



The TRIADSM Profile in Depression and Migraine Headache: A Case Study



Standard medical treatments for major depressive disorder and migraine headache are only partially effective. Clinical improvement requires correction of underlying metabolic difficulties. This case illustrates the power of multiple markers to focus on key metabolic issues. With a little training any practitioner can learn to see the patterns that emerge from a TRIADSM report where organic acids, amino acids and food-specific IgG4 antibodies are reported. Organic acids provide insight into metabolism, cellular energy production, neurotransmitters, phase 1 and phase 2 hepatic detoxification, glutathione status, and xylene exposure. Other markers indicate overgrowth of small intestine bacteria or yeast. The amino acid profile identifies amino acid precursors for neurotransmitters and energy production. It also shows digestion, absorption, long-term depletion, and utilization of amino acids. The IgG4 results identify potentially antigenic foods that may be causing patient symptoms. The following case study of Maggie, who suffered with depression and migraine headaches, demonstrates the progress that can be made when treatment is guided and monitored by functional medical testing.

Amino Acid Analysis - 20 Plasma

Methodology: ION Exchange HPLC

Ranges are for ages 13 and over. Results umol/L



95% Reference Interval

Essential Amino Acids

Rank	Amino Acid	Results umol/L	Percentile	95% Reference Interval
1	Arginine	67	63	42 - 130
2	Histidine	73	67	53 - 101
3	Isoleucine	40 L	47	37 - 98
4	Leucine	72 L	87	73 - 161
5	Lysine	115 L	135	109 - 235
6	Methionine	14 L	18	15 - 32
7	Phenylalanine	52	50	43 - 81
8	Threonine	82 L	90	67 - 166
9	Tryptophan	41 L	42	34 - 70
10	Valine	164 L	167	134 - 305

Essential Amino Acid Derivatives

Neuroendocrine Metabolism

Rank	Derivative	Results umol/L	Percentile	95% Reference Interval
11	Glycine	165 L	186	138 - 430
12	Serine	43 L	77	60 - 133
13	Taurine	35 L	37	26 - 103
14	Tyrosine	30 L	47	37 - 89

OrganixTM Comprehensive - Urine

Methodology: LC/Tandem Mass Spectroscopy, Colorimetric

Ranges are for ages 13 and over.

CELL REGULATION MARKERS

Neurotransmitter Metabolism Markers

(Tyrosine, Tryptophan, B6, antioxidants)



95% Reference Interval

Rank	Marker	Results	Percentile	95% Reference Interval
22	Vanilmandelate	2.2	1.9	1.5 - 6.1
23	Homovanillate	3.0	2.2	1.3 - 15.2
24	5-Hydroxyindoleacetate	1.3 L	1.5	1.0 - 8.5
25	Kynurenate	0.7	1.5	<= 2.5
26	Quinolate	4.0	10.2	<= 16.5

CASE STUDY

Medical History: Maggie, a 40-year-old female, suffered from severe depression as far back as she could remember. She never used antidepressants but had migraines triggered by exercise around the time of menstruation. She took fish oil and a multi-vitamin. She took Relpax for frequent, severe migraines. Relpax, or eltiptan hydrobromide, is effective for migraines because it is a 5-hydroxytryptamine (serotonin) receptor agonist.

Lab Results: In October 2006, a fasting plasma specimen revealed a general pattern of low essential amino acids (Figure 1). In particular, tryptophan and tyrosine were very low. Phenylalanine was low-normal. Vanilmandelate (VMA) and homovanillate (HVA), were low-normal; 5-hydroxyindoleacetate (5-HIA) was low (Figure 1). The other organic acids (not shown) were within normal limits. Maggie showed food antibodies to many foods (Figure 2), although she did not complain of GI symptoms. The clinician was surprised to find so many food reactions.

