healthy age-matched Italian controls were prospectively recruited over a 12-month period at the Rare Disease Center, Fondazione Policlinico Agostino Gemelli-IRCCS in Rome, Italy. All patients were previously reported, and no age limit was set for enrollment.[10]

All study procedures adhered to the Declaration of Helsinki, and patients were included in the study after signed informed consent was secured. The Local Ethical Committee (approval n.5518 of 2023) approved the study as part of an extensive protocol evaluation concerning disabilities in complex rare diseases.

Patients were enrolled based on the following criteria: a clinical diagnosis of CS/CISS1 confirmed by molecular testing, body weight of at least 10 Kg (consistent with the device specifications used to measure REE), and informed consent to the study.

To better define the identified *CRLF1*-related alterations and rule out secondary diagnoses, all patients underwent Whole Exome Sequencing (WES). Genomic DNA was isolated from peripheral blood leukocytes via an automatic procedure performed using the QIAmp DNA Mini kit on the Qiacube platform (Qiagen, Milan, Italy) according to the manufacturer's instructions. Quality checks of the extracted DNA were performed using the Qubit dsDNA BR fluorometric assay (Life Technologies, Gaithersburg, MD, USA) for quantitation and the NanoDrop® ND-1000 spectrophotometer (Life Technologies, Gaithersburg, MD, USA for purity evaluation. WES was performed using the Illumina DNA Prep with Exome 2.5 Enrichment kit (Illumina, San Diego, CA, USA), while sequencing was achieved on the NovaSeq 6000 System NGS platform (Illumina, San Diego, CA, USA). Alignment and variant detection were performed with the DRAGEN version 4.3 bioinformatics pipeline (Illumina San Diego CA, USA) with GRCh38 as the human reference genome. Tertiary analysis was performed with Emedgene variant interpretation software (Illumina, San Diego, CA, USA) to detect SNVs, indels, and Copy Number Variations (CNVs). For the *CRLF1* gene, the MANE Select Plus Clinical transcript (NM_004750.5 at the time of writing) was used for variants reporting. Identified variants were interpreted in accordance with

the American College of Medical Genetics (ACMG) guidelines and the main mutational and population databases as ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/, accessed on September 12, 2025), LOVD (https://databases.lovd.nl/shared/genes/CRLF1, accessed on September 12, 2025) and gnomAD v4.0 (https://gnomad.broadinstitute.org/, accessed on September 12, 2025).

Controls were recruited from the general healthy population afferent to our Department with a 1:1 ratio compared to cases. The control group and patients with CS/CISS1 were matched for age to reduce bias in the nutritional analysis. Participants were excluded if they did not comply with study procedures, had medical conditions known to alter energy expenditure (such as cardiovascular or respiratory failure, renal, hepatic, or inflammatory diseases), or if informed consent was not obtained.

All participants underwent anthropometric assessments, evaluation of average energy intake (AEI), resting energy expenditure (REE) by indirect calorimetry (IC), and body composition analysis by bioelectrical impedance analysis (BIA). Anthropometric measurements, including body weight, height, and body mass index (BMI), were obtained in triplicate by the same examiner following the World Health Organization standards.[11] Body weight was measured using a digital scale with a precision of 0.1 kg, while height was recorded in a standing position to the nearest 0.1 cm. Values for weight, height, and BMI were then standardized by converting them into standard deviation (SD) scores or percentiles, based on the CDC 2000 growth reference data.[12]

Dietary intake was assessed using a 3-day food diary, as previously reported.[13] All food diaries were processed using an Excel spreadsheet to estimate both macronutrient composition and food frequency. Nutrient and energy values were obtained from the Food Composition Database for Epidemiological Studies in Italy (Banca Dati di Composizione degli Alimenti per Studi Epidemiologici in Italia – BDA).[14] The recommended energy and macronutrient intake levels were determined based on age, gender, and body weight, according to the LARN (Reference Intake Levels of Nutrients and Energy for the Italian Population) guidelines issued by the Italian Society of Human Nutrition (SINU).[15]

