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Assessment of resting energy expenditure in pediatric mitochondrial diseases with indirect calorimetry

C. Fiuza-Luces [a, b, 1], A. Santos-Lozano [a, c, 1], M.T. García-Silva [a, e, f], E. Martín-Hernández [e, f], P. Quijada-Fraile [e], M. Marín-Peiró [d], P. Campos [e], J. Arenas [a, b], A. Lucía [a, d], M.A. Martín [a, b, c], M. Morán [a, b, c, *]

[a] Mitochondrial and Neuromuscular Diseases Laboratory, Hospital Universitario 12 de Octubre Research Institute (i+12), Madrid, Spain
[b] Spanish Network for Biomedical Research in Rare Diseases (CIBERER), U723, Spain
[c] MITOLAB-CM, Madrid, Spain
[d] Universidad Europea de Madrid, Villaviciosa de Odón, Madrid, Spain
[e] Unidad Pediátrica de Enfermedades Raras, Dpto. de Pediatría, Hospital Universitario 12 de Octubre, Madrid. C.S.U.R. Enfermedades Metabólicas Hereditarias, Spain
[f] Universidad Complutense de Madrid, Spain

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SUMMARY

Background & aims: Mitochondrial diseases (MD) are the most frequent inborn errors of metabolism. In affected tissues, MD can alter cellular oxygen consumption rate leading to potential decreases in whole-body resting energy expenditure (REE), but data on pediatric children are absent. We determined, using indirect calorimetry (IC), whole-body oxygen consumption (VO_2), carbon dioxide production (VCO_2), respiratory quotient (RQ) and REE in pediatric patients with MD and healthy controls. Another goal was to assess the accuracy of available predictive equations for REE estimation in this patient population.
Methods: IC data were obtained under fasting and resting conditions in 20 MD patients and 27 age and gender-matched healthy peers. We determined the agreement between REE measured with IC and REE estimated with Schofield weight and FAO/WHO/UNU equations.
Results: Mean values of VO_2, VCO_2 ($mL \cdot min^{-1} \cdot kg^{-1}$) or RQ did not differ significantly between patients and controls ($P = 0.085$, $P = 0.055$ and $P = 0.626$ respectively). Accordingly, no significant differences ($P = 0.086$) were found for REE ($kcal \cdot day^{-1}\ kg^{-1}$) either. On the other hand, although we found no significant differences between IC-measured REE and Schofield or FAO/WHO/UNU-estimated REE, Bland–Altman analysis revealed wide limits of agreement and there were some important individual differences between IC and equation-derived REE.
Conclusions: VO_2, VCO_2, RQ and REE are not significantly altered in pediatric patients with MD compared with healthy controls. The energy demands of pediatric patients with MD should be determined based on IC data in order to provide the best possible personalized nutritional management for these children.

1. Introduction

With an incidence of ~1:5000 live births, mitochondrial diseases (MD) are among the commonest inherited neuromuscular disorders [1]. MD are caused by mutations in nuclear or mitochondrial DNA with detrimental consequences in the oxidative phosphorylation system (OXPHOS) leading to a low oxygen consumption rate at the cellular level [2–4]. As a consequence, low oxygen consumption rate of the affected tissues could theoretically lead to a reduced level of whole body oxygen consumption (VO_2) in MD. In addition, as a compensatory mechanism to OXPHOS impairment glycolysis is frequently up-regulated in MD, leading to lactic acidosis that may in turn induce increases in the volume of exhaled CO_2 (VCO_2) [5,6].

* Corresponding author. Laboratorio de enfermedades raras: mitocondriales y neuromusculares, Instituto de Investigación Hospital Universitario 12 de Octubre (i+12), Centro de Actividades Ambulatorias, 6ª planta. Avenida de Córdoba s/n, 28041 Madrid, Spain. Tel.: +34 91 779 2784; fax: +34 91 390 8544.
E-mail address: mmoran@h12o.es (M. Morán).
[1] Equally contributed.

