The Significance of GAMT

Case Study by Bernarda Zenker, MD
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Chief Complaint

- 29 y.o. female, mother of 2 toddlers.
- Pain in every muscle.
- Pain every day. “Pain every day of my life.”
- Pain in every joint.
- Headache pain. “Headache every day.”
- Constant pain. Pain that never stops.
- Everywhere pain.
Symptoms

• Pain with muscle movement.
• Pain in every muscle.
• Pain in every joint.
• Pain in stomach with eating. Severe diet restrictions. “Feels better not to eat.”
• Pain in brain. Constant Headaches.
• Fatigue. Tired all the time, unrelieved w/rest.
• Insomnia: Painful to move. Stiff muscles.
Symptoms, cont.

• **Muscle pain** worsens with:
  – Weather Changes
  – Stress
  – Physical Activity

• **Started 5-Methylfolate & Methyl-B12:**
  – Felt better for 1 month, then worse
  – Migraine Headache w/ Rt-sided body weakness, worsening
  – EMG & Nerve Conduction Studies: Normal
Symptom History: Timeline

Child:  - awaken with stomach pain.
       - joints and muscle stiffen with use.
       - exercise intolerance

Teenage:  - periodic sore, swollen joints,
          - headaches,
          - stiff and painful muscles,
          - awaken tired w/ stomachache.

Young Adult:  - daily headaches, frequent migraines

Adult years:  - frozen/paralyzed “stiff” muscles at night.
              - tingling, coldness in hands, arms, feet.
              - exercise makes pain worse, even 15 minutes.
              - diet severely restricted: painful to eat. Heartburn.
              - daily headaches. Painful to think.
Review of Systems: 29 yr. old female

- **HEENT:** Headaches, daily, worse in AM
  - Ringing in ears, Sinus congestion frequent, dry mouth
- **Resp:** Difficulty catching breath
- **Cardiac:** SOB w/exertion (5-10vmnutes), Episodic Palpitations
- **GI:** Stomachache in AM, Pain w/eating, Mucous in Stools
- **GYN-Urinary:** Hx. Endometriosis
- **Neuro-Muscular:** Joints achy & swollen
  - Muscle stiff & frozen, worse at night, hurt w/exertion
- **Neurologic:** Tingling in fingers and toes, memory problems
Review of Systems: 29 yr. old female

- **Exercise:** 15 minutes of exercise causes severe pain
- **Sleep:** Awaken w/pain q 2-3 hrs, hurts to turn over in bed
  - awaken with still “frozen, paralyzed” muscles
- **Diet:**
  - Organic diet
  - Gluten Free
  - Dairy free
  - Sugar free
  - “I usually wake up with a stomachache, so I don’t want to eat. Sometimes when I don’t eat, I actually feel better.”

- **Review of old records:** “I have been complaining of the same symptoms my entire life.”
Medications

• Levothyroxine, 30-60 mcg, QOD (self-adjusting)

• Supplements:
  – D3, 5000iu/day
  – Vitamin C, 1000mg/day
  – 5-L-Methylfolate, 800mcg/day
  – Methyl-B12, 1000mcg/day
  – Omega-3, 1280 mg/day
  – Mega-Flora Probiotics, 20 billion CFU/day
Physical Findings

• HEENT:  PERRLA, EOMI, Neck-supple, TM’s-full
  Sinuses-Max Sinus full to palpation
• Cardiac:  Heart RRR, no Bruits, no JVD, Pulses equal bil
• Respiratory:  Clear, w/o wheezes or Rhonchi
• GI:  Abd soft, mild mid-epigastric tenderness, BS normal
• Neuro-Musc:  no atrophy, reflexes normal, poor strength
• Skin:  no rashes, no abnormal lesions
• Psych:  No anxiety, no depressive symptoms
Lab Testing (per Neurologist)

• Complete Blood Cell w/Diff:
  – H/H: 11.2/35.2
  – RDW: 9.8
  – MCV: 92.3
  – Platelets: 202,000
  – Indices: Normal