REE was assessed using IC with an open-circuit calorimeter (QUARK RMR, Cosmed, Italy). The device's accuracy and applicability in patients with syndromic conditions have been documented in previous research.[16] Prior to each session, the calorimeter was automatically calibrated according to the manufacturer's specifications. During the measurement, participants remained in a supine position for 30 minutes with a canopy hood placed over their heads. The initial 10 minutes allowed participants to relax and for the system to stabilise the air composition within the canopy. The subsequent 20 minutes were used to calculate REE. Participants were required to fast for at least 6 hours before to ensure accurate measurements. All assessments were performed in a thermo-neutral environment (room temperature between 24–26°C) free from external stimuli. Steady state was defined as a period of five continuous minutes during which fluctuations in oxygen consumption (VO_2) and carbon dioxide production (VCO_2) remained below 10%. The average values obtained during this steady state were used to calculate 24-hour REE using the abbreviated Weir equation: REE (kcal/day) = (3.941 × VO_2 [mL/min] +

1.106 × VCO_2 [mL/min]) × 1.44.[17] Measured REE (mREE) values were subsequently compared with predictive REE (pREE) obtained using the Schofield and Harris-Benedict equations.[18–20]

Trained personnel in accordance with the ESPEN clinical practice guidelines performed BIA.[21] All participants, comprising children and adolescents, were healthy and not pregnant. Health status was determined by the absence of any clinical conditions that might affect fluid balance, such as renal, endocrine, or cardiac disorders. Measurements were taken in a single daily session and individuals on medication were excluded from the study. BIA measurements were conducted with participants lying supine on a non-conductive surface, ensuring no contact with metallic objects. A Biodynamics model 450 tetrapolar bioimpedance analyzer (800 µA – 50 kHz) was used, with pre-recorded inputs for sex, age, weight, and height. The analyzer offers a precision of 0.1% for resistance (R), 0.2% for reactance (Xc), and 0.2% for phase angle (PA). The analyzer's precision (0.1–0.2%) allowed detection of subtle differences in tissue composition, which is crucial in syndromic conditions with potential muscle and hydration abnormalities. Participants with implanted metal devices or conditions affecting fluid balance (renal, endocrine, cardiac disorders) were excluded to ensure data validity.

Statistical Analysis

Given the small sample size, a non-parametric approach was employed. Quantitative variables were summarized using medians and interquartile ranges (IQR), while qualitative variables were presented as absolute frequencies and percentages. Comparisons between cases and controls were performed using the Wilcoxon rank-sum test for continuous variables such as age, weight-for-age, height-for-age, BMI-for-age, and bioelectrical impedance measures (resistance, reactance, and phase angle); the Chi-square or Fisher exact test were used for categorical variables.

To assess the accuracy of predictive models for REE, the Wilcoxon rank-sum test was used to compare mREE and pREE by both the Schofield and Harris-Benedict equations. Furthermore, this test was applied to compare measured and expected values of total energy intake, protein intake, and lipid intake. REE and BIA parameters (resistance, reactance, and phase angle) were also assessed in groups of patients with different genetic conditions. Patients were compared with controls without the specific genetic condition. Bioelectrical impedance vector analysis (BIVA) was performed using height-standardized resistance (R/H) and reactance (Xc/H) at 50 kHz. Individual vectors were plotted on the RXc plane with a pooled 95% confidence ellipse, and quadrant interpretation was used for qualitative assessment. Due to the small sample size and non-normal distribution of the variables, data are presented as median and interquartile range (IQR). Comparisons between groups were performed using the non-parametric Wilcoxon rank-sum test.

A p-value of less than 0.05 was considered statistically significant in all analyses.

Results

The analysis of CS/CISS1 patients' characteristics revealed a prevalence of female participants (8 females and 6 males) and a predominantly paediatric population, with a median age of 15.4 years. Six (4 females and 2 males) were adults.

No statistically significant differences were observed between cases and controls in weight-for-age, height-for-age, or BMI-for-age (Table 1). According to their BMI, 3 CS/CISS1 patients and 2 controls were underweight, and 23 had normal weight (11 cases and 12 controls), confirming the balance of weight status categories between cases and controls in our study population.

