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Concurrent Phenylalanine Hydroxylase–Related Disorder and Celiac: A Rare Co-occurrence With Implications for Clinical Management

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Abstract

Comorbid nutritional disorders can present with clinical management challenges. Phenylalanine hydroxylase (PAH) deficiency and celiac disease are both associated with dietary protein intolerance, yet they are different disorders. Phenylalanine hydroxylase deficiency is a rare genetic disorder that results in elevated levels of phenylalanine (Phe) in the blood. It causes multisystemic abnormalities, including neurologic findings, seizures, episodic tremor, ataxia, and cognitive and sensory disturbances. In contrast, celiac disease is a common nutritional disorder that arises from immune-mediated enteropathy against dietary gluten. Herein, we describe the clinical findings in an adult with PAH deficiency and celiac disease to showcase some opportunities for improved personalized nutritional management.

Keywords

Phenylketonuria; Gluten; Nutritional deficiencies; Signs and symptoms; Proteins; Diet; Metabolites; Phenylalanine; Amino acids; Genetic testing; Hyperphenylalaninemia; Neurologic; Sleep; Osteopenia

Background

Phenylalanine hydroxylase (PAH, EC 1.14.16.1) catalyzes the conversion of L-phenylalanine (L-Phe) to L-tyrosine (L-Tyr) in a tetrahydrobiopterin (BH4)-dependent

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Disclosures

Disclosure forms are available with the article online.

reaction (1). The role of PAH in the detoxification of excess L-Phe is to prevent the neurotoxic effect of hyperphenylalaninemia (2). The spectrum of clinical manifestations of PAH deficiency ranges from asymptomatic hyperphenylalaninemia to phenylketonuria (PKU), which manifests with a constellation of neurologic abnormalities and osteopenia. Advances in genomic and biochemical testing technologies are increasingly resulting in genetic diagnosis of individuals with relatively milder manifestations of PAH deficiency (2, 3). Although therapeutic benefits of dietary therapy for PKU are well recognized, potential benefits of dietary modulation in individuals with milder forms of PAH deficiency are yet to be fully understood. The possible relevance of comorbid conditions in individuals with PAH deficiencies in general are also less clear, as highlighted by the recently published American College of Medical Genetics practice guideline (4).

Unlike PAH deficiency, which is a rare Mendelian disorder, multifactorial nutritional disorders (such as celiac disease) are very common (5). Manifesting with the gastrointestinal (e.g., diarrhea, bloating, and flatulence) and extragastrointestinal symptoms of gluten intolerance (such as osteopenia, fatigue, neurologic spells, and anemia) (6), celiac disease is an autoimmune disorder (5). Gluten is ubiquitously present in staple food sources, including wheat, barley, and rye. Given the overlapping need for dietary protein management, we reasoned that insights garnered from individuals with PAH deficiency in the setting of concurrent celiac disease may help pave the way for personalized nutrigenomic management approaches. Accordingly, we hereby describe the clinical findings from a 46-year-old woman affected by both PAH deficiency and celiac disease.

Case Report

The patient is a 46-year-old woman who had a history of neurologic spells and a sleep disorder in the context of a lifelong history of protein intolerance. Her medical history was also significant for anemia, concussion, episodes of loss of consciousness, costochondritis, supraglottic mass, osteoporosis, kyphosis, and lordosis. She was first diagnosed with celiac disease following duodenal biopsy, but the neurologic symptoms and sleep abnormalities that she experienced after eating protein-rich meals lingered despite transitioning to a gluten-free diet. The patient experienced intermittent episodes of electric shock sensation in the lower limbs, with muscle twitches, leg cramps, hypnic jerks, and muscle spasm. These neurologic spells impaired her sleep pattern, resulting in difficulties concentrating at work. Electroencephalogram and magnetic resonance imaging of her brain were essentially normal. The patient had a custom gene panel test (which included genes that have been associated with hereditary forms of seizures, neurologic spells, and circadian rhythm disorders) at Invitae laboratories (San Francisco, CA) followed by genome (including nuclear and mitochondrial) sequencing at Variantyx laboratories (Framingham, MA).

The custom gene panel test was nondiagnostic, but genome sequencing was diagnostic. Following genome sequencing, quantitative amino acid analysis (QAAA) tests were performed using blood samples.