• Complete Metabolic Panel:
  – Na/K: 141/4.2
  – Creatinine: 0.70
  – AST/ALT: 16/12
Lab Testing (per Neurologist)

- TSH: 3.860
- Homocysteine: 5.8
- ANA: Negative
- CRP: 1.2 (0.0-4.9)
- Sed Rate: 12
- HIV Panel: Negative
- Hepatitis Panel: Negative
- RPR (Rapid Plasma Antigen): Negative
- Aldolase: 6.5 U/L (3.3-10.3)
- LDH: 137 IU/L (119-226)
- Lyme Western Blot: Negative
Assessment of Findings

• Fibromyalgia (Muscle stiffness) / Headaches / Arthralgia:
  – Sulfites? (upregulated CBS?)
  – Glutamate (impaired GAD?)
  – Norepinephrine elevated? (impaired COMT?)
  – Histamine? (DAO, HNMT?) Is there enough SAMe?
  – Insufficient SAMe? (dysfunctional MAT?)

• Fatigue / Neuropathy: Mitochondria (MMAB?, MUT?)

• Insomnia (pain?): Norepinephrine? Melatonin? SAMe? (MAT?, AANAT?)

• Heartburn: Norepinephrine elevated? (Insufficient SAMe? MAT?)

• Palpitations, episodic: Norepinephrine? Sulfites? Glutamate?
  – (COMT?, CBS?, MAT?)

• Hx Hashimoto’s Thyroiditis
• Hx MTHFR mutation
• Hx of Celiac (Resolved)
• Hx of Endometriosis
Causes of Inflammation & Pain?

- Sulfites (CBS ?)
- Histamine (DAO, HNMT ?)
- Glutamate (GAD ?)
- High Norepinephrine (COMT? MAT?)
- Cell Membrane Dysfunction (PEMT ?)
- Insufficient SAMe as Cofactor (MAT ?)
Initial Lab Testing (Genetic Genie)

- COMT v158m +/-
- VDR taq +/+
- MAO-A r297r +/+ 
- MTHFR a1298c +/-
- MTHFR c677t +/-
- CBS c699t +/+ -----High Sulfites?
- CBS a360a -/- ...High Glutamate?
  ...High Norepinephrine?
  (Hypothesis: Yasko, Amy)
Abstract


Cystathionine beta-synthase mutations in homocystinuria.


Abstract

The major cause of homocystinuria is mutation of the gene encoding the enzyme cystathionine beta-synthase (CBS). **Deficiency of CBS activity results in elevated levels of homocysteine as well as methionine in plasma and urine and decreased levels of cystathionine and cysteine.** Ninety-two different disease-associated mutations have been identified in the CBS gene in 310 examined homocystinuric alleles in more than a dozen laboratories around the world. Most of these mutations are missense, and the vast majority of these are private mutations. The two most frequently encountered of these mutations are the pyridoxine-responsive I278T and the pyridoxine-nonresponsive G307S. Mutations due to deaminations of methylcytosines represent 53% of all point substitutions in the coding region of the CBS gene.
A mechanism of sulfite neurotoxicity: direct inhibition of glutamate dehydrogenase

Zhang X1, Vincent AS, Halliwell B, Wong KP.