Table 1
Distribution of Characteristics of the Study Population: Comparative Analysis Between Cases and Controls

Age	**All (n = 28)**	**Cases (n = 14)**	**Controls (n = 14)**	**p**
[Years, median (IQR)]	**13.4 (9; 19.7)**	**15.4 (10.6; 24.2)**	**13 (9; 16)**	**0.346[a]**
Weight-for-age [SD, median (IQR)]	-1.80 (-2.08; 0.93)	-1.73 (-2.40; -1.03)	-1.80 (-1.88; -0.38)	0.743[a]
Height-for-age [SD, median (IQR)]	-0.86 (-1.70; -0.30)	-1.30 (-1.85; -0.13)	-0.57 (-1.28; -0.44)	0.384[a]
BMI-for-age [SD, median (IQR)]	-0.90 (-1.48; -0.78)	-0.90 (-1.37; -0.80)	-1.00 (-2.25; 0.10)	0.744[a]
Weight status category [n (%)]				0.999[b]
Underweight	5 (18)	3 (21)	2 (14)	
Normal weight	23 (82)	11 (79)	12 (86)	
p refers to: a) Wilcoxon sum-rank test, b) Fisher exact test				

All patients were of Italian ancestry, with most, 10/14, being Sardinian (77%). The pathogenic variant c.676dup (p.Thr226fs) was detected in 9/14 patients (64%) of our cohort. In five cases, it was present in a homozygous state, and in four in a compound heterozygous state, either with the c.221T > C (p.Leu74Pro) or with the c.226T > G (p.Trp76Gly) variant. A patient of Calabrian origin was found to be homozygous for the c.338A > T (p.Asn113Ile) and c.341T > C (p.Leu114Pro) variants, which were present *in cis*. Pathogenic large deletions involving the *CRLF1* gene were identified in two patients of Sicilian origin. In one case, an 8.25 kb deletion encompassing the first five exons of *CRLF1* and the *REX1BD* gene was identified in a compound heterozygous state with a larger 22.11 kb deletion spanning the entire *CRLF1* locus, as well as *TMEM59L* and *REX1B*. In a second individual, a 8.25 kb deletion was detected in a compound heterozygous state with the c.935G > A (p.Arg312His) variant (Table 5).

Bioelectrical impedance data showed significant differences between the two groups (Table 2). Resistance was significantly higher in cases with a median value measured > 750 Ohm compared to that of controls < 670 Ohm (p-value 0.004). Phase angle had a median of 5.2 degrees in cases, resulting in a significantly lower median of 5.9 degrees in controls (p-value 0.008). Reactance did not differ significantly between the two groups. The BIVA RXc plot showed a displacement of CS/CISS1 vectors toward higher R/H and lower Xc/H values compared with controls. This pattern is consistent with reduced soft tissue hydration and decreased cellular integrity (Fig. 1).

Table 2
Comparative Analysis of Bioelectrical Impedance Measures Between Cases and Controls

BIA, Resistance [Ohm, median (IQR)]	**All (n = 28)**	**Cases (n = 14)**	**Controls (n = 14)**	**p**
	706.6 (650.2; 762.1)	**755.9 (707.9; 864.7)**	**668.5 (649.0; 706.0)**	**0.004**
BIA, Reactance [Ohm, median (IQR)]	69.7 (67.0; 71.8)	71.3 (67.9; 74.5)	67.5 (67.0; 70.1)	0.066
BIA, Phase angle [Degree, median (IQR)]	5.7 (5.2; 5.9)	5.2 (4.8; 5.7)	5.9 (5.7; 5.9)	**0.008**

p refers to the Wilcoxon sum-rank test. BIA measurements were available in 14 CS/CISS1 patients and 14 controls.

Dietary intake, as assessed through the 3-days food diary, showed significant differences in total energy intake and macronutrient distribution between cases and controls (Table 3). Total energy intake, with a median of 1475 daily kilocalories, was significantly lower in cases than the 2295 kilocalories in controls (p-value < 0.001). Additionally, carbohydrate intake, representing 51% of total macronutrients, was higher in CS/CISS1 patients (p-value 0.002), whereas lipid intake, just 34% of total, resulted in lower levels in cases compared to controls (p-value < 0.001). Protein intake measured both as a percentage of total daily intake and as grams per kilogram of body weight showed no statistically significant differences between cases and controls.

