GAMT Deficiency: Natural History, Diagnostic Testing & Treatment

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Disclosures

Neither myself nor any member of my immediate family has a financial relationship or interest that related to the content of this discussion.

Background on Guanidinoacetate Methyltransferase (GAMT) Deficiency

- One of three inborn errors of **creatine** metabolism and transport
- Autosomal Recessive Inheritance
- Prevalence
  - Rare, 130 individuals diagnosed worldwide
  - Incidence in NY State & Utah estimated to be 1:405,655 (NBS pilot project)
  - Broader ranges of 1:250,000 – 1:2,640,000 reported
    - 1:250,000 (Netherlands NBS Data - PMID: 26319512)
    - 1:2,640,000 (Derived from determining carrier frequency from EVS database– PMID: 26003046)

Arginine + **Glycine** → (Arginine : Glycine Amidinotransferase) → **Ornithine** + **Guanidinoacetate**

SAM → **SAH**

Guanidinoacetate Methyltransferase

Guanidinoacetate → Creatine

CRTR

Creatine → **Creatinine**

Creatine + **ADP** + **ATP** ⇌ **Creatine phosphate** (Creatine kinase)

Presentation & Natural History

- Age of onset: varies, between 3 months to 2 years
- Symptoms can include:
  - **Developmental delay & Cognitive Impairments**
    - **severity ranges from mild to severe (~50-75% fall on more the severe end of the spectrum)**
    - **Speech/language development commonly affected**

  - Variable behavioral issues (~75%)
    - Hyperactivity
    - Autism
  - Epilepsy (~70%)
    - Varied seizure types & severity

  - Movement disorder (30%)
    - Chorea, ataxia, dystonia
  - Hypotonia

Diagnosis

1) Biochemical Testing: Measuring Guanidinoacetate (GAA) & Creatine Levels in blood or urine

   -Would expect HIGH GAA levels & LOW creatine levels

2) Molecular Genetic Testing: Analysis of GAMT Gene

-Could be accomplished via single gene testing, a multigene panel such as an epilepsy panel, or via broad genomic sequencing (e.g. exome or genome sequencing)

3) Brain magnetic resonance spectroscopy (to detect low cerebral creatine levels in the CNS)

Treatment

1) Oral creatine:

-Objective: replenishes cerebral creatine stores

-400-800 mg/kg/day divided into 3-6 doses

2) **Reduction of guanidinoacetate levels:**

-accomplished via supplementation with ornithine and dietary restriction of the amino acid arginine

-Ornithine dose: 400-800 mg/kg/day divided into 3-6 doses +/-

-Sodium benzoate: (50-130 mg/kg/day) conjugates glycine +/-

-Low arginine diet accomplished via restricting natural dietary protein & supplementation with synthetic formula that is arginine-free.

→ <u>This requires close dietary monitory.</u>

3) **Monitoring:**

-Nutrition labs every 3- 6 months (Plasma GAA levels, plasma amino acids, pre-albumin, electrolytes)

4) **Additional Supports/Services:** physical, occupational and speech therapies, applied behavioral analysis

