CASE REPORT

MIGRAINES AND MOOD DISORDERS: NUTRITIONAL AND DIETARY INTERVENTION BASED ON LABORATORY TESTING

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Current conventional treatments for migraine headache, depression, and mood disorders often fail to address the underlying cause(s) of these conditions and therefore usually require long-term medication without hope for cure or, in many cases, adequate symptom relief. Previous studies have shown that amino acids,[1-5] neurotransmitters,[6,8-16] and allergenic foods[17-23] may be involved in the pathogenesis of depression and migraine headache. This case report examines plasma amino acids, urinary neurotransmitter catabolites, and serum food antibodies in a patient with chronic depression and migraine headache before and after nutritional and dietary interventions.

CLINICAL HISTORY

A 40-year-old female, referred to as "ML" for the purpose of this case report, presented with mood swings, migraines, and weight gain. History revealed symptoms of depression that had been undiagnosed most of her life. Her migraines occurred approximately 4 to 6 times each week; they were worse around the time of menses and triggered by jogging. Her migraines would last up to 3 days without medication or would resolve within a few hours if she took medication. Additionally, she complained of mood swings, anxiety, and tension; hemorrhoids since pregnancy 8 years before; bloating, which was usually related to menstrual cramps; and mild allergy symptoms. The patient's past medical history is positive for allergy, for which she received allergy shots as a child.

The physical exam revealed varicose veins and cold extremities, but the general exam was otherwise unremarkable. Past treatment for her migraines included eletriptan hydrobromide (Relpax, Pfizer Inc, New York, New York), a serotonin receptor agonist, as needed. Additionally, the patient took ibuprofen and used an etonogestrel/ethinyl estradiol vaginal ring (NuvaRing, Organon USA, Roseland, New Jersey). She was not taking medication for the mood swings or depression. Clinical diagnoses were (1) depressive disorder not elsewhere classified with pronounced mood swings (ICD-9 code 311) and (2) other forms of migraine without mention of intractable migraine or status migrainosus (ICD-9 code 346.80).

TREATMENT

During the first office visit, ML was prescribed fish oil (1 capsule twice daily) and Women's Symmetry, a multi–vitamin-mineral from Vitanica (Tualatin, Oregon). Medical laboratory tests completed in October 2006 showed low plasma amino acids (Table 1), low and low-normal urinary neurotransmitters metabolites (Figure 1), and moderate to severe IgG1 and IgG4 food antibodies (Table 2). During the second office visit, the clinician gave ML a customized free-form amino acid blend from Metabolic Maintenance (Sisters, Oregon). The composition of the amino acid formula based on ML's test results was 7.6% arginine, 8.1% histidine, 10.2% isoleucine, 14.7% leucine, 10.2% lysine, 9.1% methionine, 10.4% phenylalanine, 3.3% taurine, 7.8% threonine, 9.3% valine, 0.24% pyridoxine-5-phosphate, 6.9% alpha-ketoglutarate, 1.6% tryptophan, and 0.33% 5-hydroxytryptophan. The clinician prescribed .25 tsp in the morning, increasing by .25 tsp every 3 to 4 days, until reaching a dose of 1.5 tsp in the mornings.

The clinician encouraged a rotation diet plan. ML eliminated all foods with IgG1 and IgG4 levels of +4 and +5 for 1 month and then rotated them sparingly into her diet. Foods with +1 to +3 reactions were rotated no more often than twice a week. ML was prescribed probiotics (1 capsule daily) and 1 tsp of glutamine twice daily.

In the first month of treatment with the elimination diet and amino acid therapy, ML's headaches were triggered when some of the reactive foods were reintroduced. ML was started on Moducare by Thorne (Sandpoint, Idaho), a plant sterol product that reduces inflammatory immune response. Thereafter, she generally avoided the allergenic foods, only occasionally rotating them into her diet.

OUTCOME

After only 30 days of the treatment, ML noticed that the intensity and frequence of her migraines had decreased. She had not used eletriptan hydrobromide for the previous 21 days. ML explained to her physician that the headaches used to start behind the eyes, but after a month of treatment, they were diffuse and spreading across the forehead.

