Increased Resting Energy Expenditure is Associated with Failure to Thrive in Infants with Severe Combined Immunodeficiency

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Objectives To measure resting energy expenditure (REE) and determine whether increased REE (hypermetabolism) is associated with failure to thrive (FTT) in patients with severe combined immunodeficiency (SCID) at diagnosis.
Study design REE was measured in 26 patients with SCID in a single transplant center. Predicted REE was determined with World Health Organization standards. Measured REE >110% of predicted REE was classified as hypermetabolism. Other data collected included FTT status, infections, genotype, phenotype, and the feeding methods used.
Results Fifteen of 26 patients (57.7%) had FTT, and 18 of 26 patients (69.2%) were hypermetabolic. Hypermetabolism occured in 14 of 15 patients (93%) with FTT, and only 4 of 11 patients (36%) without FTT had hypermetabolism ($P = .003$). There was a significant difference between the measured REE (71.75 $\pm$ 16.6 kcal/kg) and the predicted REE (52.85 $\pm$ 2.8 kcal/kg; $P < .0001$). Eleven of 17 patients (65%) required nasogastric feeding, parenteral nutrition, or both to meet their energy needs.
Conclusions Hypermetabolism is common in patients with SCID and may contribute to the development of FTT. The hypermetabolism in these patients may necessitate intensive nutrition support. *(J Pediatr 2011;159:628-32)*.

Severe combined immunodeficiency (SCID) is a group of rare inherited diseases that present in early childhood with severe dysfunction of T and B lymphocytes.[1] Patients with SCID often sustain persistent systemic infections, including pneumonia and chronic diarrhea, and inflammation manifesting as Omenn syndrome.[1] Failure to thrive (FTT) has been observed at diagnosis of SCID in 54% to 88% of patients.[2,3] In the pediatric population, FTT is caused by inadequate energy intake, malabsorption, or increased energy needs. In patients with SCID, oropharyngeal candida and chronic gastrointestinal tract infections have been associated with poor oral feeding and malabsorption, respectively, which may lead to FTT.

Improved oral intake and treatment of infections restores weight gain in some but not all patients with SCID. This suggests another cause of FTT in SCID, which may be hypermetabolism. Additionally, systemic infections and inflammation may increase REE in SCID as it does in human immunodeficiency virus and juvenile rheumatoid arthritis.[4,5] However, patients with SCID often display fatigue and lethargy, which might decrease energy requirements.[6] Predicted REE can be estimated from published data[7]; however, poor agreement between predicted REE and measured REE has been shown in children with chronic diseases,[8,9] emphasizing the need to measure the REE in patients with SCID. We report for the first time measured REE in a large group of patients with SCID and the association of hypermetabolism with the FTT seen in these patients. We also describe the feeding methods used to achieve the energy needs of patients with hypermetabolism and SCID.

Methods

All patients in whom SCID was diagnosed in a 13-year period from 1993 to 2006 who had indirect calorimetry (IC) performed shortly after diagnosis and before receiving a bone marrow transplant (BMT) at The Hospital for Sick Children (SickKids), were included in the study. Patients were excluded when they were treated for prolonged periods at other institutions before transfer to SickKids. Any patient who refused IC and any patient admitted directly to the pediatric or neonatal intensive care units and subsequently undergoing transplantation in the intensive care unit were excluded. Also, any patient in whom SCID was diagnosed who did

BMT	Bone marrow transplant
FTT	Failure to thrive
SickKids	The Hospital for Sick Children
IC	Indirect calorimetry
LAF	Laminar air flow
NG	Nasogastric
PN	Parenteral nutrition
REE	Resting energy expenditure
SCID	Severe combined immunodeficiency

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not receive a BMT was excluded. The study was approved by the Research Ethics Board at SickKids.

Other information collected retrospectively from the patient's medical charts and dietitian's records included the clinical features at presentation, SCID genotype and phenotype, weight and length at diagnosis, weight and length history, presence of FTT, microbiology for respiratory isolates, and stool culture results at diagnosis. Nutritional data including the feeding routes used to reach the patient's energy needs was also collected.

