Published in final edited form as:

Mol Genet Metab. 2013 November ; 110(3): 336–341. doi:10.1016/j.ymgme.2013.06.017.

Metabolism and energy requirements in pantothenate kinase-associated neurodegeneration

Sarah Williams^a, Allison Gregory^a, Penelope Hogarth^{a,b}, Susan J. Hayflick^{a,b,c,*}, and Melanie B. Gillingham^a

^aDepartment of Molecular and Medical Genetics, Oregon Health & Science University, Portland, USA

^bDepartment of Neurology, Oregon Health & Science University, Portland, USA

^cDepartment of Pediatrics, Oregon Health & Science University, Portland, USA

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.

Keywords

PKAN; Pantothenate kinase-associated neurodegeneration; Hallervorden–Spatz syndrome; Coenzyme A; Resting energy expenditure

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.

*Corresponding author at: Department of Molecular and Medical Genetics, Oregon Health and Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, USA. Fax: +1 503 494 6886. hayflick@ohsu.edu (S.J. Hayflick).

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 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, trunk, 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 measured 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.

2.5. Energy expenditure

Resting energy expenditure was measured after an overnight fast by indirect calorimetry using a SensorMedics Model 29N Indirect Calorimeter (SensorMedics Corp., Yorba Linda, CA). Subjects lay supine in a room with ambient temperature and low lighting. The plexiglass canopy was then placed over their head and chest and gas exchange was measured for 30 min to determine resting energy expenditure and respiratory quotient.

Measured REE was compared to predicted basal energy expenditure using the FAO/WHO/UNU prediction equations [13] and to published control values from the Dietary Reference Intake [14]. Each subject's measured height and weight were entered into the FAO/WHO/UNU gender and age specific equation to generate a predicted REE (Table 2). Measured REE in normal individuals was used [14]. Using the Appendix I: Doubly Labeled Water Data Used to Predict Energy Expenditure from [14], three controls were selected for each PKAN subject that were similar in height, weight, and BMI (for one subject only one control could be matched). REE measured by indirect calorimetry for normal individuals was compared to that of PKAN participants.

2.6. Laboratory analyses

Fasting blood samples were drawn for lipid panels, amino acids, serum ferritin, transferrin, carnitine, soluble transferrin receptor, RBC and plasma essential fatty acids, lipoprotein electrophoresis, and CBC. A 24-hour urine collection was performed to measure organic acids and mevalonic acid. All studies were performed in clinical laboratories according to standard methods.

Plasma was analyzed for triglycerides, HDL, LDL, and total cholesterol by standard autoanalyzer. Plasma and washed RBCs were analyzed for total fatty acid profile by GC-FID as previously described [15]. Results were expressed as percent of total fatty acids.

2.7. Data analysis

Data are presented as mean $\pm$ standard deviation of the mean (SD). Measured REE in subjects with PKAN was compared to predicted REE by paired t-test. Resting energy expenditure per kg of body weight for subjects with PKAN was compared to published normal values by linear regression using Prism 4.0 (Graphpad, La Jolla, CA).

3. Results

3.1. Subject characteristics

Subject characteristics including body composition, severity scale scores and nutritional assessment are recorded in Table 1.

Raw severity scores (Table 1) demonstrate a range of severity in the PKAN participants. One measure of severity, the Barry–Albright Dystonia Scale, has an inverse relationship with BMI, total cholesterol and the estimated energy intake per day suggesting that as the dystonia increases, energy balance becomes negative leading to decreased energy intake, potentially increased energy expenditure, and weight loss over time.

The mean dietary assessment scores of patients grouped by age and gender fell within the optimal scoring category of the Diet Habit Survey (all subjects 160 ± 20 , over 18 164 ± 23 , under 18 153 ± 13 , females 158 ± 21 and 163 ± 20), which corresponds with a diet of approximately 30% of energy from fat. Patients in this group of subjects consume a varied healthy diet with an appropriate amount of energy from dietary fat.