After maintaining this regimen for 90 days, ML felt more energetic and positive. She stated that she could "feel the positive

TABLE 1 Amino Acid Results for ML Before and After Treatment

	Pretreatment Results			Posttreatment Results		
Amino acid	Results umol/L	Status	Percentile ranking by quintile	Results umol/L	Status	Percentile ranking by quintile
Arginine	67	Normal	63-130	62	Normal	52-115
Histidine	73	Normal	67-101	63	Normal	54-96
Isoleucine	40	Low	47-98	33	Low	38-88
Leucine	72	Low*	87-161	72	Low	73-152
Lysine	115	Low	135-235	113	Low	117-216
Methionine	14	Low*	18-32	17	Normal	16-28
Phenylalanine	52	Normal	50-81	47	Normal	44-76
Threonine	82	Low	90-166	116	Normal	75-165
Tryptophan	41	Low	42-70	45	Normal	34-61
Valine	164	Low	167-305	135	Low	145-295
Glycine	165	Low	186-430	159	Normal	156-431
Serine	43	Low*	77-133	58	Low	59-119
Taurine	35	Low	37-103	32	Normal	32-116
Tyrosine	30	Low*	47-89	31	Low	39-85
Asparagine	37	Normal	36-60	37	Normal	31-58
Aspartic acid	9	Normal	6-15	9	Normal	5-15
Citrulline	25	Normal	25-51	23	Normal	21-49
Glutamic acid	19	Low*	33-144	20	Low	27-153
Glutamine	443	Low	456-641	402	Normal	389-626
Ornithine	32	Low	41-107	19	Low*	33-99

Before treatment, ML had many low amino acids and some were very low. After treatment, 6 amino acids increased and were within normal limits, but some amino acids were still low. Results below the 20th percentile are designated as low. Results falling between the 21st percentile and 97.5th percentile are normal.

*Results that were lower than the 2.5th percentile (95% reference limit).

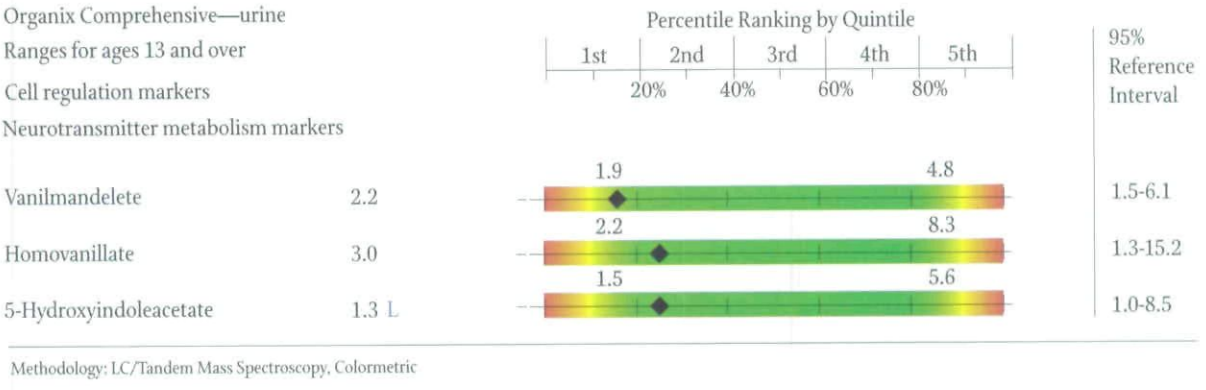

FIGURE 1 Organic acid results for ML in October 2006. Neurotransmitter markers are low to low-normal, indicating depletion of precursor substrate.

effects of the amino acids on mood and energy" and that the frequency of migraine attacks was greatly reduced. She stated that her mood was much more even, without the big swings she experienced in the past. She said that after treatment she experienced migraine attacks only with menses, whereas she used to get migraines "all the time." Previously, she took medication weekly for migraines, but after treatment, she needed it only once per month and sometimes did not take it during an attack. She did occasionally use eletriptan hydrobromide for exertion migraines. She admitted that the rotation diet, especially avoidance of eggs and dairy, was difficult, and she believed if she could comply with the diet better, she would feel even better.