All patient weights and lengths were plotted by age and sex on Tanner-Whitehouse growth charts, which were the standard curves used at SickKids at the time of the study. Data for patients with cartilage hair hypoplasia were plotted on an achondroplasia growth curve.[10] FTT was defined as previously described by Zenel as either (1) both height and weight less than the third percentile or (2) weight that has crossed two or more percentiles downward compared with the height percentile.[11] Additionally, any patients with documented FTT, as defined as aforementioned, with growth stunting were also deemed to have FTT. This method for defining FTT is used for patients ≤24 months of age, therefore we excluded any patient who was >24 months of age at diagnosis.[11]

IC was performed with the Deltatrac II Metabolic Monitor (Sensor Medics Co, Yorba Linda, California). REE was measured with indirect open-circuit calorimetry in the method previously described by Green et al.[12] All patients were placed in laminar air flow (LAF) isolation on admission to the immunology/BMT unit, and the metabolic cart was calibrated to the air flow in each room before data collection. Calorimetry measurements were obtained by a trained research nurse on patients in the fasted state. Patients were afebrile and not receiving supplemental oxygen at the time of the measurements. All calorimetry measurements were performed after admission and before conditioning for BMT.

A normal metabolic rate was defined as a measured REE within 90% to 110% of the predicted REE for age and sex. Hypermetabolism was defined as a measured REE >110% of the predicted REE for age, weight, and sex, as suggested by the standard normative data published by the World Health Organization[7] on the basis of the Schofield equations.[13]

Results are expressed as means plus or minus SD. Statistical tests, including descriptive statistics, χ^2, Fisher exact, paired *t* test, Bland and Altman analysis, Pearson correlation, and logistic regression, were performed with Excel (Microsoft Inc, Redmond, Washington) and SAS softwares (SAS Institutes Inc, Cary, North Carolina).

Results

Of the 38 patients in whom SCID was diagnosed and who underwent transplantation at SickKids in the 13-year period, 26 met the study criteria. Excluded were 3 patients who underwent transplantation in the intensive care unit, 3 patients extensively treated at other centers, one patient whose guardians refused IC, and one patient for whom the IC results were unavailable. Four patients were >24 months at diagnosis and therefore were excluded. Of the 26 study patients, there were 20 male patients (77%) and 6 female patients (23%). Most patients were >3 months of age at diagnosis (mean, 4.7 months; SD, 3.1 months; range, 0 to 10 months), and SCID was diagnosed in 4 patients at birth on the basis of family history. Patient data is outlined in the Table.

Failure to Thrive and Hypermetabolism

Fifteen of 26 patients (58%) met the criteria for FTT; 9 of 15 patients (60%) had a descrepancy of two or more percentiles between their weight and height; 5 of 15 patients (33%) had both weight and height less than the third percentile, and 1 patient (7%) presented to HSC with growth stunting and documented FTT. Eighteen of 26 patients (69%) in the study were hypermetabolic. There was a significant difference between the mean measured REE (71.75 ±16.6 kcal/kg/day) compared with the mean predicted REE (52.85 ± 2.8 kcal/kg/day), a difference of 18.9 ± 16.7 kcal/kg/day ($P < .0001$, paired *t* test). The predicted REE was unable to accurately estimate measured REE (r = 0.03, Pearson correlation; Figure 1; available at www.jpeds.com). With the Bland and Altman analysis, a poor agreement between the measured REE and the predicted equations was shown (Figure 2; available at www.jpeds.com). The measured REE ranged from 66% to 196% of the predicted REE (mean, 136%; SD, 32.5). Measured REE was reduced in two patients, within reference range in 6 patients, and increased in 18 patients.

We found that there was a significantly positive association between FTT and hypermetabolism. Fourteen of 15 patients (93%) with FTT had hypermetabolism, compared with only 4 of 11 patients (36%) without FTT who had hypermetabolism ($P = .003$, Fisher exact test). The odds of hypermetabolism in FTT in this study was 24.5x times (95% CI, 2.3 to 262.5; $P = .0019$, χ^2). One of 4 patients in whom SCID was diagnosed at birth had hypermetabolism, and none of them had FTT. Hypermetabolism was significantly more common in infants 3 to 12 months old, in 17 of 20 patients (85%) compared with 1 of 6 patients <3 months of age ($P = .005$, Fisher exact). The most common genetic mutation was IL2Rγ, and hypermetabolism occurred in 7 of 9 (78%) of these patients (Table).

Nutrition

The mean weight of our patients was 6.27 kg (SD, 1.8 kg; range, 3.45 to 13.00 kg). Nutrition data was available for 17 of 18 patients who were hypermetabolic. For the 17 patients to meet their energy needs, it took a mean of 25 days (range, 0 to 82 days) by using a variety of nutrition support modalities. Six of 17 patients (35%) met their needs via the oral route with increased energy infant formula; 9 of 17 patients (53%) needed parenteral nutrition (PN); 4 of 17 patients (24%) needed nasogastric (NG) feeding, and 2 of the 4