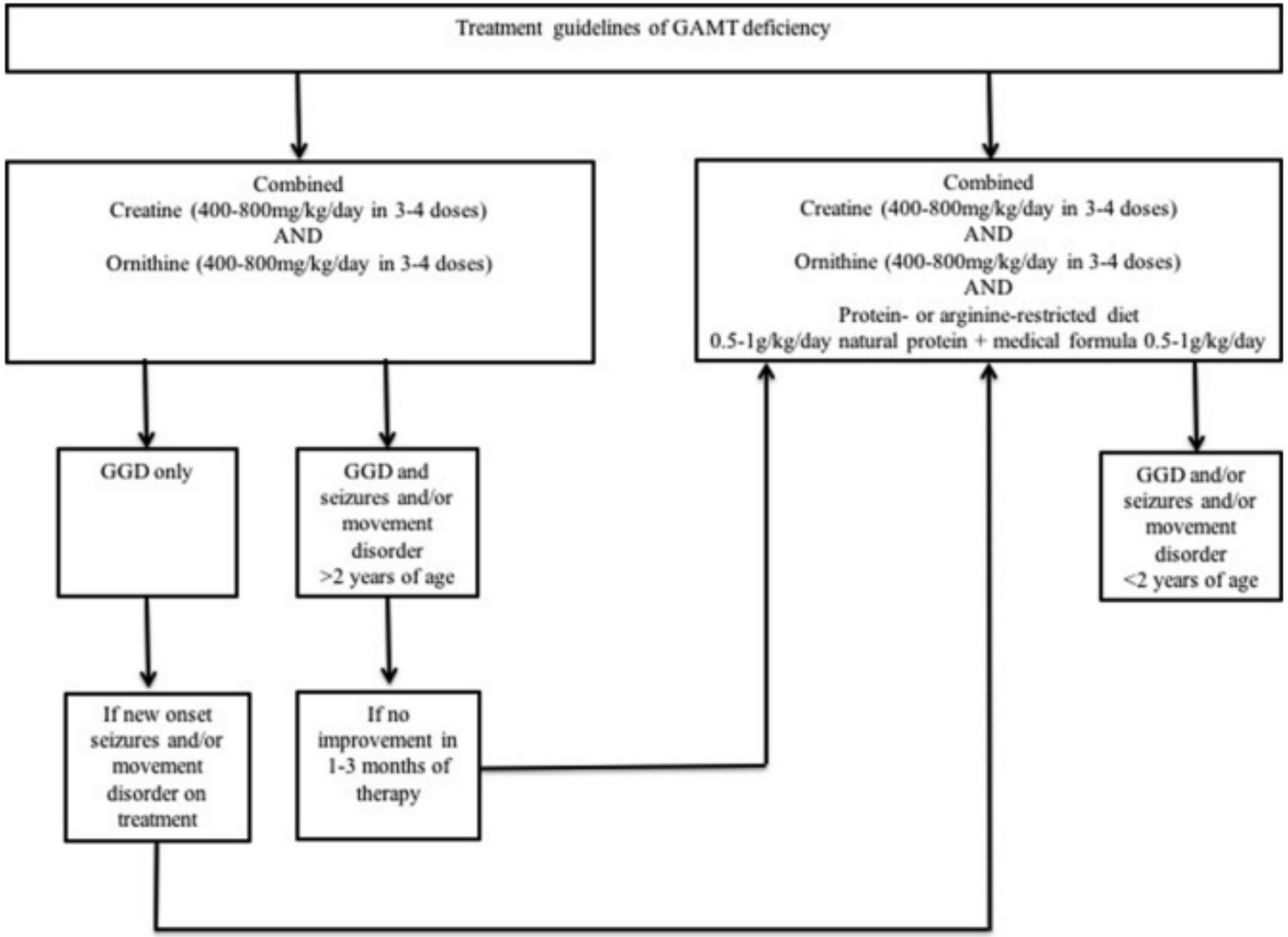

Fig. 4 – Treatment guidelines of GAMT deficiency are depicted in Figure 4 based on the symptoms of the patients with GAMT deficiency. GDD = global developmental delay.

PMID: 29506905

Treatment Efficacy

Outcomes in 48 Individuals with GAMT Deficiency

- 44 individuals treated after age 9 months – 100% with developmental delays or cognitive disability
  - 57% had severe developmental delays/cognitive disability
    - Individuals with severe delays started treatment at a median age of 51 months
  - 43% had mild/moderate developmental delays/cognitive disability
    - Individuals with moderate delays started treatment at a median age of 39 months
    - Individuals with mild delays started treatment at a median age of 25.5 months
  - 79% had epilepsy and/or symptoms of a movement disorder
  - All showed some improvement while on treatment. 50% showed resolution of epilepsy or movement disorder symptoms

- 1 individuals treated a 9 months had borderline delays/cognitive disability (currently 21 months)

- 1 individual treat at 3 weeks had borderline delays/cognitive disability (Treatment was interrupted, currently 8 years-old)

- 2 individuals treated shortly after birth or prenatally had normal development (Currently ages 14 month & 41 months)

PMID: 24268530

Outcome in 22 individuals with GAMT Deficiency

- Developmental delays present in all
  - Improved in 5 individuals with resolution in 1 individual **(started treatment at 1 year of age)**
  - Remained stable in 16 individuals
  - 1 individuals showed regression.
- Seizures present in 17 individuals
  - Resolved in 11
  - Did not improvement in 6
- Movement disorder present in 7 individuals
  - Resolved in 4
  - Did not show improvement in 3

PMID: 29506905

Long-term Outcomes of Individual Diagnosed Prospectively via Newborn Screening (PMID 34389248)

- Started on therapy at 11 days of life
- Therapy consisted of creatine & ornithine supplementation, sodium benzoate and a moderate protein (arginine) restriction
- Per personal communication with authors, individual is now in middle school performing at grade level with no IEP/need for additional educational supports

Future Perspectives

- Gene therapy currently under investigation in animal models (PMID: 35505663)
  - Improves biochemical abnormalities
  - Improves weight gain
  - Improves brain metabolism & behavioral abnormalities
- Pre-clinical work exploring small molecules to serve as AGAT-inhibitors
  - Dr. Nicola Longo (University of Utah)

Summary of existing literature & limitations

- Appears to be highly treatable if therapy is initiated early
- Partially treatable if therapy is initiated in childhood
- As a field, still learning what constitutes “ideal” treatment
- Sample size limits ability to make genotype-phenotype correlation
- Limited long-term follow-up

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