Table 3
Total Energy Intake and Macronutrient Intake Obtained From A 3-Day Food Diary

Total energy intake	**All (n = 28)**	**Cases (n = 14)**	**Controls (n = 14)**	**p**
[Kcal/day. median (IQR)]	**1600 (1475; 2295)**	**1475 (1313; 1550)**	**2295 (1932; 2335)**	**< 0.001**
Carbohydrates [% of daily food. median (IQR)]	50.0 (50.0; 52.25)	51.0 (50.0; 52.3)	47.7 (47.7; 47.7)	**0.002**
Lipids [% of daily food. median (IQR)]	35.0 (33.5; 38.5.0)	34.0 (33.0; 35.0)	39.9 (39.9; 39.9)	**< 0.001**
Proteins [% of daily food. median (IQR)]	15.0 (12.4; 16.5)	15.5 (14; 16.75)	12.4 (12.4; 15.0)	0.067
Proteins [g/kg. median (IQR)]	55.0 (51.4; 66.5)	55 (50.0; 63.75)	52.0 (51.4; 69.0)	0.464
p refers to the Wilcoxon sum-rank test				

No significant difference was found comparing mREE with the predictive formulas (Table 4). However, a lower mREE was found in CS/CISS1 patients compared to controls (p = 0.0019) (data not shown in the table) and to the Italian population of the same age.[14]

Table 4
Comparative Analysis Between Measured REE And Predicted REE

All (n = 28)	**Measured**	**Schofield**	**p**	**Harris-Benedict**	**p**
[median (IQR)]	1346 (1136; 1468)	1241.5 (1104.8; 1514)	0.941[a]	1303.9 (1153.3; 1454)	0.898[b]
Cases (n = 14)					
[median (IQR)]	1123 (1037; 1274)	1142.3 1067.2; 1312.3)	1[a]	1157.2 (1116.5; 1283)	0.761[b]
Controls (n = 14)					
[median (IQR)]	1448 (1357; 1475)	1511 (1147; 1537)	0.432[a]	1426 (1256; 1514)	0.593 [b]

p refers to the Wilcoxon sum rank test: a) Measured REE vs predicted REE according to the Schofield equation; b) Measured REE vs predicted REE according to the Harris-Benedict equation.

Patients with compound heterozygous *CRLF1* deletions exhibited higher REE compared with patients carrying other *CRLF1* genotypes (p-value = 0.044) (Fig. 2).

Discussion

In our study, children and young adults with CS/CISS1 were compared with a control population with the same anthropometric variables, such as age, weight-for-age, height-for-age, and BMI-for-age, making the two groups well comparable for the subsequent analysis. This matching strategy minimizes potential confounders and strengthens the validity of the metabolic and nutritional comparisons between groups.

REE represents the energy expended by the body during a 24 h non-active period to maintain involuntary functions such as substrate turnover, respiration, cardiac output, and body temperature regulation. IC is still considered the gold standard to measure it.[22] Its clinical relevance becomes even greater in rare genetic syndromes, where predictive equations may be inaccurate due to altered body composition or atypical physiological profiles.

BIA is a method that provides information on the amount of fat mass (FM) and fat free mass (FFM), as well as on the quality of lean mass through body cell mass (BCM) and phase angle (PA). Both parameters are increasingly being used to assess malnutrition and sarcopenic obesity. Moreover, FFM and BCM are also used to evaluate different aspects of fitness, such as the ability of working muscles to extract and utilise oxygen. [23] In addition, PA has proven to be an excellent predictor of prognosis in critically ill patients since it reflects the quality of soft tissue mass giving information about cell

membrane permeability and soft tissue hydration.[23] These parameters therefore offer a multidimensional view of nutritional status, which is particularly valuable in conditions marked by chronic feeding difficulties such as CS/CISS1.