Exposure of Neuro-2a and PC12 cells to micromolar concentrations of sulfite caused an increase in reactive oxygen species and a decrease in ATP. Likewise, the biosynthesis of ATP in intact rat brain mitochondria from the oxidation of glutamate was inhibited by micromolar sulfite. Glutamate-driven respiration increased the mitochondrial membrane potential (MMP), and this was abolished by sulfite but the MMP generated by oxidation of malate and succinate was not affected. The increased rate of production of NADH from exogenous NAD+ and glutamate added to rat brain mitochondrial extracts was inhibited by sulfite, and mitochondria preincubated with sulfite failed to reduce NAD+. Glutamate dehydrogenase (GDH) in rat brain mitochondrial extract was inhibited dose-dependently by sulfite as was the activity of a purified enzyme. An increase in the Km (glutamate) and a decrease in Vmax resulting in an attenuation in Vmax/Km (glutamate) at 100 microm sulfite suggest a mixed type of inhibition. However, uncompetitive inhibition was noted with decreases in both Km (NAD+) and Vmax, whereas Vmax/Km (NAD+) remained relatively constant. We propose that GDH is one target of action of sulfite, leading to a decrease in alpha-ketoglutarate and a diminished flux through the tricarboxylic acid cycle accompanied by a decrease in NADH through the mitochondrial electron transport chain, a decreased MMP, and a decrease in ATP synthesis. Because glutamate is a major metabolite in the brain, inhibition of GDH by sulfite could contribute to the severe phenotype of sulfite oxidase deficiency in human infants.
Abstract

Cysteine, sulfite, and glutamate toxicity: a cause of ALS?

Woolsey PB.  

CONCLUSIONS:

Since elevated plasma cysteine has been reported in other ALS patients, sulfite and cysteine toxicity may be involved in other cases of ALS. Patients with ALS with nonmutant-SOD should be tested for sulfite toxicity, cysteine, glutamate and GSH levels, and whether they have low levels of GSH metabolism enzymes.

Since glutamate metabolism appears to be inhibited by sulfite, research on the effect of sulfite on glutamate levels in patients with ALS should be pursued. Life might be prolonged in those patients with ALS with sulfite toxicity by closely monitoring the blood cysteine and urine sulfite levels and minimizing their dietary intake, as well as increasing GSH by using sublingual GSH. A long-term solution might be found through research to determine methods to increase GSH synthesis without using sulfur-containing supplements that may add to the cysteine and sulfite toxicity.
CBS: Sulfites need Molybdenum

CBS c699t  +/-
CBS a360a  -/-
Lab Testing (Genetic Genie)

- COMT v158m: +/-
- VDR taq: ++
- MAO-A r297r: ++
- MTHFR a1298c: +/-
- MTHFR c677t: +/-
- CBS c699t: ++ ...High Sulfites
- CBS a360a: +/- ...High Glutamate
  ...High Norepinephrine
  (Hypothesis: Yasko, Amy)

**Hmmm?? Muscle tension**

*Need SAMe!*

*What’s MAT enzymes?*
Additional Genetic SNP’s

- COMT v158m +/-
- VDR taq +/-
- MAO-A r297r +/-
- MTHFR a1298c +/-
- MTHFR c677t +/-
- CBS c699t +/+  
- CBS a360a -/-
- AANAT +/-
- MAT +/-
- MAT +/-
- MAT -/-
- MAT -/-

- DAO +/+  
- DAO +/-  
- DAO -/-
- HNMT +/-  
- HNMT -/-
- MMAB +/+  
- MMAB +/-  
- MMAB -/-
- MUT +/-
- PEMT +/-
- PEMT +/-
- PEMT -/-
COMT
Metabolizes Norepinephrine, requires SAMe & Mg
PEMT: Cell Membrane Permeability? Pain?
PEMT: Pain?

https://upload.wikimedia.org/wikipedia/commons/thumb/e/e4/PEMT_Roles_and_Regulation.jpg/440px-PEMT_Roles_and_Regulation.jpg
MAT:
SAMe: enzymes Cofactor for methyltransferase enzymes
DAO & HNMT: Histamine: Inflammation?

- DAO $^{++}$
- DAO $^{+-}$
- DAO $^{-/-}$
- HNMT $^{-/-}$
- HNMT $^{-/-}$
Adeno-B12 (MUT, MMAB)
Fatigue? Mitochondrial Dysfunction?

MMAB +/-
MMAB +/+
MUT +/-
Adeno-B12 (MUT, MMAB)
Fatigue? Mitochondrial Dysfunction?