Figure 1. Amino acid and organic acid results for Maggie in October 2006. Many essential and conditionally essential amino acids (or essential amino acid derivatives) are low and neurotransmitter markers are low to low-normal, indicating slow rates of formation and high utilization that may be improved by increasing amino acid plasma levels through supplementation.

IgG1 & 4 Food Antibodies (90 Antigens)		
Class Definitions		
Class	Cutoffs	
Negative	0 - 75	
Mild (+1/+2)	75 - 150	
Moderate (+3/+4)	300/500/800	
Severe (+5)	> 801	
Results ng/mL	Class	
Meat and Poultry		
Beef	32	
Casein	1,101	Severe +5
Chicken	182	Moderate +2
Egg, White	1,418	Severe +5
Egg, Yolk	697	Moderate +4
Lamb	36	
Milk	1,149	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		
Avocado	184	Moderate +2
Asparagus	154	Moderate +2
Broccoli	66	
Cabbage	<25	
Carrot	<25	
Celery	<25	
Cauliflower	199	Moderate +2
Cucumber	170	Moderate +2
Garlic	203	Moderate +2

Figure 2. IgG1 & IgG4 antibodies found in Maggie's serum in October, 2006.

Background Biochemistry: VMA is the break-down product of norepinephrine and epinephrine. HVA is the break-down product of dopamine. 5-HIA is the break-down product of serotonin. Norepinephrine, epinephrine, and dopamine are all derived from the essential amino acid phenylalanine, later converted to tyrosine (Figure 3). Serotonin is derived from tryptophan (Figure 4). Due to these biochemical relationships, patients with psycho-emotional disorders should have amino acids and organic acids evaluated as part of a standard work-up. Note that the prognosis of positive response to amino acids is greatly strengthened by examining both the metabolic precursors and products of neurotransmitter pathways. Maggie may have experienced a vicious cycle of maldigestion and malabsorption along with depression leading to poor appetite and little hope for achieving wellness. Daily dosing with free-form amino acids requires no digestive power. Amino acids quickly enter the blood and can enhance production of these catecholamine neurotransmitter compounds.

Moderate to severe antibody production to many foods shows that Maggie may have leaky gut or increased intestinal permeability. This means that large food peptides cross the intestinal membrane into circulation where the immune system recognizes them as foreign, thereby producing antibodies against the peptides. Maggie may have had poor amino acid absorption due to the intestinal permeability which may have also been aggravated by low amino acids. It is possible that Maggie's reactions to foods created maldigestion and malabsorption, ultimately leading to depletion of amino acids and serotonin with resulting depression and migraines. Treatment for increased intestinal permeability includes nutrients for the enterocytes (glutamine, zinc, pantothenic acid), anti-inflammatory medical food, and eliminating allergens. The massive metabolic task of maintaining tight small intestinal cell-cell junctions requires sustained levels of plasma essential amino acids during overnight fasting when anabolic processes are maximal.

Treatment: The clinician encouraged the dietary changes as directed in the TRIAD rotation diet plan and gave Maggie a basic amino acid blend (Metabolic Maintenance) starting at ¼ teaspoon in the morning and increasing ¼ teaspoon until reaching 1½ tsp in the mornings. In addition, Maggie took one teaspoon of glutamine twice daily. She eliminated all foods with IgG4 levels of +3, +4, and +5 for 1 month and then rotated them sparingly into her diet. In the first month of treatment with the elimination diet and amino acid therapy, Maggie's headaches were triggered when some of the reactive foods were reintroduced. Maggie was started on Moducare (Thorne) which is a plant sterol product that is an immune modulator. Thereafter, she avoided the allergenic foods but occasionally rotated them into her diet.