Genome (nuclear and mitochondrial) sequencing raised concerns for PAH deficiency due to biallelic pathogenic variants in *PAH* (that are denoted as c.1139C>T (p.Thr380Met)

[1, 7] and c.935A>G (p.Ser155pro) [8, 9]). Following the genome sequencing results, the patient immediately eliminated protein products drastically from her diet for 6 weeks before her follow-up clinic appointment and blood sample collection for QAAA. She reported resolution of her neurologic symptoms as well as increased mental clarity but also experienced rapid weight loss associated with the intense dietary protein restriction. The QAAA test showed a modestly elevated Phe level in the blood (153 μmol/L; Table 1) in parallel with low levels of valine (an essential amino acid) in the setting of the severe protein restriction. The patient was advised of the target plasma Phe level being <360 μmol/L and of the options of Phe- and gluten-free protein formula as well as the importance of dietary protein in the maintenance of good health, including bone health (10), considering her history of osteoporosis. She received Phe- and gluten-free protein formula, which has resulted in sustained improvements in her neurologic symptoms, with follow-up Phe levels being <360 μmol/L (Table 1), although she experienced some logistic challenges with securing combined Phe- and gluten-free protein formula. Considering the nutritional comorbid conditions (PAH deficiency and celiac disease) and the need for a combined Phe- and gluten-restricted diet, metabolomic profiling (Tables 2 and 3) was performed to investigate metabolic imbalances. Metabolomic profiling of the patient's plasma sample was performed via the Global Metabolomic Assisted Pathway Screen test at Baylor Genetics Laboratory (https://www.baylor-genetics.com/global-maps/), utilizing Metabolon, Inc. (Durham, NC) technology. More than 750 metabolites were detected. The metabolites were analyzed based on a reference library that contains approximately 2500 unique human metabolites. The levels of several metabolites (including lipid species, amino acids, bilirubin-related analytes and pantothenate) were altered, with Z scores ≥ 2 (Table 2) or ≤ −2 (Table 3).

Discussion

To our knowledge, this is the first report of co-occurrence of PAH deficiency and celiac disease, an important milestone in highlighting the potential clinical needs of patients who have PAH-related disorders in a setting of comorbid conditions as highlighted by the recent guideline issued by the American College of Medical Genetics for PAH deficiency (4). Even though celiac disease and PAH deficiency arise from very different causes, both are disorders that manifest with dietary protein intolerance. Considering that the clinical management of both PAH deficiency and celiac disease involves dietary modification, treating a patient with both conditions introduces distinctive clinical challenges. The simultaneous requirement for a gluten-free and low-phenylalanine diet may influence patient adherence, nutritional sufficiency, and metabolic control. While the dietary management strategy for celiac disease and PAH deficiency presented in this study adheres to standard guidelines, applying both simultaneously proved operationally complex. Our patient's experience underscores the need for strategies that can overcome logistic barriers and metabolic derangements encountered by patients requiring customized dietary formulas for co-occurring nutritional disorders. For patients who already must follow a gluten-free diet for celiac disease, additional dietary protein restrictions may potentially increase the risk for metabolic imbalances. The metabolic imbalances identified in our patient, most notably the markedly reduced pantothenate levels, may have contributed, at least in part, to her

clinical symptoms. Personalized dietary recommendations tailored to unforeseen metabolic abnormalities may be necessary for patients with concurrent nutritional disorders such as comorbid celiac disease and PAH deficiency.

Additionally, this case highlights how overlapping dietary restrictions can obscure symptom attribution and delay the recognition of nutritional deficiencies as well as metabolic derangements. Notably, the neurologic findings in our patient cannot be attributed solely to PAH deficiency. Symptoms such as fatigue and episodic neurologic spells may potentially reflect contributions from celiac-associated micronutrient deficiencies and a history of concussion or metabolic imbalance. Our findings also support previous observations that PAH deficiency may present with atypical neurologic symptoms (2, 8) while simultaneously highlighting the potential benefits of dietary therapy. Finally, this study suggests that clinicians should be mindful of the potential compound risk for osteoporosis in patients affected by both celiac disease and PAH deficiency. Overall, this report highlights the pertinent clinical challenges associated with the co-occurrence of celiac disease and PAH deficiency.

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Table 1.