Because nutritional impairment is a persistent concern throughout the lifespan of individuals with CS/CISS1, an in-depth evaluation combining dietary intake, IC, and BIA is essential to understand the mechanisms underlying their recurrent feeding challenges.

BIA measures demonstrated significant differences between the two groups (Table 2). Resistance was significantly higher in cases compared to controls, whereas PA was significantly lower in cases. According to the ESPEN recommendations for BIVA interpretation, this pattern reflects marked alterations in body composition in cases compared with controls.[21] More precisely, in CS/CISS1 patients, a lower PA (p 0.008) may be due to reduced fat free mass and body cell mass, while a higher resistance (p 0.004) indicates a poorer hydration condition. Taken together, these findings are consistent with a state of diminished cellular integrity and reduced muscle quality, which may reflect chronic undernutrition or long-standing feeding challenges.[24] When plotted on BIVA nomograms, this constellation is typically associated with increased malnutrition risk and lower functional reserves. According to the BIVA nomogram, this can indicate an increased risk of malnutrition compared to controls.[23] Clinically, this pattern reflects diminished nutritional reserves and reduced muscle cell mass, both of which may contribute to greater vulnerability to disease-related complications.

Previous studies have demonstrated that PA is a useful indicator of cellular integrity and body cell mass, with lower values suggesting compromised cell function and nutritional status. Our findings extend these observations to CS/CISS1 patients, a population in which body composition has never been systematically evaluated.

The systematic review by Ballarin et al. (2022) further corroborates that PA is positively associated with fat-free mass and muscle quality, providing valuable insights into nutritional assessment and metabolic health.[25] These results also align with Almeida et al.'s study (2021), which highlights that the BIVA tool, through bioelectrical impedance variables such as resistance and reactance, can effectively differentiate nutritional status and investigate body compartments in children and adolescents.[26] However, very few studies have investigated the effectiveness of BIVA evaluation in syndromic patients. Vermeulen et al. (2019) reported that BIVA and PA are sensitive in detecting alterations in cellular integrity and body composition in boys with Duchenne muscular dystrophy, further supporting the clinical relevance of this method in pediatric populations with chronic conditions.[27] Despite this, BIVA has never been applied to children with CS/CISS1, making our study the first to identify measurable alterations in tissue quality and hydration status in this syndrome.

In our cohort, dietary intake, as assessed through the 3-day food diary, showed significant differences in total energy intake and macronutrient distribution between cases and controls (Table 3, $p < 0.001$). Total energy intake was significantly lower in cases compared to controls. Also analyzing the average

requirements for energy intake supplied by the European Food Safety Agency (EFSA) at the median age of our population, the total energy intake was considerably low.[28] This suggests that chronic underfeeding may contribute to the observed alterations in body composition, particularly reduced FFM and lower PA. The lower lipid intake largely affected these results, while patients with CS/CISS1 had higher carbohydrate levels. These differences may stem from feeding difficulties that individuals with these conditions can experience throughout their lives, leading to reduced food intake, especially of lipid-rich foods.[25]Additionally, foods high in lipids often need longer chewing or have textures that patients with dysphagia or oral–motor issues might find difficult to tolerate, which can lead to lower energy density in their diet.

When comparing mREE with predicted values using the Schofield and Harris–Benedict equations, no significant differences were observed in both cases and controls. This finding suggests that commonly used predictive equations may still be applicable in special populations, such as individuals with CS/CISS1. However, this apparent agreement should be interpreted cautiously, as predictive equations cannot account for qualitative differences in tissue composition or episodic metabolic stressors such as hyperthermia, which are characteristic of the syndrome. However, mREE in the cases tended to be lower than that of controls, suggesting underlying metabolic or body-composition differences, such as reduced fat-free mass, altered tissue quality, or differences in autonomic or endocrine regulation that standard predictive models may not fully capture. As previously demonstrated, a single equation cannot adequately capture variation across age, race ethnicity, gender, and body composition; therefore, predictive equations must be carefully selected. Research has emphasized the need for accurate prediction equations in special populations, particularly in individuals with altered body composition, to ensure precise assessments of energy requirements.[19] Thus, while predictive equations may serve as an approximate reference, direct IC measurements remain essential for tailored nutritional planning in CS/CISS1.