Clinical Follow-up: After maintaining this regimen for 90 days, the clinician reported that the patient was feeling more energetic and more positive. Previously, she took Relpax once every week for migraines, but after treatment, Maggie was able to reduce the Relpax to just once per month. For her most recent 3 migraine headaches, she only had to take the Relpax once. The use of free-form essential amino acids, glutamine and Moducare, resulted in less severe and less frequent migraine headaches. Her depression was also much improved. Maggie's affect had dramatically changed. Initially she had a flat affect because she was in chronic pain and depressed, the clinician explained. In January, Maggie said that running still triggered migraine headaches. Maggie was steadily improving at the time of her last visit at which time the clinician planned a follow-up visit in 3 months. The follow-up testing confirmed Maggie's metabolic improvement.

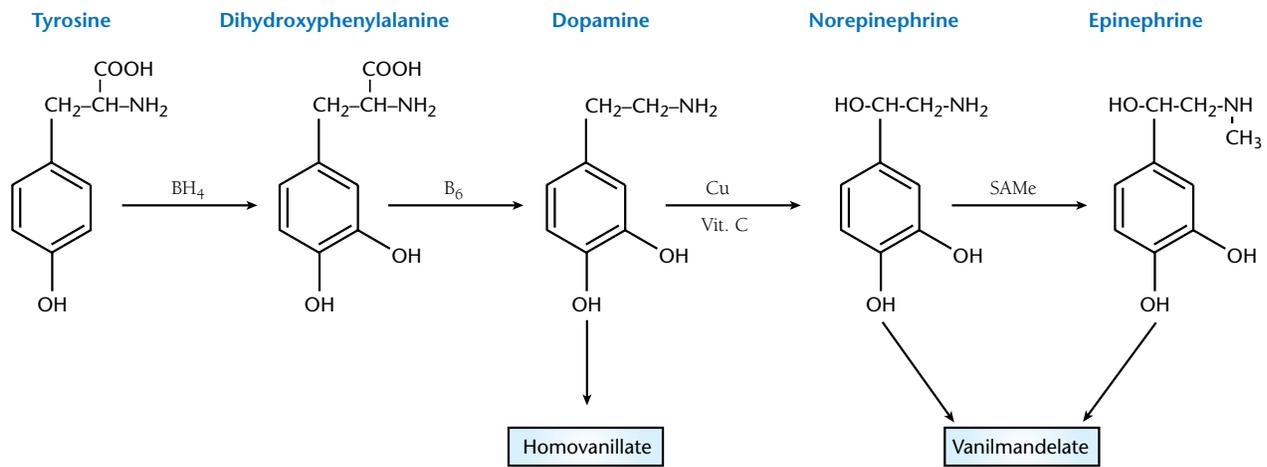


Figure 3. Dopamine, norepinephrine, and epinephrine production. Tyrosine is the amino acid precursor of dopamine (catabolized to homovanillate) and norepinephrine and epinephrine (catabolized to vanilmandelate). Some cofactors in these reactions are shown: tetrahydrobiopterin (BH₄), pyridoxine (B₆), copper (Cu), vitamin C, and SAMe. Phenylalanine is the essential amino acid precursor to tyrosine, not shown here.

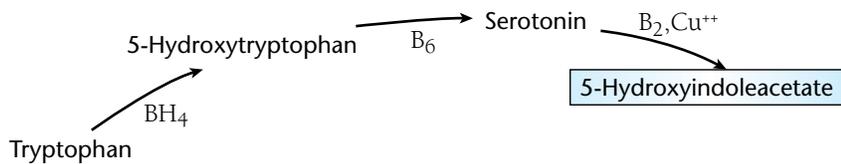


Figure 4. Serotonin production. Tryptophan is the amino acid precursor to serotonin which is catabolized to 5-hydroxyindoleacetate. Cofactors shown in these reactions are tetrahydrobiopterin (BH₄), pyridoxine (B₆), riboflavin (B₂) and copper (Cu).

Lab Results: The second TRIAD panel, completed in April 2007, shows some essential amino acids were still low, but improved (Figure 5). Fasting phenylalanine, and especially tryptophan, have risen and are within normal limits. Tyrosine was still low, as well as other amino acids. In the interim, reference ranges changed, so quantitative results cannot be compared directly. Low, normal or high results may be compared relative to their previous quintile positions. Maggie should continue on amino acid supplementation as well as protein digestion and absorption support.