3.2. Body composition and energy expenditure

The mean respiratory quotient for subjects with PKAN was 0.90 ± 0.04 suggesting subjects were oxidizing primarily carbohydrate with some small amount of fatty acids and/or amino acids. Resting Energy Expenditure (REE) was 1400 ± 210 for females and 1850 ± 250 for males. REE is a function of lean body mass (LBM) however LBM was not available for normal individuals so total BW was used as a surrogate of LBM. REE for subjects with PKAN and for normal individuals is shown in relationship to total BW in Fig. 1. Both subjects with PKAN and normal controls had increasing REE with increasing BW, but REE was about 8% higher among subjects with PKAN compared to controls. In addition, measured REE in subjects with PKAN was higher than predicted REE based on FAO/WHO/UNU prediction equations (116 kcal/day , 95% CI: $37.5\text{--}295 \text{ kcal/day}$, $p = 0.007$; Table 2). There was a positive correlation between severity score and measured REE. This relationship most likely reflects an increased energy expenditure due to involuntary muscle contractions in a posture of rest with the dystonia rather than a true increase in basal cellular energy expenditure per kg LBM.

3.3. Laboratory analyses

Average values for the lipid panel, urinary mevalonate, plasma and erythrocyte fatty acids, and iron storage markers are shown in Table 3.

Results from a standard lipid panel indicate subjects with PKAN had normal total cholesterol and some subjects had slightly increased LDL cholesterol over the optimal 100 mg/dL (average of all participants 105.8 ± 30.6 , over 18 years 115.2 ± 33.0). As expected, adult males had higher LDL than females and those under 18 (males 125.8 ± 35.5 , under 18 years 90.0 ± 19.4 , females 93.7 ± 20.9).

Plasma and erythrocyte fatty acid group averages show mild increases in erythrocyte total polyunsaturated fatty acids (45.13 ± 1.59 , 106.4% of the normal mean) with normal values for the essential fatty acids, arachidonic acid and docosahexaenoic acid. Saturated fatty acids were within normal limits.

Total urinary mevalonate excretion was higher than normal among subjects with PKAN. When normalized to body weight, 12 of the 16 values are above the normal range of 23.1

± 1.76 nmol/day*kg. The group average is above normal range at 29.96 ± 10.32 nmol/day*kg (Fig. 2).

Urine organic acid analysis by gas chromatography-mass spectrometry showed no qualitative abnormalities. Lipoprotein electrophoresis showed no qualitative or quantitative abnormalities. Plasma amino acid results demonstrate amounts within the normal range, with the exception of no more than one or two abnormal individual values per amino acid. Specifically, alanine levels were normal. Ferritin and transferrin values were within normal limits, with the exception of one low transferrin value.

4. Discussion

Coenzyme A is essential for many biochemical processes in humans, and defects in coenzyme A homeostasis would be predicted to lead to widespread perturbations in intermediary metabolism, including fatty acid synthesis and oxidation, and pyruvate oxidation. PKAN is a defect in the coenzyme A biosynthesis pathway, and while the main phenotypic features are limited to a degenerative process in the central nervous system, systemic involvement has been observed in some cases by presentation with acanthocytosis, plasma lipoprotein defects, and possible spermatogenic defects [2]. Only recently, systemic metabolic perturbations in patient plasma samples have been reported in PKAN [4]. In our cohort of 16 subjects with PKAN, we found remarkably few metabolic abnormalities. These observations suggest there are minimal peripheral metabolic derangements in PKAN despite the significant central nervous system phenotype.

We found no evidence for significant differences in body composition between people with PKAN and normal published control values. On average, people with PKAN have a normal weight for height and thus a normal body mass index. Fat and non-fat body mass were within a normal range. We did observe a negative correlation between disease severity score and body mass index suggesting patients are losing weight as the disease progresses. Negative energy balance due to increased energy demands with greater dystonia and muscle contractions in combination with declining ability to chew and swallow can lead to weight loss in these patients and increase their risk for protein-calorie malnutrition during late stages of the disease.

Measured resting energy expenditure of subjects with PKAN was higher than predicted based on age, gender and body weight. In addition, REE was higher in subjects with PKAN than published data in normal controls. The data suggest patients with PKAN have a higher resting energy need. This too is associated with disease severity. We suspect the increased energy demand is related to the excess energy of involuntary muscle contractions but this has not been proven. Clinically, our data suggests health providers should be attentive to the energy needs in this patient population. Common formulas used to estimate basal metabolic rate will underestimate needs by about 8%. The total energy estimate can be adjusted by using a greater activity factor to account for the potential increased disease-related energy requirements.