METHODS

Fasting blood was drawn then centrifuged, yielding 3 mL plasma and 3 mL serum. The patient collected first morning

TABLE 2 IgG1 and IgG4 Antibodies (90 Antigens) Found in Serum in October 2006

IgG1 and 4 Food Antibodies		
Class Definitions		
Class		**Cutoffs**
Negative		0-75
Mild (+1/+2)		75-150
Moderate (+3/+4)		300/500/800
Severe (+5)		> 801
Meat and Poultry	**Results ng/mL**	**Class**
Beef	32	
Casein	1101	Severe +5
Chicken	182	Moderate +2
Egg, White	1418	Severe +5
Egg, Yolk	697	Moderate +4
Lamb	36	
Milk	1149	Severe +5
Nuts/Seeds		
Almond	234	Moderate +2
Cashew	348	Moderate +2
Coconut	<25	
Pecan	<25	
Pistachio	142	Mild +1
Sesame	26	
Sunflower	171	
Walnut	<25	
Vegetables		
Asparagus	154	Moderate +2
Avocado	184	Moderate +2
Broccoli	66	
Cabbage	<25	
Carrot	<25	
Cauliflower	199	Moderate +2
Celery	<25	
Cucumber	170	Moderate +2
Garlic	203	Moderate +2

urine, and all plastic tubes were frozen and shipped with ice packets to Metametrix Clinical Laboratory (Duluth, Georgia), where urine and blood were processed.

Urine was analyzed for homovanillate (HVA), 5-hydroxyindoleacetate (5-HIAA), and vanilmandelate (VMA), among other organic acids. 5-HIAA was measured as described by Bishop et al[24] using high-performance liquid chromatography (HPLC) separation prior to tandem mass spectrometry (LC/MS/MS) with an electrospray source in positive mode. VMA and HVA were separated using reversed phase HPLC prior to detection via negative mode electrospray ionization and introduction to a tandem mass spectrometer, as described by Crow et al.[25]

Plasma amino acids were measured using reversed phase HPLC. The amino acids were precolumn derivitized using orthophthaldehyde. The optically active derivatives were detected with a Waters 2475 fluorescence detector.

Reference ranges for amino acids and organic acids were established using a nonparametric method consistent with medical laboratory procedures.[26] Results for an outpatient population consisting of more than 120 people were ranked in order of increasing concentration. The 95% reference limits are defined by the 2.5th percentile and the 97.5th percentile and enclose 95% of the values. Results that fall within these limits are "normal." Results outside of the 95% limits are approximately 2 standard deviations from the mean and are abnormal. Percentile ranking by quintile was used to detect preclinical abnormalities. Using the same method as described above, the results for a population were listed in order of magnitude and divided into quintiles. The reference limits enclose 80% of the values and are shown in small numbers above the bar graphs on the laboratory report. The green color on the bar graphs indicates the 80% range.

Quantitative measurement of human IgG1 and IgG4 was done by enzyme immunoassay. Food antigens from a standard preparation were adsorbed to the wells of a microtiter plate. Nonspecific protein binding was blocked with casein. Human serum reacted with the plastic-bound food antigens. The specifically bound human IgG food-specific antibodies were reacted with a mouse antihuman IgG1 and 4 biotin conjugated antibody. The biotin conjugated antibody was detected using an horseradish peroxidase (HRP)–based signal amplification system. An enzyme substrate was added, and the color reaction measured was directly proportional to the quantity of specific IgG1 and 4 present in the serum sample. Antibody concentrations in ng/mL were calculated by comparing them to standard preparations of human IgG1 and IgG4 (Sigma-Aldrich, St Louis, Missouri).