Other organic acids were elevated (Figure 6). Previously she did not show B-vitamin or CoQ10 need. This is commonly seen after supplementing amino acids in an amino-acid deplete individual because amino acids are the precursors of organic acids. Further, the higher rates of protein synthesis, due to additional amino acids, places new strain on cofactor pools such as B vitamins and CoQ10. In the second TRIAD panel, Maggie showed need for CoQ10 and B vitamins to support the new levels of tissue maintenance and neurotransmitter synthesis.

An analogy can be made comparing the body's metabolism with a car. A car must have gas in order to see if the transmission is working properly. If the car is out of gas, then one can only assume the transmission is in good working order. However, once gas is put in the car and the engine is running, the underlying transmission problem can be identified. When Maggie put more amino acids (fuel) into her energy production and biosynthesis pathways, underlying deficiencies of B vitamins and CoQ10 (or problematic transmission) were discovered. The changes in her laboratory data inform the clinician of Maggie's need for added support during this transitional rebuilding phase. As the needed cofactors are supplied, the dosing with free form amino acids may be increased to twice daily to enhance progress.

Amino Acid Analysis - 20 Plasma

Methodology: ION Exchange HPLC

Ranges are for ages 13 and over.

Results umol/L

Percentile Ranking by Quintile



95% Reference Interval

Essential Amino Acids

Rank	Amino Acid	Result (umol/L)	Percentile	95% Reference Interval
1	Arginine	62	52	39 - 115
2	Histidine	63	54	42 - 96
3	Isoleucine	33 L	38	31 - 88
4	Leucine	72 L	73	60 - 152
5	Lysine	113 L	117	95 - 216
6	Methionine	17	16	13 - 28
7	Phenylalanine	47	44	39 - 76
8	Threonine	116	75	57 - 165
9	Tryptophan	45	34	26 - 61
10	Valine	135 L	145	118 - 295

Essential Amino Acid Derivatives

Neuroendocrine Metabolism

Rank	Amino Acid	Result (umol/L)	Percentile	95% Reference Interval
11	Glycine	159	156	124 - 431
12	Serine	58 L	59	48 - 119
13	Taurine	32	32	25 - 116
14	Tyrosine	31 L	39	31 - 85

Figure 5. Amino acid results for Maggie in April 2007. Some amino acids are low.

5-Hydroxyindoleacetate was low before but in the second test, 5-HIA was normal, showing a stimulation of serotonin production and utilization. Normalized serotonin probably explains Maggie's reports of fewer and less severe migraine headaches with less reliance on the serotonin agonist medication. Her previously low vanilmandelate and homovanillate, due to phenylalanine and tyrosine depletion, shifted to normal and even fifth quintile, respectively. The increased bacterial and fungal activity in the gut, indicated by high bacterial and fungal compounds in urine, may be further signs of the generally increased nutrient intake and digestive system activity.

Food antibodies dramatically improved, attesting to a strengthened physical barrier to antigen penetration (Figure 7). After treatment, Maggie showed only mild and moderate IgG4 production to milk, egg, and mustard greens. Although her intestinal permeability appears to have improved, Maggie still needs to be vigilant with her GI health by using probiotics and prebiotics and eliminating or rotating IgG4-positive foods. There may be fluctuations in food antibodies and dysbiosis markers as gut mucosa and microbiota are restored to healthy balance.

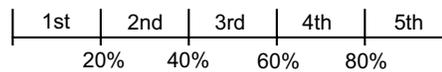
0091 OrganixTM Comprehensive Profile

Methodology: LC/Tandem Mass Spectroscopy, Colorimetric

This report is not intended for the diagnosis of neonatal inborn errors of metabolism.

Ranges are for ages 13 and over.