Active and resting energy expenditures determine total caloric needs. Basal ganglia damage in PKAN causes severe dystonia, which leads to high rates of energy expenditure from nearly constant large muscle contractions during awake periods. We report that resting energy expenditure in PKAN is increased. People with PKAN utilize more calories even during presumed periods of rest. We observed a trend towards higher REE in more severely affected patients, which suggests that some may have been ‘active’ with dystonia even while appearing to be at rest. Regardless of the etiology, the implications for their increased caloric needs remain relevant. People with PKAN need an average of 8% more calories than those without PKAN in order to meet their basal energy demands. Their respiratory quotient signifies that they use a mix of carbohydrates, fats and proteins as fuel. Nutritional management should be individualized in this population.

PKAN shares phenotypic features, including basal ganglia degeneration, retinopathy and acanthocytosis, with abetalipoproteinemia, a defect in intestinal fat and fat-soluble vitamin absorption. This is intriguing because a recent metabolomics analysis of patient plasma suggested decreased bile acid conjugation [4]. Decreased bile acid synthesis and release into the small intestine could decrease the digestion and absorption of multiple essential lipid molecules including fatty acids and fat-soluble vitamins. Though lipoprotein defects have been reported in rare PKAN patients, we found no evidence for a lipoprotein defect in our analyses. Bile acids were not measured in the current study, and patients showed no evidence for fat-soluble vitamin deficiency. Plasma lipid profiles were within the normal expected range and plasma LDL was slightly higher than optimal in some adult patients.

Despite evidence for low cellular fatty acid synthesis in cultured fibroblasts of patients with PKAN, we observed normal plasma and RBC saturated fatty acids with normal or slightly elevated polyunsaturated fatty acids [4]. Whether the palmitic acid was endogenously synthesized or exogenously consumed in foods is unknown. The Diet Habit survey suggested most subjects were consuming a diet with approximately 30% of the energy from fat, and palmitate is an abundant fatty acid in the American diet. The strongest dietary factors associated with endogenous cholesterol biosynthesis include positive energy balance with a high saturated fatty acid intake that is digested and absorbed. Based on the plasma fatty acid profiles, subjects with PKAN consume adequate amounts of fatty acids, including the essential fatty acids linoleic, arachidonic and DHA with adequate absorption from the gastrointestinal tract. Others have reported decreased triglyceride and phospholipid concentrations among patients with PKAN compared to controls and have suggested that dietary supplements with fatty acids may improve the tri-acyl glycerol and phospholipid profiles [4]. However, based on our data, the precursor fatty acids are available for complex lipid synthesis. Decreased phospholipid or TAG synthesis may be at the level of the fatty acid acyl-CoAs being esterified to complex lipid moieties such as triacylglycerols and sphingolipids. If that is the case, further increases in the substrate pool by increasing dietary saturated fat intake will not improve TAG or phospholipid synthesis.

We did observe elevated urinary mevalonate in most patients. Mevalonate is the product of the rate-limiting step in cholesterol biosynthesis and is formed from 3 acetyl-CoA molecules. In the process of synthesizing mevalonate from acetyl-CoA, three molecules of free CoA are released. It is possible that cytosolic synthesis of mevalonate is upregulated by

a cellular need for free CoA for other biological processes. Elevated urinary mevalonate with normal or mildly elevated cholesterol concentrations suggest potentially elevated stage 1 cholesterol biosynthesis with normal concentrations of the endproduct for the entire pathway in PKAN. Given the high energy demand required to synthesize cholesterol, it seems counterintuitive that subjects with PKAN would have increased cholesterol biosynthesis. Further studies of metabolic changes using complementary methods are needed. Pantethine supplementation, which has been used to treat hyperlipidemia, may serve a dual therapeutic role in PKAN by also increasing the substrate pool for pantothenate kinase.

Despite known mutations in the *PANK2* gene, subjects with PKAN had normal body composition, dietary intake, and energy expenditure. We did not find evidence for altered lipid, amino acid, or organic acid metabolites in a single fasting blood sample from our subjects. Our observations suggest the phenotype for PKAN is predominately a central nervous system disorder with little or no changes in resting intermediary metabolism. We did observe a slightly higher resting energy expenditure than expected which we believe is related to the increased energy demands of dystonia as the disease progresses. Health professionals caring for patients with PKAN should consider increased energy demands when providing nutrition recommendations for this patient group. Alternatively, tissue-specific perturbations in coenzyme A levels could alter many intermediary biochemical reactions leading to transient changes that are difficult to capture and analyze in a single fasting blood sample. The absence of a consistent pattern of metabolic changes that pinpoint key contributors to pathogenesis makes this latter concept more attractive. More detailed studies of intermediary metabolism in the pre and post-prandial state would provide additional information to determine if the presumed changes in metabolism due to defects in coenzyme A biosynthesis do or do not exist.