MMAB +/+
MMAB +/+
MUT +/-
Adeno-B12 (MUT, MMAB)
Fatigue? Mitochondrial Dysfunction?

MMAB +/+  MMAB +/+  MUT +/-
Genetic SNP’s

- COMT v158m +/-
- VDR taq ++
- MAO-A r297r +/
- MTHFR a1298c +/-
- MTHFR c677t +/-
- CBS c699t ++
- CBS a360a --

- DAO ++
- DAO +/
- DAO --
- HNMT --
- HNMT --

- MMAB ++
- MMAB +/
- MUT +/

- PEMT ++
- PEMT +/
- PEMT --

- AANAT +/-
- MAT +/-
- MAT +/
- MAT --
- MAT --

What Else?
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Genetic SNP’s

- COMT v158m +/-
- VDR taq +/+
- MAO-A r297r +/+
- MTHFR a1298c +/-
- MTHFR c677t +/-
- CBS c699t +/+  
- CBS a360a -/-

***************

- DAO +/+  
- DAO +/-  
- HNMT -/-  
- HNMT -/-

- MMAB +/+  
- MMAB +/+  
- MUT +/-

- PEMT +/+  
- PEMT +/+  
- PEMT -/-

- GAMT +/+  
- GAMT +/+
Question... What is GAMT?

GAMT +/-
GAMT +/+
Creatine Deficiency Syndrome
History: Timeline, Revisited

Child: - awakens with stomach pain. (DAO, GAMT)
  - joints and muscle stiffen with use. (GAMT)
  - exercise intolerance (GAMT, MUT, MMAB)

Teenage: - periodic sore, swollen joints, (GAMT)
  - headaches, (GAMT, MAT)
  - stiff and painful muscles, (GAMT)
  - awaken tired w/stomachache (DAO, GMAT)

Adult years: - paralyzed “stiff” muscles at night (GMAT)
  - tingling, coldness in hands, feet. (MMAB, MUT)
  - fatigue. (MMAB, MUT)
  - diet severely restricted: painful to eat (DAO, GMAT)
  - headaches. Painful to think. (GAMT, DAO, )
Pathway Planner Application

CBS
DAO HNMT
MUT, MMAB
PEMT
COMT
GAMT
Case Review: Triggers

• 1. Energy needs exhaust mitochondria supply
  – Insufficient Adeno-B12 for Mitochondria
  – Insufficient GAMT gives insufficient Creatine
  – Insufficient Creatine for brain and muscles
• 2. Sulfites (CBS):
  – Inflaming GI tract, inhibiting GAD
  – increasing Norepinephrine,
• 3. Histamines: inflaming GI tract (DAO)
• 4. Cell lipid bilayer (PEMT): compromised?
Treatment: Resolution

• 1. Molybdenum 75 mcg, BID
  (Manage Sulfites)
• 2. Creatine, 2.5 mg, BID
  (Needed by mitochondria in muscles and brain)
• 3. Diamine Oxidase, 1-2 caps, with meals
  (Manage food related histamine)
• 4. Probiotics/prebiotic fiber
  (Restore GI health)
• 5. Prenatal Vitamin
  (Methylfolate, Methyl & Adebno-B12)
• 6. Phosphatidylcholine
  (Protect cell lipid bilayer)
## Follow-up

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6 weeks pregnant!
Key Insights

• 1. **GAMT** enzyme is essential to produce Creatine.
• 2. Creatine is required by all mitochondria, for muscles and brain.
• 3. **SAMe** is the required cofactor for **GAMT**.
• 4. Headaches and body pain can be key symptoms of **GAMT** deficiency.
• 5. There can be multiple causes for body pain (creatine deficiency, increased glutamate, increased norepinephrine, toxins).
In addition... Key Insights

• 1. Always be willing to learn.
• 2. There may be more than one problem.
• 3. Keep a 3-Dimensional perspective.
  – Rarely are problems “linear.”
• 4. If something is new, or different...
  – Look it up.
  – It may contain needed answers.

Thank you!