Understanding Growth Failure in Costello Syndrome: Increased Resting Energy Expenditure

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Costello syndrome is a rare multisystem disorder caused by mutations in the proto-oncogene *HRAS*. Failure to thrive is one of its cardinal clinical features. This study documents that individuals with Costello syndrome have increased resting energy expenditure. We speculate this could be one of the potential mechanisms causing failure to thrive. *(J Pediatr 2016;170:322-4).*

Costello syndrome (OMIM# 218040) is a rare developmental disorder caused by germline activating mutations in the proto-oncogene HRAS,[1,2] which encodes a member of the RAS subfamily of small monomeric GTPases controlling several intracellular signaling pathways with roles in cell proliferation, differentiation, and survival.

Clinically, Costello syndrome[3] is recognizable by a distinctive facies, reduced postnatal growth, intellectual disability, and cardiac and musculoskeletal anomalies. The growth phenotype presents with severe failure to thrive and swallowing/sucking difficulties after birth, followed by a mild improvement in gaining weight usually occurring after the third year of life.[3] Most infants require nasogastric or gastrostomy tube feeds because of the severe feeding difficulties.[3] During childhood, individuals are able to take oral feeds, yet they continue to have growth failure. Herein we report the results of a case/control study evaluating the energy balance in Costello syndrome to further investigate the mechanisms underlying failure to thrive.

Methods

Eleven subjects (3 male and 8 female) with Costello syndrome were enrolled at the Center for Rare Diseases of Catholic University, Rome, Italy. Parents of all participants signed written informed consent for this study. Clinical assessment included anthropometric evaluation (weight, height, and head circumference), measurement of body mass index and body surface area, and indirect calorimetry to evaluate the resting energy expenditure (QUARK RMR open-circuit indirect calorimeter by Cosmed, Pomezia, Italy).[4] Fasting biochemical analysis and microbiological tests (complete blood count; kidney, liver, and thyroid function; glucose, insulin-like growth factor 1 [IGF-1], lipid profile; celiac disease antibodies; 24-hour urine collection; macroscopic/microscopic analysis on stool sample) were performed to exclude gastrointestinal or other diseases causing failure to thrive. Seven-day diet records were completed by families and used to evaluate energy intake.

Eleven apparently healthy, sex- and age-matched individuals were enrolled as controls, and underwent anthropometric evaluation and indirect calorimetry. The baseline characteristics of the patients and controls were evaluated by means of simple descriptive analysis. Because each group was composed by 11 subjects, we compared groups with Mann–Whitney U test. We used 0.05 as level of significance. Analysis was done by running the Prism software version 5.00 (GraphPad, San Diego, California).

Results

Biochemical and molecular data collected for the 11 subjects with Costello syndrome included in the study are reported in Table I. All individuals had postnatal history of failure to thrive (11/11), and swallowing difficulties, weak suck, and gastroesophageal reflux diagnosed by pH test were also frequently recorded (7/11, 10/11, and 6/11, respectively), requiring the use of a nasogastric-tube (10/11) or a gastrostomy-tube (3/11). At the time of clinical evaluation, all individuals were able to eat by mouth without needing supplemental nutritional support delivery mechanisms. Affected subjects exhibited a significantly lower weight and height compared with the control group ($P = .03$ and .04, respectively). All individuals with Costello syndrome showed relative/absolute macrocephaly. Biochemical tests detected relatively low fasting blood glucose (Table I). IGF-1 was lower than normal in 9/11 cases. Total cholesterol concentrations were higher than normal in 3/11. One patient had hypothyroidism requiring treatment; otherwise, all other biochemical tests performed were normal. No

GH	Growth hormone
IGF-1	Insulin-like growth factor 1

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Table I. Biochemical measurements in Costello group

Subjects	Amino acid change	Age years	Glucose 65-110 mg/dL	Total cholesterol 130-200 mg/dL	LDL <130 mg/dL	Triglycerides 20-170 mg/dL	IGF-1 (†)
1	Gly12Ser	2	59	210	134	83	17
2	Gly12Ser	3	57	198	129	78	19
3	Gly13Cys	5	81	167	105	37	89
4	Gly12Ser	8	67	191	125	56	40
5	Gly12Ser	8	43	232	130	60	20
6	Gly12Ser	9	64	183	109	55	40*
7	Gly12Ser	12	77	196	126	55	92
8	Gly12Ser	17	74	119	72	48	196*
9	Gly12Ser	19	70	121	58	45	115
10	Gly12Ser	21	82	189	120	58	189
11	Gly12Ser	28	70	223	130	66	35*

LDL, low-density lipoproteins.
Age refers to time of clinical evaluation and biochemical assessment. Biochemical markers are followed by laboratory intervals of references.
All biochemical tests were performed after 7-8 hours fasting period.
*Individuals with GH deficiency.
†Range by age: 2-9 years 30-310 ng/mL; 9-16 years: 165-650 ng/mL; 16-25 years: 240-540 ng/mL; >25 years: 80-330 ng/mL.

enteric pathogens or parasites were detected, and no occult blood was found in stool samples.