Acknowledgments

We are grateful to the patients and their families for their participation, enthusiasm and support. This work was funded by the NBIA Disorders Association and made possible with support from the Oregon Clinical and Translational Research Institute (OCTRI), grant number TL1 RR024159 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. This work was also supported by PHS Grants 1R01 EY12353 and 5M01 RR000334. We are grateful to Cary Harding, Robert Steiner, Louise Merckens, Anuradha Pappu and Mike Lasarev for their assistance and helpful discussions.

References

1. Zhou B, Westaway SK, Levinson B, Johnson MA, Gitschier J, Hayflick SJ. A novel pantothenate kinase gene (*PANK2*) is defective in Hallervorden–Spatz syndrome. *Nat Genet.* 2001; 28:345–349. [PubMed: 11479594]
2. Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, Gitschier J. Genetic, clinical, and radiographic delineation of Hallervorden–Spatz syndrome. *N Engl J Med.* 2003; 348:33–40. [PubMed: 12510040]
3. Ching KH, Westaway SK, Gitschier J, Higgins JJ, Hayflick SJ. HARP syndrome is allelic with pantothenate kinase-associated neurodegeneration. *Neurology.* 2002; 58:1673–1674. [PubMed: 12058097]
4. Leoni V, Strittmatter L, Zorzi G, Zibordi F, Dusi S, Garavaglia B, Venco P, Caccia C, Souza AL, Deik A, Clish CB, Rimoldi M, Ciusani E, Bertini E, Nardocci N, Mootha VK, Tiranti V. Metabolic consequences of mitochondrial coenzyme A deficiency in patients with *PANK2* mutations. *Mol Genet Metab.* 2012; 105:463–471. [PubMed: 22221393]

5. Campanella A, Privitera D, Guaraldo M, Rovelli E, Barzaghi C, Garavaglia B, Santambrogio P, Cozzi A, Levi S. Skin fibroblasts from pantothenate kinase-associated neurodegeneration patients show altered cellular oxidative status and have defective iron-handling properties. *Hum Mol Genet.* 2012; 21:4049–4059. [PubMed: 22692681]
6. Brunetti D, Dusi S, Morbin M, Uggetti A, Moda F, D'Amato I, Giordano C, d'Amati G, Cozzi A, Levi S, Hayflick S, Tiranti V. Pantothenate kinase-associated neurodegeneration: altered mitochondria membrane potential and defective respiration in *Pank2* knock-out mouse model. *Hum Mol Genet.* 2012; 21:5294–5305. [PubMed: 22983956]
7. Freeman K, Gregory A, Turner A, Blasco P, Hogarth P, Hayflick S. Intellectual and adaptive behaviour functioning in pantothenate kinase-associated neurodegeneration. *J Intellect Disabil Res.* 2007; 51:417–426. [PubMed: 17493025]
8. Egan RA, Weleber RG, Hogarth P, Gregory A, Coryell J, Westaway SK, Gitschier J, Das S, Hayflick SJ. Neuro-ophthalmologic and electroretinographic findings in pantothenate kinase-associated neurodegeneration (formerly Hallervorden–Spatz syndrome). *Am J Ophthalmol.* 2005; 140:267–274. [PubMed: 16023068]
9. Barry MJ, VanSwearingen JM, Albright AL. Reliability and responsiveness of the Barry–Albright Dystonia Scale. *Dev Med Child Neurol.* 1999; 41:404–411. [PubMed: 10400175]
10. Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stebbins GT, Stern MB, Tilley BC, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, Van Hilten JJ, LaPelle N. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. *Mov Disord.* 2007; 22:41–47. [PubMed: 17115387]
11. Nemer McCoy R, Blasco PA, Russman BS, O'Malley JP. Validation of a care and comfort hypertonicity questionnaire. *Dev Med Child Neurol.* 2006; 48:181–187. [PubMed: 16483393]
12. Connor SL, Gustafson JR, Sexton G, Becker N, Artaud-Wild S, Connor WE. The Diet Habit Survey: a new method of dietary assessment that relates to plasma cholesterol changes. *J Am Diet Assoc.* 1992; 92:41–47. [PubMed: 1728622]
13. Food and Agriculture Organization of the United Nations, United Nations University, World Health Organization Human energy requirements: report of a joint FAO/WHO/UNU expert consultation; Rome. 17–24 October 2001; Rome: Food and Agricultural Organization of the United Nations; 2004
14. Institute of Medicine (U.S.), Panel on Macronutrients, Institute of Medicine (U.S.) Standing committee on the scientific evaluation of dietary reference intakes, Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids National Academies Press; Washington, D.C: 2005
15. Connor WE, Neuringer M, Lin DS. Dietary effects on brain fatty acid composition: the reversibility of n–3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocytes, and plasma of rhesus monkeys. *J Lipid Res.* 1990; 31:237–247. [PubMed: 2139096]