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There is yet no cure or effective treatment for MD [7,8]. Current treatment is based on symptoms' management and nutritional care, which is especially important for pediatric patients because failure to thrive and low weight are prevalent among them [9,10]. It is thus critical to avoid insufficient energy intake in MD in order to ensure proper growth rate. A higher age-related BMI has been associated with higher skeletal muscle ATP production, and an improved diet is linked with enhanced cellular energy production [10,11]. In turn, excessive energy intake might lead to respiratory muscle dysfunction owing to increased ventilatory muscle demand (due to excess VCO_2 production), and, later in life, to increases in body weight adding comorbidities to the primary disease [12,13]. Thus, accurate assessment of resting energy expenditure (REE) is necessary to provide appropriate nutritional care for pediatric MD patients, which can be done with indirect calorimetry (IC), through the determination of both VO_2 and VCO_2 according to Weir's equation [14]. The respiratory quotient (RQ, i.e., VCO_2/VO_2) can be also determined with IC; this parameter accounts for substrate utilization (and thus might be altered by metabolic disturbances), with the complete oxidation of glucose yielding a RQ value of 1.0 [15]. Although IC is a non-invasive, accurate tool for REE determination under standardized conditions, this technique is relatively expensive and requires trained personnel. For this reason, in healthy individuals REE is frequently estimated indirectly with predictive equations [16,17]. However, it has been reported that REE-predictive equations could either under- or overestimate REE in healthy people, and the accuracy of these equations is questionable in pathological states, as they were originally obtained using data from healthy subjects [18]. To our knowledge, IC has yet not been used to report REE in pediatric MD patients. The main purpose of the present study was twofold. First, we compared using IC VO_2, VCO_2, RQ and REE (at rest in fasted state) among pediatric MD patients and healthy age and gender-matched controls in order to assess to what extent these variables are altered due to the OXPHOS defect. Another goal was to determine, whether predictive equations can be applied in pediatric MD patients to assess REE.

2. Materials and methods

All procedures were carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), were previously approved by the Ethical Committee of the "Hospital 12 de Octubre", and written informed consent was obtained from parents/caregivers.

2.1. Participants

The participants of the present study were 20 patients who are routinely followed at the "Pediatric Unit of Rare Diseases" of the "*Hospital Universitario 12 de Octubre*", and 27 healthy children (controls) attending a Summer Camp at the "*Universidad Europea Madrid*" (UEM). The main characteristics of the two groups are shown in Table 1 and the main clinical features of the patients are shown in Table 2. Patients were diagnosed of OXPHOS defect using one or more of the following criteria: presence of low muscle enzyme activity of one or more RC complexes; muscle mitochondrial DNA depletion (low copy-number); or evidence of histological markers of mitochondrial dysfunction in skeletal muscle biopsy (e.g., cytochrome c oxidase deficient fibers or subsarcolemmal ragged red/blue fibers). Exclusion criteria were ketogenic diet, fever or recent acute illness.

2.2. Anthropometric evaluation

Prior to IC, participants' weight and height were determined with light clothes, and measurements were performed in a room with ambient temperature and low lighting, and children were accompanied by their parents/caregivers. Body mass index [BMI, weight (kg)/height (meters)^2] and weight- and height-to-age percentiles were calculated with the WHO Anthropometric Calculator "AnthroPlus" (http://www.who.int/growthref/en/).

2.3. IC

Basal VO_2, VCO_2, RQ and REE were measured with an open-circuit calorimeter (CCM Express, MCG Diagnostics, St Paul, MN, USA) in the morning (08:00–10:00am) with children awake after an overnight fast in the aforementioned hospital (patients) or university (controls). In those patients in whom overnight fasting was not possible due to the specific management of the disease, determination was performed following a 5-h fast. After a 10-min acclimation period at rest, a face tent was placed over children's mouth and nose, and gas exchange was measured during 15–30 min (depending on the time required for the child to stay quiet and relaxed). The first 10 min of testing were discarded in terms of data analysis. The values of VO_2 and VCO_2 were used to calculate RQ as the VCO_2/VO_2 ratio, and REE (in kcal·day^{-1}) with the Weir's equation, where $REE = 1.44\ (3.9VO_2 + 1.1VCO_2)$ [14].

2.4. Predictive equations

Children's REE (kcal·day^{-1}) was estimated using the Schofield and FAO/WHO/UNU equations which are based on weight and age as detailed elsewhere [16,17].

2.5. Statistical analysis

All statistical analyses were performed with the IBM SPSS 22.0 package for MAC (SPSS, Inc., Chicago, IL). Descriptive statistics are presented as mean ± standard deviation (SD). Normal distribution of the data was checked with the Kolmorov–Smirnov's test.

Table 1
Participants' main characteristics by group.

	Controls (n = 27)	Patients (n = 20)	*P*-value*
Girls, n (%)	11 (41%)	8 (40%)	0.960
Mean ± SD age (years)	8 ± 3	8 ± 3	0.929
Age range (years)	3, 13	2, 13	
Combined RC deficiency, n (%)		7 (35%)	
Complex I deficiency, n (%)		5 (25%)	
Complex III deficiency, n (%)		1 (5%)	
Complex IV deficiency, n (%)		4 (20%)	
mtDNA depletion, n (%)		5 (20%)	
Mitochondrial proliferation, n (%)		1 (5%)	

Abbreviations: RC, respiratory complex; mt, mitochondrial. Symbol: *determined with a Student's t test.

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