In the interim between the first test and the posttreatment test, the method was modified to detect only IgG4 antibody production and class definitions were adjusted. The resulting data for the IgG concentrations bound to 90 common food antigens was reported, along with a ranking of the degree of response: mild, moderate, or severe.[27]

LABORATORY RESULTS

Analysis of plasma amino acids revealed a general pattern of low essential amino acids (Table 1). In particular, tryptophan and tyrosine were very low (below the 95% reference limits). Phenylalanine was low-normal. Fourteen of 20 amino acids measured were below the 20th percentile of the population. Five out of 20 were in the lower 2.5th percentile of the population. As shown in Figure 1, VMA and HVA were below the 30th percentile of the population and 5-HIAA was low. The other organic acids (not shown) were within normal limits. ML showed severe IgG1 and IgG4 food antibodies to casein, milk, and egg white (Figure 2). She showed moderate antibody reactions to 22 foods and mild antibody reactions to 5 foods.

The second battery of tests, completed after 6 months of treatment showed that plasma amino acids overall increased, yet

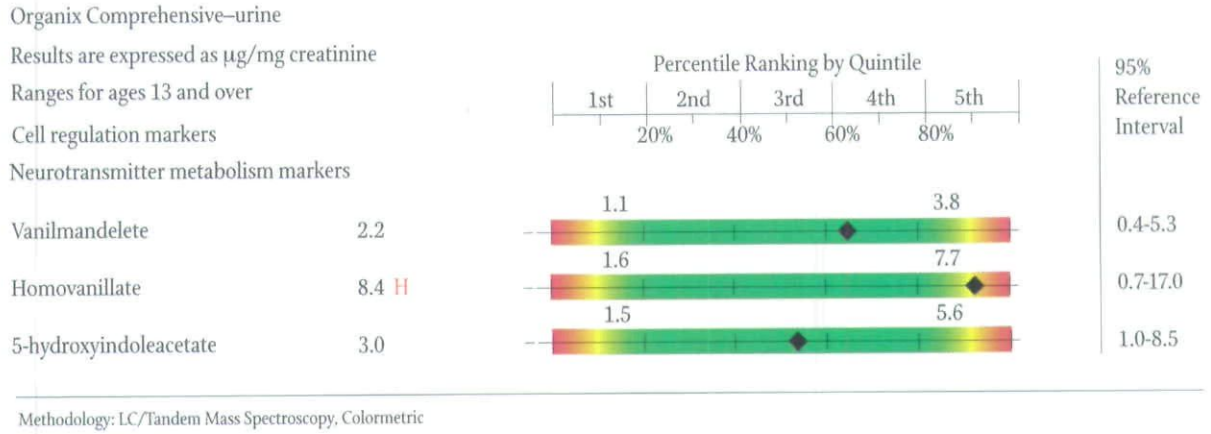

FIGURE 2 Organic acid results for ML in October 2006. Neurotransmitter markers are low to low-normal, indicating depletion of precursor substrate.

some were still low (Table 1). Methionine, tryptophan, threonine, glycine, and glutamine increased and were within normal limits after treatment. The following amino acids increased in plasma but were below the 20th percentile even after treatment: tyrosine, leucine, serine, and glutamic acid. Ornithine was even lower after treatment.

Neurotransmitter metabolic products, VMA, HVA, and 5-HIAA all increased significantly, and HVA was higher than the 90th percentile of the population (Figure 2). Food antibody production was lowered significantly, both the number of foods and the class of reaction (Table 3). ML showed a moderate antibody response to egg white and mild antibody reactions to casein, milk, and mustard greens. All other foods were negative.