Quantitative Plasma Amino Acid Concentrations Before and After Dietary Intervention*

Test	Current Result	Previous Result	Reference Interval
Taurine[A,01]	62.8	66.9	29.2–132.3
Aspartate[A,01]	1.6	1.8	0.0–7.4
Hydroxyproline[A,01]	29.7	8.1	4.7–35.2
Threonine[A,01]	234.6 High	197.7	67.8–211.6
Serine[A,01]	116.4	103.0	48.7–145.2
Asparagine[A,01]	67.5	61.1	29.5–84.5
Glutamate[A,01]	26.8	45.3	18.1–155.9
Glutamine[A,01]	519.4	449.3	372.8–701.4
Sarcosine[A,01]	<0.5	<0.5	0.0–4.0
Alpha-aminoadipate[A,01]	1.3	<0.5	0.0–1.9
Proline[A,01]	142.5	101.2	84.8–352.5
Glycine[A,01]	386.0	362.7	144.0–411.0
Alanine[A,01]	276.4	241.9	209.2–515.5
Citrulline[A,01]	30.3	21.0	15.6–46.9
Alpha-aminobutyrate[A,01]	17.3	8.9	5.4–34.5
Valine[A,01]	228.7	124.5	133.0–317.1
Cystine[A,01]	9.3 Low	14.7	15.8–47.3
Methionine[A,01]	22.6	18.3	14.7–35.2
Homocitrulline[A,01]	<0.5	<0.5	0.0–1.7
Cystathionine[A,01]	<0.5	<0.5	0.0–0.7
Alloisoleucine[A,01]	1.0	1.0	0.0–3.2
Isoleucine[A,01]	64.2	33.2	32.8–88.3
Leucine[A,01]	95.6	75.1	66.7–165.7
Tyrosine[A,01]	64.2	36.5	27.8–83.3
Phenylalanine[A,01]	223.8 High	153.5	35.8–76.9
Argininosuccinate[A,01]	<0.1	<0.1	0.0–3.0
Beta-alanine[A,01]	2.6	2.2	1.1–9.0
Beta-aminoisobutyrate[A,01]	1.8	1.6	0.0–4.3
Homocystine[A,01]	<0.3	<0.3	0.0–0.2
Gamma-aminobutyrate[A,01]	<0.5	<0.5	0.0–0.6
Tryptophan[A,01]	29.7	44.8	23.5–93.0
Hydroxylysine[A,01]	0.3	0.2	0.1–0.8
Ornithine[A,01]	58.0	40.4	30.1–101.3
Lysine[A,01]	121.4	98.1	94.0–278.0
Histidine[A,01]	53.1	55.9	47.2–98.5

[*] "Previous Result" refers to plasma amino acid values obtained during a period of intensive dietary protein restriction prior to initiation of medical nutrition therapy. "Current Result" refers to plasma amino acid values obtained following initiation of phenylalanine- and gluten-free protein formula supplementation. A,01 denotes the analytical assay code used by the reference laboratory for quantitative amino acid analysis. All concentrations are reported in μmol/L.

Table 2.

