Diagnostic Testing

Proper diagnosis and early intervention is critical to establish treatments needed to improve life quality and longevity for the CCDS patient.

Metabolite screen of urine and plasma (see table 1)

- Testing in both urine and plasma is recommended to screen for all three disorders.
- For AGAT and GAMT deficiency, creatinine concentrations may be below reference intervals. Creatinine may trend in the low-normal range in patients with CTD.
- The concentrations of creatine (Cr), guanidinoacetate (GAA), and creatinine (Crn) are measured.
- At a minimum, a urine specimen should be tested. Note: this analysis is not sensitive for females with CTD. Gene sequencing should be considered if there is suspicion for CTD in a female with normal metabolite screening.

Proton magnetic resonance spectroscopy (1H-MRS) of the brain

- Can be requested at the same time as brain MRI. Useful for measuring creatine levels in the brain.
- Decreased/absent creatine peak in the brain for all three disorders. Cerebral creatine level on 1H-MRS is low in females heterozygous for CTD, but may overlap with unaffected individuals.
- Brain MRI may show non-specific findings such as delayed myelination, hyperintensities of the globus pallidus, and cerebral atrophy.

Gene sequencing

Sequencing of the genes *GATM, GAMT*, and *SLC6A8*.

Enzyme assays

Cultured skin fibroblasts are not usually required for diagnosis, but may be helpful when metabolite and gene sequencing test results are unclear. This includes measurement of AGAT and GAMT activity and creatine uptake studies for CTD.

Laboratory Testing

For information on laboratories offering testing for CCDS, go to:

GeneTests: www.genetests.org

Genetic Testing Registry (GTR®): www.ncbi.nlm.nih.gov/gtr/

TABLE 1

	AGAT	GAMT	CTD
Plasma	**GAA:** Low **Creatine:** Low/normal	**GAA:** Elevated **Creatine:** Low	**GAA:** Normal **Creatine:** Normal[b]
Urine[a]	**GAA:** Low **Creatine:** Low/normal	**GAA:** Elevated **Creatine:** Low/normal	**GAA:** Normal **Creatine:** Elevated in males; may be normal in females[c]

[a]Urine metabolites are measured relative to creatinine.

[b]Urine is needed to diagnose creatine transporter deficiency (CTD) in males. CTD will be missed in males if only plasma is screened.

[c]Urine creatine can be normal in females who are heterozygous for CTD. Sequencing of the *SLC6A8* gene is needed for assessment of females for CTD.

A SIMPLE SCREEN CAN **CHANGE A LIFE**

Cerebral Creatine Deficiency Syndromes

If you suspect Autism, Cerebral Palsy, Mitochondrial Disorder, Failure to Thrive, Global Developmental Delay, or Mental Disability, screen for **Cerebral Creatine Deficiency Syndromes.**

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Cerebral Creatine Deficiency Syndromes (CCDS) are inborn errors of metabolism affecting the synthesis and transport of creatine.

Creatine Transporter Defect (CTD) is a mutation in the creatine transporter gene. This results in a blockage in the transportation of creatine to the brain and muscles.

- The most common CCDS
- Estimated to account for about 2% of all unexplained X-linked intellectual disabilities
- Inheritance pattern: X-linked
- Gene: *SLC6A8*
- Protein: Creatine transporter 1 (CT1)
- Female heterozygotes may be asymptomatic, or may have variable degrees of learning difficulty and other symptoms, such as constipation. In rare cases, females can have symptoms as severe as those observed in affected males

Guanidinoacetate Methyltransferase Deficiency (GAMT) is a mutation in the gene that makes the enzyme that creates creatine, resulting in a shortage of creatine.

- In general, the most severe of the three CCDS due to elevation of guanidinoacetate (which is neurotoxic) in addition to creatine deficiency
- More than 100 cases have been reported in medical literature
- Inheritance pattern: Autosomal recessive
- Gene: *GAMT*
- Protein: GAMT enzyme

Arginine: Glycine Amidinotransferase Deficiency (AGAT) is the first step of creatine synthesis, resulting in the formation of guanidinoacetate, the immediate precursor of creatine. Mutations found in the AGAT gene impair the body's production of creatine.

- Fewer than 20 cases reported
- Inheritance pattern: Autosomal recessive
- Gene: *GATM*
- Protein: AGAT enzyme

Who Should be Tested?

Any child with global developmental delay should be tested. In addition, patients with generalized organic and aminoaciduria should be screened as these findings can be an indicator of the creatine synthesis disorders and are caused by low creatinine concentrations in urine.

Clinical Symptoms

Global developmental delay affects all children with these disorders and may be the first sign, appearing before other symptoms. **Speech delay** may be particularly severe and is present in all affected children. Many individuals develop no speech, or speak only in single words. **Intellectual disability** of variable severity is typically present in all older children and adults.

Additional Symptoms may include:

Seizure disorders, the onset of which and severity are variable

Hypotonia, muscle weakness, and muscle hypotrophy

Behavioral disorders including autism-like behaviors and hyperactivity

Movement disorders including dystonia and dyskinesia (sometimes labeled Cerebral Palsy)

Gastrointestinal problems such as chronic constipation and vomiting

Failure to thrive

Autism

It is encouraged that an individual with any of these presentations be screened for CCDS as early as possible.

Common Misdiagnoses

CCDS patients are frequently misdiagnosed with Cerebral Palsy as infants and as toddlers. Children are often misdiagnosed with Autism or Global Developmental Delay.

Treatment

Treatment with oral supplementation is available and effective, if initiated early for the AGAT and GAMT deficiencies. To date, this type of treatment has not shown to improve outcomes in individuals with CTD.

- Oral Creatine Monohydrate is given to replenish creatine levels in the brain and other tissues in individuals with AGAT and GAMT deficiencies.
- Low Arginine/protein diet, L-Ornithine supplementation, and Sodium Benzoate are used to reduce toxic levels of guanidinoacetate in individuals with GAMT deficiency.
- There may be some clinical benefit to a subset of individuals with CTD when treated with Creatine Monohydrate, L-Arginine, and Glycine. Additional treatments for CTD are under investigation.

**The ACD does not recommend or advise any supplementation to be taken without physician supervision.*

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