Concerning genotype–phenotype correlation, albeit in a small cohort, the elevated REE observed in patients with compound heterozygous *CRLF1* deletions may suggest a distinct metabolic phenotype, potentially reflecting complete loss of function (Fig. 2). This finding should be interpreted with caution and requires confirmation in larger cohorts.

Our study comes with some limitations. First, the sample size was limited to 14 cases due to the ultra-rare nature of the pathology. The heterogeneity of patient ages and clinical severity may also have influenced metabolic and nutritional profiles, suggesting the need for stratified analyses in larger cohorts. Longitudinal studies would allow assessment of how nutritional status evolves across the characteristic clinical evolution of CS/CISS1, and whether early interventions can modify long-term outcomes.

Conclusions

In this study, individuals with CS/CISS1 demonstrated significantly lower total energy intake, lower resting energy expenditure and distinct alterations in body composition, likely reflecting persistent feeding difficulties, chronic undernutrition, and metabolic vulnerabilities that characterize the condition from birth through adulthood. These findings highlight the importance of specialized nutritional counseling to optimize daily caloric intake and improve dietary energy density. Tailored interventions should also focus on maintaining adequate hydration and promoting the accrual of fat-free mass, which is critical for sustaining the functional capacity and mitigating the impact of common clinical stressors in the syndrome, such as episodic hyperthermia, fever, diarrhea, and vomiting, that can rapidly exacerbate nutritional deficits. Given the ultra-rare nature of CS/CISS1 and the complexity of its clinical course, our results emphasize the need for longitudinal, multicenter studies to better characterize nutritional trajectories, metabolic demands, and the efficacy of targeted dietary strategies across the lifespan. A deeper understanding of these factors will be crucial to establishing evidence-based nutritional guidelines and improving long-term health outcomes in individuals with CS/CISS1.

Abbreviations

AEI *average energy intake*

BCM *body cell mass*

BIA *bioelectrical impedance analysis*

BIVA *bioelectrical impedance vector analysis*

BMI *body mass index*

CISS1 *cold-induced sweating syndrome type 1*

CNV *copy number variations*

CRLF1 *cytokine receptor-like factor 1*

CS *Crisponi syndrome*

FFM *fat free mass*

FM *fat mass*

IQR *interquartile range*

mREE *measured resting energy expenditure*

PA *phase angle*

pREE *predicted resting energy expenditure*

REE *resting energy expenditure*

R *resistance*

R/H *height-standardized resistance*

SD *standard deviation*

WES *whole exome sequencing*

Xc *reactance*

Declarations

Ethics approval and consent to partecipate

As previously reported in the article all study procedures adhered to the Declaration of Helsinki, and participants were included in the study after signed informed consent was secured. The Local Ethical Committee (approval n.5518 of 2023) approved the study as part of an extensive protocol evaluation concerning disabilities in complex rare diseases.

Competing interests

The authors declare no conflict of interest.

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Author Contribution

F.P. and P.P. designed the experimental plan , collected data and drafted the manuscript. G.S, V.T., F.M. acquired data, patients' consent and contributed to draft the manuscript. L.C., G.C., G.Z., C.L., R.O., V.G. supervised patients care and revised the manuscript. A.F. performed statistical analysis. R.B. and E.M.K. contibuted data analysis. All authors reviewed the manuscript and approved the final version.

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Table

Table 5 is available in the Supplementary Files section.

