

Metamatrix Teleconference

Evaluating Mitochondrial Function in Chronic Disease

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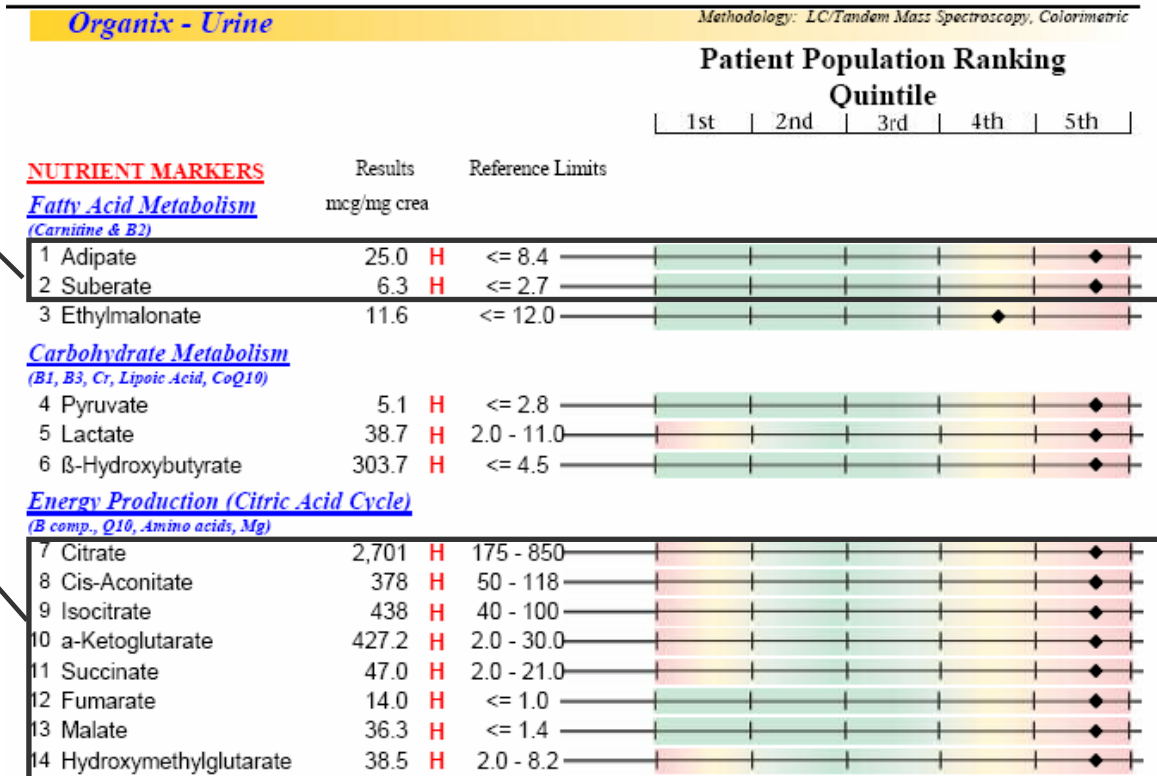
Mitochondrial Function Assessment by Urinary Organic Acids

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Case 1 – Neonatal mitochondrial disorder diagnosis confirmed by muscle biopsy

2 y/o F who had been diagnosed with a mitochondrial disorder at Mayo clinic



Here we see multiple, profound elevations of both carnitine and CoQ10 markers. Note that it is the markers specific for fatty acid transfer into the mitochondrion, adipate and suberate, which are elevated. Ethylmalonate is an intermediate in an extra-mitochondrial carnitine requiring step. Thus, the dysfunction is specific to mitochondrial activity in this case rather than a dietary or intestinal origin of carnitine insufficiency.

Note also how the mitochondrial dysfunction results in ketosis, indicated by the very high beta-hydroxybutyrate, along with pyruvic and lactic acidurias as a consequence of glycolytic pathway intermediate accumulation and overflow into urine. The extremely high level of hydroxymethylglutarate is a sign that the biochemical lesion may lie in the CoQ10 biosynthetic pathway rather than polymorphism of citric acid cycle or electron transport enzymes. Such a mitochondrial blockage at the level of the electron transport system causes cytosolic accumulation of pyruvate and lactate as well.