Metabolites With Z Scores ≥ 2 Under Phenylalanine- and Gluten-Restricted Diet*

Metabolite	Z score	Superpathway	Subpathway
Bilirubin (E,Z or Z,E)	3.0	Cofactors and vitamins	Hemoglobin and porphyrin metabolism
Eicosapentaenoate (EPA; 20:5n3)	3.0	Lipid	Long chain polyunsaturated fatty acid (n3 and n6)
1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6)	3.0	Lipid	Phosphatidylcholine
Pregnanolone/allopregnanolone sulfate	2.9	Lipid	Progestin steroids
Hydroxy-CMPF	2.9	Lipid	Fatty acid, dicarboxylate NA
Ethylmalonate	2.9	Amino acid	Leucine, isoleucine and valine metabolism
5-dodecenoylcarnitine (C12:1)	2.8	Lipid	Fatty acid metabolism (acylcarnitine, monounsaturated)
Guanidinoacetate	2.8	Amino acid	Creatine metabolism
Glutarate (C5-DC)	2.8	Lipid	Fatty acid, dicarboxylate
2-hydroxyglutarate	2.7	Lipid	Fatty acid, dicarboxylate
1-(1-enyl-stearoyl)-2-linoleoyl-GPC (P-18:0/18:2)	2.7	Lipid	Plasmalogen
Palmitoylcarnitine (C16)	2.6	Lipid	Fatty acid metabolism (acylcarnitine, long-chain saturated)
Behenoylcarnitine (C22)	2.5	Lipid	Fatty acid metabolism (acylcarnitine, long-chain saturated)
Hexadecadienoate (16:2n6)	2.5	Lipid	Long-chain polyunsaturated fatty acid (n3 and n6)
Docosahexaenoate (DHA; 22:6n3)	2.5	Lipid	Long-chain polyunsaturated fatty acid (n3 and n6)
N-acetylglycine 2.5 amino acid glycine, serine and threonine metabolism HMDB0000532	2.5	Amino acid	Glycine, serine and threonine metabolism
3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF)	2.5	Lipid	Fatty acid, dicarboxylate
Creatinine	2.4	Amino acid	Creatine metabolism
1-docosahexaenoyl-GPE (22:6)	2.4	Lipid	Lysophospholipid
Octadecenedioylcarnitine (C18:1-DC)	2.4	Lipid	Fatty acid metabolism (acylcarnitine, dicarboxylate)
N-oleoylserine	2.4	Lipid	Endocannabinoid
Alpha-hydroxyisocaproate	2.3	Amino acid	Leucine, isoleucine, and valine metabolism
Ximenoylcarnitine (C26:1)	2.3	Lipid	Fatty acid metabolism (acylcarnitine, monounsaturated)
Bilirubin (Z,Z)	2.3	Cofactors and vitamins	Hemoglobin and porphyrin metabolism
1-palmitoyl-2-eicosapentaenoyl-GPC (16:0/20:5)	2.3	Lipid	Phosphatidylcholine
1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC (P-16:0/16:1)	2.3	Lipid	Plasmalogen
1-(1-enyl-palmitoyl)-2-docosahexaenoyl-GPC (P-16:0/22:6)	2.2	Lipid	Plasmalogen

Metabolite	Z score	Superpathway	Subpathway
1-behenoyl-GPC (22:0)	2.2	Lipid	Lysophospholipid
1-(1-enyl-stearoyl)-2-docosahexaenoyl-GPC (P-18:0/22:6)	2.2	Lipid	Plasmalogen
1-(1-enyl-stearoyl)-2-oleoyl-GPC (P-18:0/18:1)	2.2	Lipid	Plasmalogen
1-(1-enyl-oleoyl)-GPC (P-18:1)	2.2	Lipid	Lysoplasmalogen
Palmitoyl dihydrosphingomyelin (d18:0/16:0)	2.2	Lipid	Dihydrosphingomyelins
1-eicosapentaenoyl-GPE (20:5)	2.1	Lipid	Lysophospholipid
3-hydroxybutyrate (BHBA)	2.1	Lipid	Ketone bodies
2-stearoyl-GPC (18:0)	2.1	Lipid	Lysophospholipid
Oleoyl ethanolamide (18:1)	2.1	Lipid	Endocannabinoid
N-acetyl-isoputreanine	2.1	Amino acid	Polyamine metabolism
Alpha-hydroxyisovalerate	2.0	Amino acid	Leucine, isoleucine and valine metabolism
Sebacate (C10-DC)	2.0	Lipid	Fatty acid, dicarboxylate
1-eicosapentaenoyl-GPC (20:5)	2.0	Lipid	Lysophospholipid
1-(1-enyl-oleoyl)-2-docosahexaenoyl-GPE (P-18:1/22:6)	2.0	Lipid	Plasmalogen

* Metabolites listed have plasma Z scores ≤ −2 relative to the laboratory reference population. “Superpathway” denotes broad metabolic categories defined by the metabolomics platform (e.g., lipid, amino acid, nucleotide metabolism), while “subpathway” refers to more specific biochemical pathways within each superpathway.

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Table 3.

