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Metabolism and energy requirements in pantothenate kinase-associated neurodegeneration

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ABSTRACT

Pantothenate kinase-associated neurodegeneration (PKAN) is an autosomal recessive disorder of coenzyme A homeostasis caused by defects in the mitochondrial pantothenate kinase 2. Patients with PKAN present with a progressive neurological decline and brain iron accumulation, but general energy balance and nutrition status among these patients has not been reported. To determine if defects in *PANK2* change basic energy metabolism in humans, we measured body composition, resting energy expenditure, dietary intake, and blood metabolites among 16 subjects with PKAN. Subjects had a broad range of disease severity but, despite the essential role of coenzyme A in energy metabolism, the subjects had remarkably normal body composition, dietary intake and energy metabolism compared to population normal values. We did observe increased resting energy expenditure associated with disease severity, suggesting increased energy needs later in the disease process, and elevated urinary mevalonate levels.

1. Introduction

Pantothenate kinase-associated neurodegeneration (PKAN, formerly Hallervorden–Spatz syndrome, OMIM ID: 234200) is the first reported inborn error of coenzyme A biosynthesis [1]. This autosomal recessive disorder is associated with progressive dystonia, retinal degeneration and iron accumulation in the globus pallidus observed on brain MRI [2]. Why the phenotypic features should be limited largely to the central nervous system remains unclear.

PKAN is caused by mutations in *PANK2*, which encodes a mitochondrial pantothenate kinase that is an essential regulatory enzyme in the biosynthesis of coenzyme A, critical to energy metabolism, fatty acid synthesis and degradation, and other functions [1]. Substrates include pantothenic acid, pantetheine and N-pantothenoylcysteine. Disease pathogenesis is thought to follow from putative cellular coenzyme A defects.

Some patients with PKAN harbor signs of abnormal lipid metabolism, including acanthocytosis and hypoprebetalipoproteinemia [2,3]. Recent metabolomic profiles of patient plasma have again focused attention on derangements in triglyceride synthesis and bile acid conjugation in PKAN [4]. Other studies in cultured fibroblasts have suggested that increased oxidative stress due to altered iron metabolism also may contribute to the pathology in subjects with PKAN [5]. In a murine model of PKAN, there was defective respiratory capacity and altered mitochondrial membrane potential suggesting poor mitochondrial function and energy production in the *Pank2* knock-out mouse [6]. Alterations in energy and lipid metabolism, bile acid conjugation, oxidative stress and mitochondrial function in patients with PKAN seems likely because of the central role of CoA in these cellular processes.

We sought to investigate the metabolic phenotype in PKAN in order to address questions of energy balance, nutrition status and lipid metabolism. Weight loss frequently occurs during the later stages of PKAN as progressive dystonia and spasticity contribute to a decline in nutritional status. Even when patients are no longer ambulatory, many maintain a muscular appearance, likely due to their severe dystonia. Energy expenditure and body composition studies have not been described in the PKAN population. This study analyzed various aspects of metabolism in 16 patients with PKAN in order to better understand energy expenditure and metabolic perturbations that may contribute to disease.

2. Material and methods

All study procedures were approved by Oregon Health & Science University Institutional Review Board (IRB # 7175). Participants who were *PANK2* mutation-positive were recruited over a period of 18 months. Subjects were enrolled from June 2003 to March 2004. The participants or their legal guardians provided informed consent to participate in the study. This study was conducted prior to the

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existence of clinical trials registration but conformed to all of the human subjects regulations at the time of the study.

2.1. Participants and setting

Sixteen individuals (ten female, 6 male, ages 7–69 years) diagnosed with PKAN with a spectrum of disease severity were recruited for participation (see Table 1). Three participants had gastrostomy tubes, one of which also had a tracheostomy. Six individuals were non-ambulatory, and three more elected to use a wheelchair regularly. Some adults participated in work or college courses, and most children and adolescents participated in school or day programs. Study participants and their caregivers flew to Portland, OR for three days of evaluation in the Oregon Clinical and Translational Research Institute (OCTRI). During this time a battery of studies was performed, some of which have been described in separate publications [7,8].

2.2. Clinical rating scales

Participants were evaluated clinically using four tools:

Barry–Albright Dystonia Scale [9]. The BAD scale indicates degree of secondary dystonia evidenced by abnormal movements or postures of the following eight regions: eyes, mouth, neck, truck, and each upper and lower extremity. The participant's score is the sum of each of eight regions on a 4-point scale (higher scores represent more advanced disease, range = 0–32).

Unified Parkinson's Disease Rating Scale [10]. The Motor Examination section of the UPDRS, consisting of 14 questions graded on a 5-point scale, was used to evaluate participants. This section encompasses speech, facial expression, limb movements, posture, gait and specific movement patterns. A higher score indicates greater impairment (range = 1–108).