Case 2 – Effects of supplementation effects on depression

50 y/o F

Test 1- while on CoQ & B-complex supplements

0091 Urine Organix Profile			
	Results	Reference Limits	
	mcg/mg crea		
Fatty Acid Metabolism (Carnitine & B2)			
1 Adipate	2.1	<= 3.0	
2 Suberate	2.0	<= 4.0	
3 Ethylmalonate	5.6 H	<= 4.0	
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8 Citrate	1.3/3	500 - 2,300	
9 Cis-Aconitate	156	5 - 250	
10 Isocitrate	793	50 - 800	
11 a-Ketoglutarate	14.9	3.0 - 25.0	
12 Succinate	6.6	5.0 - 35.0	
13 Fumarate	1.6 H	0.2 - 1.2	
14 Malate	5.7	<= 6.0	
15 Hydroxymethylglutarate	0.51	0.20 - 1.00	

Test 2 - after one week off of supplements

0091 Urine Organix Profile			
	Results	Reference Limits	
	mcg/mg crea		
Fatty Acid Metabolism (Carnitine & B2)			
1 Adipate	2.5	<= 3.0	
2 Suberate	1.6	<= 4.0	
3 Ethylmalonate	6.0 H	<= 4.0	
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8 Citrate	2,759 H	500 - 2,300	
9 Cis-Aconitate	381 H	5 - 250	
10 Isocitrate	> 2000.00 H	50 - 800	
11 a-Ketoglutarate	22.7	3.0 - 25.0	
12 Succinate	73.9 H	5.0 - 35.0	
13 Fumarate	4.7 H	0.2 - 1.2	
14 Malate	5.6	<= 6.0	
15 Hydroxymethylglutarate	3.00 H	0.20 - 1.00	

Note worsening of markers for CoQ10 when supplemental CoQ10 and multivitamin/mineral is discontinued. This individual has greater mitochondrial efficiency when micronutrient (esp. CoQ10) intake is increased.

Test 3 - 23 months later during episode of depression and memory loss

0091 Urine Organix Profile			Methodology: LC/Tandem Mass Spectroscopy, Colorimetric				
This report is not intended for the diagnosis of neonatal inborn errors of metabolism.			Patient Population Ranking Quintile				
			1st	2nd	3rd	4th	5th
NUTRIENT MARKERS							
Fatty Acid Metabolism (Carnitine & B2)							
	Results	Reference Limits					
	mcg/mg crea						
1 Adipate	12.0 H	<= 8.4	[Progressive Quintile Scale]				
2 Suberate	3.3 H	<= 2.7	[Progressive Quintile Scale]				
3 Ethylmalonate	22.2 H	<= 12.0	[Progressive Quintile Scale]				
Carbohydrate Metabolism (B1, B3, Cr, Lipoic Acid, CoQ10)							
4 Pyruvate	2.1	<= 2.8	[Progressive Quintile Scale]				
5 Lactate	4.2	2.0 - 11.0	[Progressive Quintile Scale]				
6 a-Hydroxybutyrate	13.5 H	<= 11.0	[Progressive Quintile Scale]				
7 β-Hydroxybutyrate	12.5 H	<= 4.5	[Progressive Quintile Scale]				
Energy Production (Citric Acid Cycle) (B comp., Q10, Amino acids, Mg)							
8 Citrate	716	175 - 850	[Progressive Quintile Scale]				
9 Cis-Aconitate	93	50 - 118	[Progressive Quintile Scale]				
10 Isocitrate	73	40 - 100	[Progressive Quintile Scale]				
11 a-Ketoglutarate	25.2	2.0 - 30.0	[Progressive Quintile Scale]				
12 Succinate	4.3	2.0 - 21.0	[Progressive Quintile Scale]				
13 Fumarate	0.3	<= 1.0	[Progressive Quintile Scale]				
14 Malate	0.4	<= 1.4	[Progressive Quintile Scale]				
15 Hydroxymethylglutarate	9.2 H	2.0 - 8.2	[Progressive Quintile Scale]				

Note full set of carnitine markers now appearing (box). These findings strongly suggest that a specific carnitine requirement has arisen from the stress that led to the depressive episode. The CoQ10 markers are largely clear at this time.

Case 3 – Chronic (genetic?) energetic factor in autism

- 4 y/o F, autistic
- 7 Organix profiles ordered between Jan. '02 and Nov. '03 (see next page)
- The severity of the initial abnormalities was lessened with supplemental carnitine and CoQ10 along with significant improvement in autistic behavior.
- Rather than simple dietary/digestive insufficiency, genetic origins of the metabolic disorder are indicated by the persistence of abnormalities over the two-year interval.
- Multiple additional abnormalities were found initially in the other organic acids not shown for this discussion. Many of those showed responses to nutrient interventions as will be discussed in future conference presentations.
- This data suggests that mitochondrial dysfunction of genetic origin contributed to the autistic presentation of this child.