Fig. 1.

Resting energy expenditure (REE, kcal/day) vs. body weight (kg) depicts the data for each subject and a line of best fit for the two groups, those with and without PKAN. The slopes of the lines are equal (increasing weight corresponds with increasing REE), and the PKAN REE is 8% higher than that of the control group.

Fig. 2. Urinary mevalonate levels in PKAN subjects cluster significantly above the normal range. There is an elevated median, with also greater spread, and the minimum and maximum samples are outside the normal limits.

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.

Table 1

	PKAN participants				Control participants			
	All (n = 16)	Ages 19+ (n = 10)	Ages 18 & under (n = 6)	Females (n = 6)	Males (n = 6)	All (n = 16)	Females (n = 10)	Males (n = 6)
<i>Body habitus:</i>								
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		
<i>Severity scales:</i>								
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			
<i>Diet:</i>								
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 = quotient calculated as VCO_2/VO_2 .

^aPredicted intake for normal health.

Table 2

Energy and body composition data. Resting energy expenditure (REE) as measured by indirect calorimetry (gold standard) and as predicted by the FAO/WHO/UNU in subjects with PKAN and controls is given as well as comparison between the two and normalized to fat free mass (FFM). Respiratory quotient given for PKAN subjects using indirect calorimetry. Body composition done by bioelectrical impedance for PKAN subjects but not available for controls.

PKAN participants					
	All	Ages 18 & up	Ages 18 & under	Females	Males
<i>Gold-standard measurements of REE (mREE) and FFM</i>					
Indirect calorimetry:					
REE (kcal/day)	1570 ± 310	1610 ± 266	1500 ± 393	1401 ± 209	1810 ± 248
RQ	0.90 ± 0.04	0.89 ± 0.04	0.91 ± 0.04	0.89 ± 0.03	0.91 ± 0.05
Bioelectrical impedance:					
FM (kg)	13.2 ± 8.90	15 ± 10	10 ± 6	13 ± 11	13 ± 4
FFM (kg)	45.3 ± 15.2	50 ± 14	36 ± 14	38 ± 10	58 ± 14
REE normalized to FFM	36.9 ± 7.27	33.6 ± 4.62	43.4 ± 7.51	37.8 ± 5.22	35.4 ± 10.0
<i>Prediction equation of REE (pREE)</i>					
FAO/WHO/UNU	1450 ± 300	1490 ± 296	1386 ± 323	1280 ± 193	1740 ± 205
<i>Comparing mREE to pREE</i>					
Predicted as % of measured	108.7 ± 10.6%	109.0 ± 10.6%	108.1 ± 11.5%	110 ± 9.7%	106.5 ± 12.5%
Control participants					
	All		Females		Males
<i>Gold-standard measurements of REE (mREE) and FFM</i>					
Indirect calorimetry:					
REE (kcal/day)	1466.1 ± 266.5		1328.8 ± 170.3		1680.6 ± 249.3
RQ					
Bioelectrical impedance:					
FM (kg)					
FFM (kg)					
REE normalized to FFM					
REE (kcal/day)/FFM (kg)					
<i>Prediction equation of REE (pREE)</i>					
FAO/WHO/UNU	1463.3 ± 243.0		1317.5 ± 141		1690.0 ± 287.3
<i>Comparing mREE to pREE</i>					
Predicted as % of measured	100.5 ± 10.2%		101.1 ± 9.6%		99.6 ± 11.4%

Footnotes: mREE = measured resting energy expenditure; FM = fat mass; FFM = fat free mass; pREE = predicted resting energy expenditure.

Table 3

Laboratory analyses. Iron studies, lipid panel, urinary mevalonate, and plasma and RBC fatty acids were drawn.