DISCUSSION

The patient's initial amino acid results showed many low amino acids, including low tryptophan and tyrosine, which is consistent with other reports of mood disorders and depression.[1,3] Her low 5-HIAA and low-normal VMA corroborate accounts of low serotonin and low norepinephrine in migraine headache attacks.[1,11] Serotonin (5-hydroxytryptamine) is derived from the amino acid tryptophan, and serotonin is excreted in urine as 5-HIAA. Initially, ML's tests showed low tryptophan and low 5-HIAA, suggesting that her available serotonin pool was low. With treatment, tryptophan and 5-HIAA normalized, suggesting that tryptophan levels and serotonin synthesis in the central nervous system improved.[28,29] It is likely that both tryptophan and 5-HTP in the amino acid mixture contributed to the increased 5-HIAA and much of this 5-HIAA may have come from the gastrointestinal tract.[30] While tryptophan normalization alone could have resulted in improved mood and decreased depression,[1,3] the patient dramatically reduced her dosage of eletriptan hydrobromide, the serotonin receptor agonist. This would be additional evidence that endogenous serotonin production normalized.

Increases in norepinephrine, epinephrine, and dopamine may have explained ML's improved mood. Dopamine, norepinephrine, and epinephrine are derived from the amino acids phenylalanine and tyrosine. These neurotransmitters are then catabolized to VMA (norepinephrine and epinephrine) or HVA (dopamine). Norepinephrine is decreased in depression,[1] and pharmacological therapies for depression often target norepinephrine; low levels of HVA have been seen in depression with suicide attempts, alcoholism, and aggression.[15,16] Mild increases in ML's plasma levels of tyrosine, while still below the 20th percentile, could have increased norepinephrine and dopamine levels and thereby increased VMA and HVA. Finally, increases in methionine may have increased S-adenosyl-L-methionine levels, resulting in an antidepressant effect.[29]

The patient showed severe reactions to casein, milk, and egg white. This is consistent with findings that cheese,[31] dairy, and eggs trigger migraines.[18] Moderate to severe IgG1 and IgG4 antibody production to many foods showed that ML had increased intestinal permeability.[32-34] After eliminating the offending foods, reintroduction of the foods triggered migraines, suggesting that antigenic foods may have been one causative factor of ML's migraine attacks. After treatment, ML showed only mild and moderate IgG4 antibody production to milk, egg, and mustard green antigens.

After the first test, the serum food antibody method was modified to detect only IgG4 antibody production, and this could explain the decrease of food antibodies. However, a similar principal underlies both tests: reactions to many foods indicate intestinal permeability. The follow-up IgG4 test showed a dramatic decrease in antibodies produced against different foods. Thus, the results suggested that ML had a less permeable intestinal barrier and decreased exposure to the food antigens. This was consistent with her symptomatic improvement: fewer and less severe migraine headaches.

Food allergy, inflammation, and intestinal permeability may have caused depletion of amino acids and subsequent depletion of neurotransmitters, contributing to depression and migraines. After treatment with a rotation diet, individualized free-form amino acids, glutamine, and an immune response modulator, plasma amino acids increased, 5-HIAA and VMA normalized, and the patient showed less food antibody production. Her

TABLE 3 IgG4 Antibodies Found in Serum in April 2007

Class Definitions		
Class		**Cutoffs**
Negative		0-40
Mild (+1/+2)		80/150
Moderate (+3/+4)		500/900
Severe (+5)		> 900
Meat and Poultry	**Results ng/mL**	**Class**
Beef	12	
Casein	76	Mild +1
Chicken	<10	
Egg, white	240	Moderate +3
Egg, yolk	38	
Lamb	<10	
Milk	50	Mild +1
Pork	<10	
Turkey	18	
Nuts/Seeds		
Almond	<10	
Cashew	<10	
Coconut	<10	
Pecan	<10	
Pistachio	<10	
Sesame	<10	
Sunflower	171	
Walnut	<25	
Vegetables		
Asparagus	<10	
Avocado	<10	
Broccoli	<10	
Cabbage	<10	
Carrot	<10	
Cauliflower	17	
Celery	<10	
Cucumber	<10	
Garlic	<10	

migraines decreased in frequency and severity, her reliance on eletriptan hydrobromide was reduced, her energy levels increased, and her mood swings resolved.

Based on these results, it appears that amino acid abnormalities, subsequent neurotransmitter dysregulation, and compromised intestinal barrier function were underlying the patient's chief complaints. This therapeutic approach may be a useful, cost-effective method for the treatment of patients with depression and migraine headache.

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