Percentile Ranking by Quintile



95% Reference Interval

Energy Production (Citric Acid Cycle)
(B comp., CoQ10, Amino acids, Mg)

11 Succinate	24.3	H	18.6	1.1 - 34.0
12 Fumarate	1.36	H	0.71	<= 1.40
13 Malate	2.4	H	2.3	<= 4.3
14 Hydroxymethylglutarate	5.3		6.8	<= 9.7

B-Complex Vitamin Markers
(B1, B2, B3, B5, B6, Biotin)

15 a-Ketoisovalerate	1.43	H	0.60	<= 0.94
16 a-Ketocaproate	0.59	H	0.39	<= 0.58
17 a-Keto-β-Methylvalerate	1.6		1.6	<= 2.7
18 Xanthurenate	1.0	H	0.70	<= 1.2

Neurotransmitter Metabolism Markers
(Tyrosine, Tryptophan, B6, antioxidants)

22 Vanilmandelate	2.6		1.1, 3.8	0.4 - 5.3
23 Homovanillate	8.4	H	1.6, 7.7	07 - 17.0
24 5-Hydroxyindoleacetate	3.0		1.5, 5.6	1.0 - 8.5

COMPOUNDS OF BACTERIAL OR YEAST/FUNGAL ORIGIN

Bacterial - general

35 Benzoate	12.0	H	2.5	<= 8.2
36 Hippurate	312		542	<= 1,099
37 Phenylacetate	< 0.06		0.06	<= 0.20
38 Phenylpropionate	< 0.5		0.5	<= 0.5
39 p-Hydroxybenzoate	1.7	H	1.2	<= 2.8
40 p-Hydroxyphenylacetate	18		20	<= 35
41 Indican	113	H	80	<= 124
42 Tricarballoylate	2.3	H	1.6	<= 3.6

L. acidophilus / general bacterial

43 D-Lactate	2.0		5.5	<= 11.0
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Clostridial species

44 3,4-Dihydroxyphenylpropionate	< 0.16		0.16	<= 0.40
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Yeast / Fungal

45 D-Arabinitol	35	H	32	<= 59
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Figure 6. Organic acid results for Maggie in April 2007. Markers for CoQ10 and B vitamins are elevated.

IgG4 Food Antibodies (90 Antigens)		
Class Definitions		
Class	Cutoffs	
Negative	0 - 40	
Mild (+1/+2)	80/150	
Moderate (+3/+4)	500/900	
Severe (+5)	> 900	
Results ng/mL	Class	
Meat and Poultry		
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		
Avocado	< 10	
Asparagus	< 10	
Broccoli	< 10	
Cabbage	< 10	
Carrot	< 10	
Celery	< 10	
Cauliflower	17	
Cucumber	< 10	
Garlic	< 10	

Figure 7. IgG4 antibodies found in Maggie's serum in April 2007.

Conclusions: The TRIAD includes 20 amino acids, 90 food allergens, and 45 organic acids and can be used to evaluate multiple aspects of digestion, absorption, GI membrane permeability, long-term food reactions, small intestinal dysbiosis, energy metabolism, vitamin deficiencies, neurotransmitters and biotransformation. This case illustrates how simple dietary modification and focused nutrient interventions can bring relief from life-long depression and severe migraine headaches. The patient experienced great improvement in symptoms and decreased her reliance on prescription medication because she addressed the underlying causes of her illness, rather than the symptoms alone. While this approach takes time and patience, Maggie has been given tools for her body to achieve long-term normalcy and health. This not only improves Maggie's health in the short-term but may decrease her risk of developing complex, chronic disease as she ages.



Case contributed by Dr. Stephanie Kaplan, ND. Case analysis by Cass Nelson-Dooley, MS in the Science & Education Department, Metametrix Clinical Laboratory.

If you have an interesting case you would like to see developed into a case study by the Metametrix Science and Education Department, please contact us at 800.221.4640 or e-mail to memo@metametrix.com.