Figures

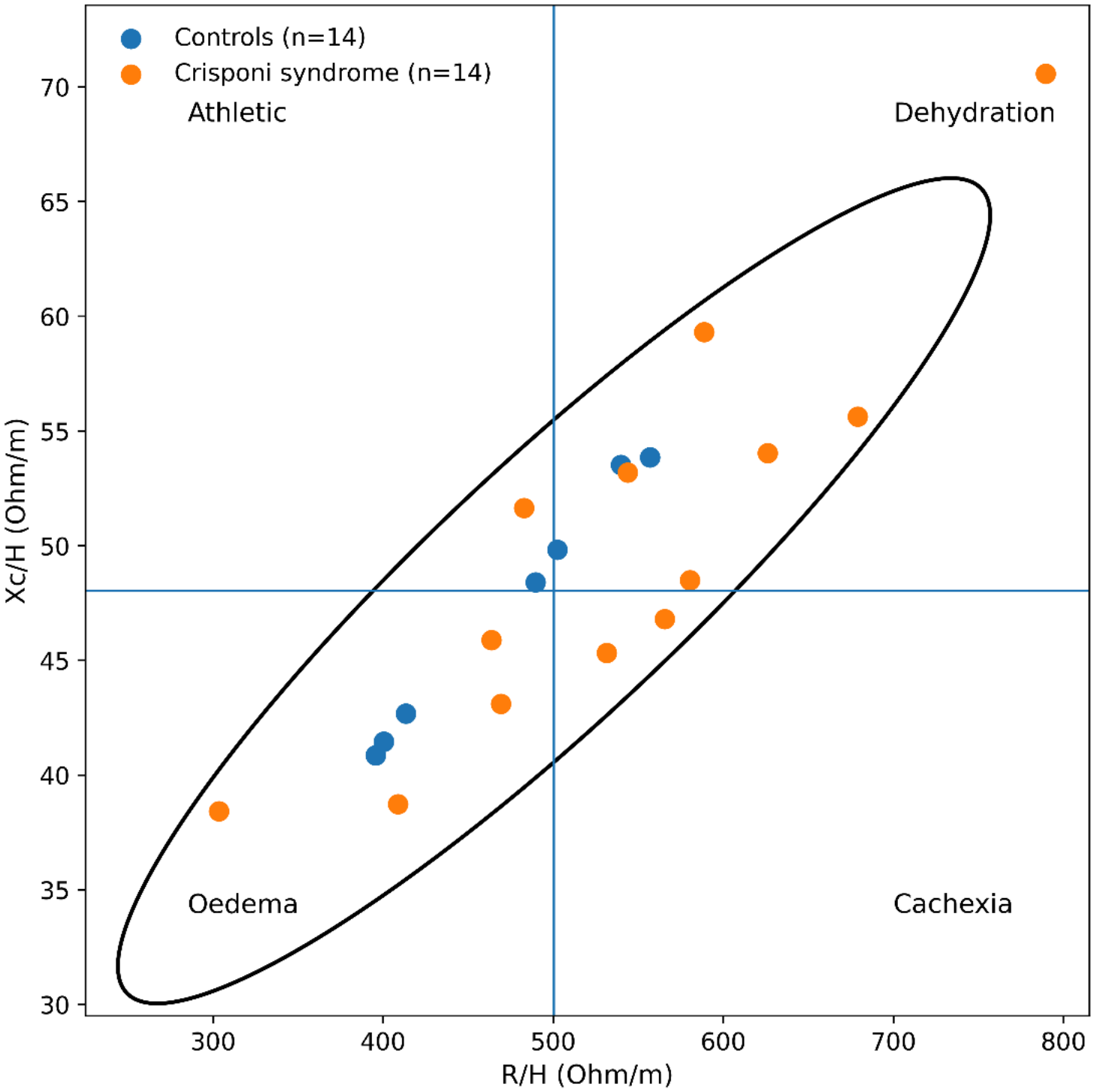


Figure 1

Bioelectrical Impedance Vector Analysis (BIVA) in cases and controls

Bioelectrical Impedance Vector Analysis (BIVA) in cases and controls. Bioelectrical impedance vector analysis (BIVA) based on height-standardized resistance (R/H) and reactance (Xc/H) measured at 50 kHz in patients with CS/CISS1 (n = 14) and healthy controls (n = 14). Individual impedance vectors are plotted on the RXc plane with confidence ellipses representing the overall vector distribution.