Metabolites With Z Scores ≤ −2 Under Phenylalanine- and Gluten-Restricted Diet*

Metabolite	Z score	Superpathway	Subpathway
N-acetyl-2-aminooctanoate	−2.0	Lipid	Fatty acid, amino
Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1]	−2.1	Lipid	Diacylglycerol
1-docosapentaenoyl-GPC (22:5n6)	−2.1	Lipid	Lysophospholipid
4-hydroxyphenylpyruvate	−2.1	Amino acid	Tyrosine metabolism
1-(1-enyl-palmitoyl)-2-arachidonoyl-GPC (P-16:0/20:4)	−2.1	Lipid	Plasmalogen
1-stearoyl-2-arachidonoyl-GPE (18:0/20:4n6)	−2.3	Lipid	Phosphatidylethanolamine
1-arachidonoyl-GPA (20:4)	−2.3	Lipid	Lysophospholipid
N4-acetylcytidine	−2.3	Nucleotide	Pyrimidine metabolism, cytidine containing
Trans-4-hydroxyproline	−2.3	Amino acid	Urea cycle; arginine and proline metabolism
1-(1-enyl-stearoyl)-2-arachidonoyl-GPC (P-18:0/20:4)	−2.3	Lipid	Plasmalogen
Sphingomyelin (d18:1/25:0, d19:0/24:1, d20:1/23:0, d19:1/24:0)	−2.3	Lipid	Sphingomyelins
Palmitoyl-linoleoyl-glycerol (16:0/18:2) [1]	−2.4	Lipid	Diacylglycerol
Aspartate	−2.4	Amino acid	Alanine and aspartate metabolism
5-hydroxylysine	−2.4	Amino acid	Lysine metabolism
1-(1-enyl-stearoyl)-2-dihomo-linolenoyl-GPE (P-18:0/20:3n3 or n6)	−2.4	Lipid	Plasmalogen
Pantothenate	−2.4	Cofactors and vitamins	Pantothenate and coenzyme A metabolism
Indoleacetate	−2.4	Amino acid	Tryptophan metabolism
6-bromotryptophan	−2.5	Amino acid	Tryptophan metabolism
Methylmalonate (MMA)	−2.5	Lipid	Fatty acid metabolism (also BCAA metabolism)
Beta-alanine	−2.5	Nucleotide	Pyrimidine metabolism, uracil containing
Inosine	−2.6	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing
Argininate	−2.6	Amino acid	Urea cycle; arginine and proline metabolism
Succinylcarnitine (C4-DC)	−2.6	Energy	TCA cycle
1-palmitoyl-GPA (16:0)	−2.7	Lipid	Lysophospholipid
Glycocholate	−2.7	Lipid	Primary bile acid metabolism
1-(1-enyl-palmitoyl)-2-linoleoyl-GPE (P-16:0/18:2)	−2.8	Lipid	Plasmalogen
1-linoleoyl-GPA (18:2)	−2.8	Lipid	Lysophospholipid

Metabolite	Z score	Superpathway	Subpathway
1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)	−2.8	Lipid	Phosphatidylinositol
1-pentadecanoyl-2-arachidonoyl-GPC (15:0/20:4)	−2.9	Lipid	Phosphatidylcholine
1-margaroyl-2-arachidonoyl-GPC (17:0/20:4)	−2.9	Lipid	Phosphatidylcholine
N-acetylhistidine	−2.9	Amino acid	Histidine metabolism
2-arachidonoyl-GPE (20:4)	−2.9	Lipid	Lysophospholipid
1-palmityl-2-arachidonoyl-GPC (O-16:0/20:4)	−3.0	Lipid	Plasmalogen
1-stearyl-2-arachidonoyl-GPC (O-18:0/20:4)	−3.1	Lipid	Plasmalogen
1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE (P-16:0/20:4)	−3.2	Lipid	Plasmalogen
1-palmitoyl-2-adrenoyl-GPC (16:0/22:4)	−3.3	Lipid	Phosphatidylcholine
1-stearoyl-2-adrenoyl-GPC (18:0/22:4)	−3.3	Lipid	Phosphatidylcholine
N,N,N-trimethyl-5-aminovalerate	−3.4	Amino acid	Lysine metabolism
1-(1-enyl-stearoyl)-2-arachidonoyl-GPE (P-18:0/20:4n6)	−3.4	Lipid	Plasmalogen
1-adrenoyl-GPC (22:4)	−3.5	Lipid	Lysophospholipid
Pro-hydroxy-pro	−3.7	Amino acid	Urea cycle; arginine and proline metabolism
1-stearoyl-2-docosapentaenoyl-GPC (18:0/22:5n6)	−6.0	Lipid	Phosphatidylcholine

*Metabolites listed have plasma Z scores ≤ −2 relative to the laboratory reference population. “Superpathway” denotes broad metabolic categories defined by the metabolomics platform (e.g., lipid, amino acid, nucleotide metabolism), while “subpathway” refers to more specific biochemical pathways within each superpathway.

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