	PKAN participants				
	All (n = 16)	Adults (n = 10)	Children (n = 6)	Males (n = 6)	Females (n = 10)
Lipid panel					
Total cholesterol	165.4 ± 25.7	174.4 ± 26.5	150 ± 16.9	178.5 ± 26.0	157.5 ± 23.2
VLDL cholesterol	12.1 ± 7.5	13.8 ± 7.4	9.3 ± 7.3	11.0 ± 6.5	12.8 ± 8.2
LDL cholesterol	105.8 ± 30.6	115.2 ± 33.0	90.0 ± 19.4	125.8 ± 35.5	93.7 ± 20.9
HDL cholesterol	53.4 ± 9.5	50.9 ± 10.1	57.7 ± 7.1	52.0 ± 10.7	54.3 ± 9.2
Total triglycerides	95.6 ± 41.3	102.6 ± 39.5	83.8 ± 45.1	102.7 ± 38.7	91.3 ± 44.3
VLDL triglyceride	56.5 ± 32.3	59.3 ± 30.3	51.8 ± 38.0	68.3 ± 31.8	49.4 ± 32.1
VLDL-C/total TG	1.0 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
LDL-C/HDL-C	2.1 ± 1.0	2.4 ± 1.1	1.6 ± 0.5	2.6 ± 1.3	1.8 ± 0.7
Total C/HDL-C	3.2 ± 1.1	3.6 ± 1.2	2.7 ± 0.5	3.7 ± 1.3	3.0 ± 0.9
Urinary mevalonic acid					
μmol/day	1.76 ± 0.97	2.04 ± 1.0	1.3 ± 0.8	2.5 ± 1.2	1.3 ± 0.5
nmol/day*kg (23.1 ± 1.76 ^a)	29.96 ± 10.32	31.7 ± 10.8	27.0 ± 9.7	36.0 ± 11.7	26.4 ± 7.9
Plasma fatty acids (% of total)					
Palmitic	20.0 ± 1.6	20.1 ± 1.38	19.8 ± 2.0	20.0 ± 1.3	20.0 ± 1.8
Stearic	6.7 ± 1.05	6.2 ± 0.7	4.7 ± 1.2	6.8 ± 0.6	6.5 ± 1.3
Linoleic	31.7 ± 3.1	31.5 ± 2.7	31.9 ± 4.2	31.2 ± 2.3	21.9 ± 3.7
Linolenic	0.54 ± 0.24	0.46 ± 0.14	0.67 ± 0.33	0.45 ± 0.09	31.9 ± 3.7
Arachidonic	7.8 ± 1.0	8.0 ± 1.0	7.4 ± 0.9	8.0 ± 1.1	0.59 ± 0.29
DHA	1.4 ± 0.82	1.4 ± 0.9	1.4 ± 0.8	1.7 ± 1.1	1.3 ± 0.6
RBC fatty acids (% of total)					
Palmitic	18.1 ± 1.4	17.9 ± 1.1	18.4 ± 1.8	14.4 ± 0.5	18.3 ± 1.5
Stearic	14.0 ± 1.0	13.7 ± 0.9	14.5 ± 1.0	17.7 ± 1.2	13.7 ± 1.1
Linoleic	13.0 ± 1.2	12.9 ± 1.3	13.2 ± 1.3	12.7 ± 1.3	13.2 ± 1.3
Linolenic	0.15 ± 0.07	0.12 ± 0.03	0.20 ± 0.08	0.13 ± 0.04	0.16 ± 0.08
Arachidonic	16.8 ± 1.0	17.4 ± 1.0	16.4 ± 1.0	16.7 ± 0.8	16.9 ± 1.2
DHA	3.9 ± 1.4	3.9 ± 1.6	3.9 ± 0.9	4.2 ± 1.7	3.67 ± 1.2

PKAN participants					
	All (n = 16)	Adults (n = 10)	Children (n = 6)	Males (n = 6)	Females (n = 10)
Iron storage and transport					
Transferrin (mg/dL)	47.0 ± 34.1	57.5 ± 39.2	31.3 ± 17.3	34.9 ± 24.4	65.2 ± 40.4
Ferritin (ng/mL)	296.7 ± 52.5	268 ± 32.7	339.7 ± 48.0	303.1 ± 54.5	287.0 ± 52.6

Footnotes: VLDL = very low density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein; C = cholesterol; TG = triglycerides DHA = docosahexaenoic acid (C22:6n-3); RBC = red blood cell.

^aNormal value.