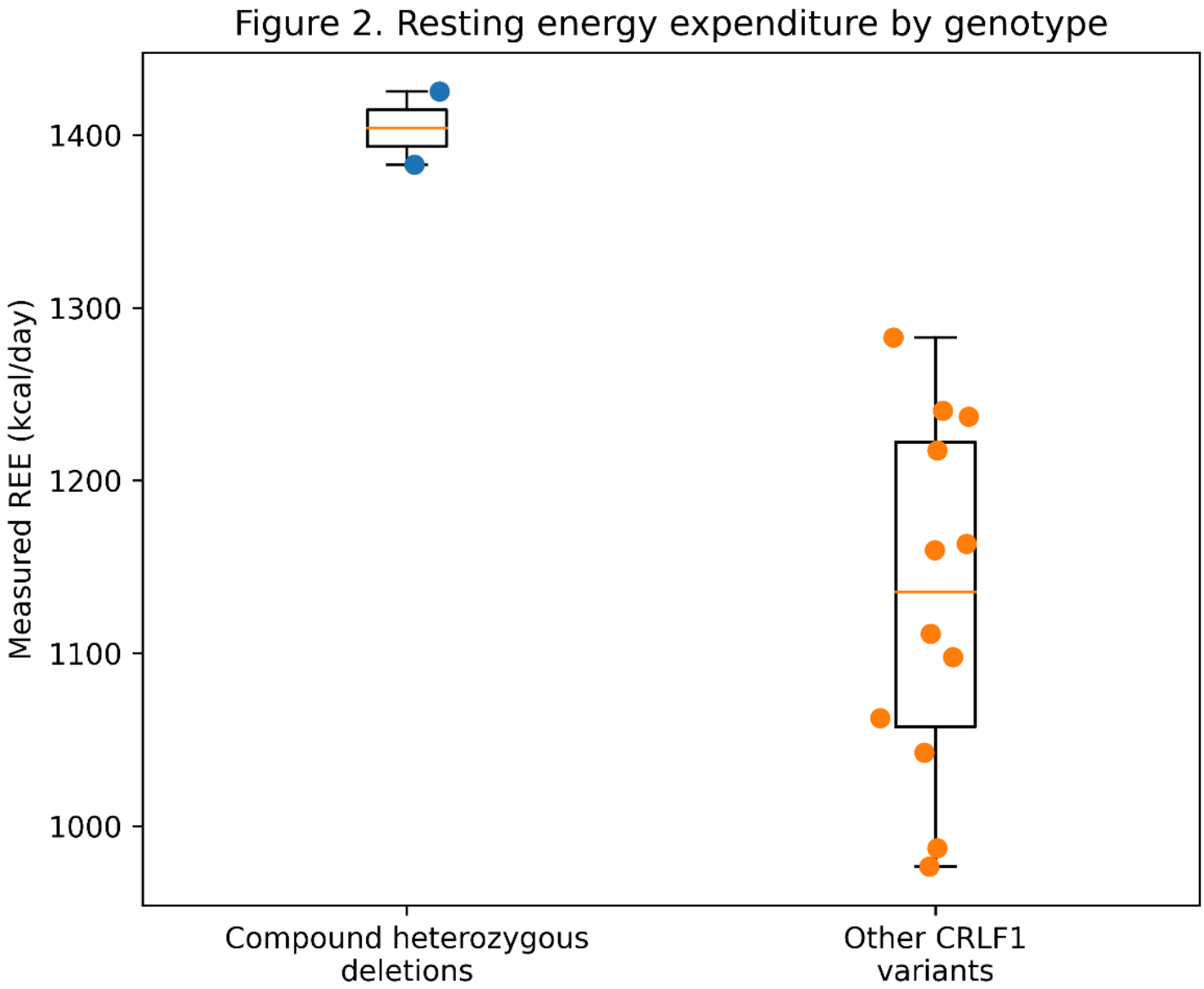


Figure 2

Resting energy expenditure in CS/CISS1 cases by genetic subgroup

Indirect calorimetry-derived resting energy expenditure (REE) according to CRLF1 genotype. Patients carrying large compound heterozygous CRLF1 deletions exhibited higher REE compared to those with

other CRLF1 variants. Data are shown as median (IQR) with individual values. Wilcoxon rank-sum test, p = 0.044.

Supplementary Files

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- Table5.docx