Care and Comfort Hypertonicity Questionnaire [11]. The CCHQ estimates disease severity in terms of degree of disability, considering functional limitations and quality-of-life elements in the context of four sections: personal care, positioning/transferring, comfort, and interacting/communication. It takes approximately 10 min to administer and consists of 27 questions answered using a 7-point Likert scale; final score is the mean scale score (range = 1–7).

Global rating. A medical geneticist and neurologist independently assigned a subjective estimate of neurological and adaptive impairment on a 7-point scale (range = 1–7, lower scores represent less impairment) based on the histories and physical examination at the time of the visit.

2.3. Nutritional assessment

A registered dietitian administered a 39-question Diet Habit Survey [12] to each participant or their caregiver to assess the intake of meats, dairy, fats, oils, sweets, fruits, vegetables, legumes, grains, beans, beverages, salt, seafood, and prepared foods. Each question was scaled by an estimated quantity of intake. A higher score indicated lower consumption in the categories of high-fat meats, cheese, eggs, fats and oils, sweets, beverages, salt and number of meals at restaurants. A higher score indicated greater consumption in the categories of fish, seafood and complex carbohydrates (including grains, beans, fruit and vegetables). Therefore, a higher total score indicates a diet higher in complex carbohydrates, low-fat protein, fish and seafood; and lower in: fat, salt, sugar, alcohol, coffee, juices, and eggs. Dietary intake of saturated fat, total fat, carbohydrate, and protein expressed as a percent of total energy, as well as intake of cholesterol, sodium and potassium (mg/day) can be estimated from the total Diet Habit Survey score [12].

2.4. Body composition assessment

Weight was measured in light clothing after overnight fast. Height was measure with a stadiometer to the nearest centimeter. For participants who could not stand, length was measured in a supine position using a tape measure. BMI was calculated as mass (kg)/height $(m)^2$.

Body composition was measured by bioelectrical impedance analysis (BIA) with the Body Composition Analyzer, Model 310e (Biodynamics Corp, Seattle, WA). Electrodes were placed on the wrist and ankle and a small electrical current was used to measure resistance. Resistance (Ohms) was used to estimate total body water, fat-free mass, and fat mass.

Table 1
Selected characteristics of PKAN study subjects including disease severity scales, diet survey results and body habitus. Body habitus of matched controls are also reported here.

	PKAN participants					Control participants		
	All (n = 16)	Ages 19+ (n = 10)	Ages 18 & under (n = 6)	Females (n = 10)	Males (n = 6)	All (n = 16)	Females (n = 10)	Males (n = 6)
Body habitus:								
Age (y)	25 ± 15	31 ± 15	14 ± 4	25 ± 18	24 ± 10	25 ± 15	25.6 ± 18.0	24.0 ± 8.8
Weight (kg)	57.9 ± 18.5	64 ± 17	49 ± 18	52 ± 19	67 ± 15	58.1 ± 13.5	53.8 ± 11.8	64.3 ± 13.5
Height (cm)	162 ± 16.1	167 ± 12	153 ± 20	157 ± 14	170 ± 18	164.5 ± 15.1	159.0 ± 14.0	173.1 ± 12.8
BMI (kg/m^2)	22 ± 5	23 ± 5	20 ± 4	21 ± 6	23 ± 2	21.1 ± 2.6	20.9 ± 2.5	21.4 ± 2.7
Body fat (% weight)	21.4 ± 10.0	22 ± 11	21 ± 9	23 ± 11	19 ± 8	Not given		
Severity scales:								
Global	3.4 ± 1.5	3.3 ± 1.5	3.5 ± 1.5	3.6 ± 1.5	3.0 ± 1.4	NA		
BAD	19 ± 7	17 ± 6.6	21 ± 7.5	21 ± 6.7	15 ± 6.4			
UPDRS	42 ± 17	39 ± 17	45 ± 18	44 ± 20	38 ± 11			
CCHQ	2.5 ± 1.1	2.1 ± 0.7	3.0 ± 1.4	2.9 ± 1.1	1.8 ± 0.4			
Electroretinogram scale	2.3 ± 1.2	2.0 ± 1.1	2.8 ± 1.3	2.4 ± 1.3	2.2 ± 1.2			
Diet:								
Diet Habit Survey Score	160 ± 20	164 ± 23	153 ± 13	158 ± 21	163 ± 20			
Estimated kcal/day	2150 ± 510	2360 ± 340	1820 ± 600	1990 ± 540	2430 ± 340		1800[a]	2200[a]
Estimated % fat in diet	30%	30%	30%	30%	30%			

Footnotes: y = years; kg = kilograms; cm = centimeters; BMI = body mass index; m = meters; body fat expressed as a percent (%) of total body weight; RQ = respiratory quotient calculated as VCO_2/VO_2.

[a] Predicted intake for normal health.