Date of test: 1/22/2002 7/14/2002 9/30/2002

Fatty Acid Metabolism

(Carnitine & B2)

1 Adipate	3.5 H	<= 3.0	2.6	<= 3.0	1.4	<= 3.0
2 Suberate	6.4 H	<= 4.0	1.7	<= 4.0	5.1 H	<= 4.0
3 Ethylmalonate	3.0	<= 4.0	3.9	<= 4.0	2.0	<= 4.0

Carbohydrate Metabolism

(B1, B3, Cr, V)

4 Pyruvate	5.0 H	<= 0.7	< 0.10	<= 0.7	2.0 H	<= 0.7
5 Lactate	98.9 H	4.0 - 30.0	197.4 H	4.0 - 30.0	247.6 H	4.0 - 30.0
6 a-Hydroxybutyrate	76.8 H	<= 50.0	56.2 H	<= 50.0	10.1	<= 50.0
7 β-Hydroxybutyrate	70 H	<= 40	32	<= 40	20	<= 40

Energy Production (Citric Acid Cycle)

(B comp., Q10, Amino acids)

8 Citrate	> 7500.00 H	500 - 2,300	2,530 H	500 - 2,300	5,770 H	500 - 2,300
9 Cis-Aconitate	474 H	5 - 250	227	5 - 250	183	5 - 250
10 Isocitrate	1,751 H	50 - 800	1,982 H	50 - 800	1,415 H	50 - 800
11 a-Ketoglutarate	7.7	3.0 - 25.0	4.8	3.0 - 25.0	0.5 L	3.0 - 25.0
12 Succinate	236.8 H	5.0 - 35.0	352.5 H	5.0 - 35.0	136.2 H	5.0 - 35.0
13 Fumarate	1.7 H	0.2 - 1.2	1.0	0.2 - 1.2	2.1 H	0.2 - 1.2
14 Malate	6.9 H	<= 6.0	3.9	<= 6.0	7.7 H	<= 6.0
15 Hydroxymethylglutarate	2.78 H	0.20 - 1.00	1.59 H	0.20 - 1.00	1.15 H	0.20 - 1.00

Date of test: 12/26/2002 4/11/2003 7/6/2003 11/27/2003*

Fatty Acid Metabolism

(Carnitine & B2)

1 Adipate	19.9 H	<= 8.4	6.5	<= 8.4	17.4 H	<= 8.4	20.0 H	<= 8.4
2 Suberate	5.2 H	<= 2.7	4.9 H	<= 2.7	6.8 H	<= 2.7	5.0 H	<= 2.7
3 Ethylmalonate	5.2	<= 12.0	4.9	<= 12.0	7.8	<= 12.0	16.1 H	<= 12.0

Carbohydrate Metabolism

(B1, B3, Cr, Lipoic Acid, CoQ10)

4 Pyruvate	1.9	<= 2.8	2.5	<= 2.8	0.4	<= 2.8	3.1 H	<= 2.8
5 Lactate	0.3 L	2.0 - 11.0	25.4 H	2.0 - 11.0	35.4 H	2.0 - 11.0	16.3 H	2.0 - 11.0
6 a-Hydroxybutyrate	25.7 H	<= 11.0	18.9 H	<= 11.0	17.5 H	<= 11.0	16.3 H	2.0 - 11.0
7 β-Hydroxybutyrate	1.8	<= 4.5	2.6	<= 4.5	12.7 H	<= 4.5	375.0 H	<= 4.5

Energy Production (Citric Acid Cycle)

(B comp., Q10, Amino acids, Mg)

8 Citrate	1,283 H	175 - 850	898 H	175 - 850	1,196 H	175 - 850	953 H	175 - 850
9 Cis-Aconitate	252 H	50 - 118	183 H	50 - 118	168 H	50 - 118	236 H	50 - 118
10 Isocitrate	168 H	40 - 100	149 H	40 - 100	172 H	40 - 100	194 H	40 - 100
11 a-Ketoglutarate	0.9 L	2.0 - 30.0	17.1	2.0 - 30.0	8.4	2.0 - 30.0	101.3 H	2.0 - 30.0
12 Succinate	97.2 H	2.0 - 21.0	124.7 H	2.0 - 21.0	109.4 H	2.0 - 21.0	52.0 H	2.0 - 21.0
13 Fumarate	0.4	<= 1.0	1.0	<= 1.0	0.8	<= 1.0	3.8 H	<= 1.0
14 Malate	5.3 H	<= 1.4	3.4 H	<= 1.4	2.9 H	<= 1.4	6.3 H	<= 1.4
15 Hydroxymethylglutarate	19.9 H	2.0 - 8.2	10.3 H	2.0 - 8.2	24.3 H	2.0 - 8.2	15.5 H	2.0 - 8.2

*A rearrangement of analytes was done on the final report for the 11/27/2003 specimen so •-Hydroxybutyrate is not shown in these data. The 375.0 result is for •-hydroxybutyrate, showing a severe ketosis at this time.