In consideration of the different body sizes between groups, including the decreased muscle mass clearly apparent in the Costello syndrome group, measured resting energy expenditure (kcal/d) was adjusted for body measurements (body weight and body surface area) resulting in significantly increased values in individuals with Costello syndrome (Table II). The seven day nutritional recall in the Costello syndrome group showed normal/high daily caloric intake compared with the recommended levels of nutrients (Table II). In particular, a high protein and lipid, and low carbohydrate diet was observed.

Discussion

Costello syndrome is a multisystem disorder caused by de novo heterozygous mutations in the *HRAS* gene.[1,2] Of the clinical problems usually associated with this condition, failure to thrive is one of the most difficult challenges to manage for families and physicians. Growth delay in Costello syndrome likely arises from a combination of feeding (swallowing and sucking difficulties), nutritional (low caloric intake at birth), neurological (oro-motor incoordination), and gastrointestinal (severe gastro-esophageal reflux) problems. Remarkably, even after supporting all these problems with specific therapies, patients continue to have delays in growth.

In this study, we provided evidence that individuals with Costello syndrome have increased resting energy expenditure measured by indirect calorimetry, which likely reflects an increased cellular basal metabolism, regardless of age. We speculate this could represent a major factor accounting for the observed failure to thrive and poor weight occurring in this syndrome, in addition to other contributing issues, such as feeding, neurologic, gastrointestinal, and nutritional problems. Using the diet record, we excluded low caloric intake as a likely reason for poor growth.

To our knowledge, high cholesterol concentrations have never been reported to date as a constant biochemical/metabolic feature of Costello syndrome, and hypoglycemia has

Table II. REE in case and control group; energy intake in Costello group

REE in Costello and control group			
	Cases (n = 11)	**Controls (n = 11)**	***P* value**
REE			
Kcal/d	1114.91 ± 461.08	1340.00 ± 391.40	.27
Kcal/kg/d*	54.51 ± 17.78	37.47 ± 11.26	.04
Kcal/m^2†	1360.21 ± 317.42	1122.97 ± 173.55	.04
Energy intake in Costello individuals compared with recommended level of nutrients			
	Cases (n = 11)	**LARN/RDA**	***P* values**
Energy intake kal/kg/d	85.56 ± 43.28	65.00 ± 24.38/63.55 ± 25.97	.23/.21
CHO %	47.20 ± 5.74	55.00 ± 3.5/55.00 ± 3.5	.004/.004
Lipid %	40.02 ± 5.65	33.88 ± 2.20/33.88 ± 2.20	.01/.01
Protein g/kg/d	3.21 ± 1.04	1.17 ± 0.20/0.96 ± 0.16	<.001/<.001
Calcium mg/d	645.23 ± 438.37	977.7 ± 120.1/944.4 ± 320.5	.05/.11

CHO, carbohydrate; *LARN*, Italian recommended level of nutrients; *RDA*, American Recommended Dietary Allowance; *REE*, resting energy expenditure.
Significant *P* value resulting from Mann–Whitney U test was set at .05.
*REE adjusted for body weight.
†REE adjusted for BSA.

been previously documented in affected individuals attributable to growth hormone (GH) and cortisol deficiency,[5] pancreatic hyperplasia,[6] and hyperinsulinemic hypoglycemia.[7] In this cohort, 3 out of 8 individuals were previously tested for GH deficiency resulting in abnormal values (after arginine and clonidine stimuli tests). To date, we are still not able to state why IGF-1 levels were so much below the ranges by age, in particular in those who were not found to have GH deficiency on stimulation testing. However, even though the small number of tested individuals and the different age distribution in the cohort make it difficult to speculate about the possible mechanism underlying these biochemical abnormalities in Costello syndrome, our hypothesis is that this is partially related to poor muscle mass and also to the effect played by the hyperactivation of *HRAS* in disturbing other intracellular pathways linked to RAS/MAPK pathway. Of note, studies show that RAS proteins function as nodes controlling multiple signaling pathways, including the RAF/MEK/ERK and PI3K/PTEN/AKT/mTOR cascades,[8] modulating cellular metabolism, growth, glucose-insulin homeostasis, and lipolysis in response to different extracellular stimuli.[9-13] Consistently, it has been demonstrated that SHP2, a signal transducer positively controlling RAS signaling and the upregulated function of which accounts for approximately 50% of Noonan syndrome, the most common RASopathy, plays a critical role in the central control of body weight, energy metabolism, and glucose homeostasis through the leptin circuit in the hypothalamus.[14] Understanding the role of dysregulation of RAS signaling modulating leptin signal in the hypothalamus may provide new insights on the growth profile in Costello syndrome. ■

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