TRACKING CREATINE DEFICIENCY

Think your loved one may have a CCDS? Recently diagnosed with a CCDS? (Cerebral Creatine Deficiency Syndrome)

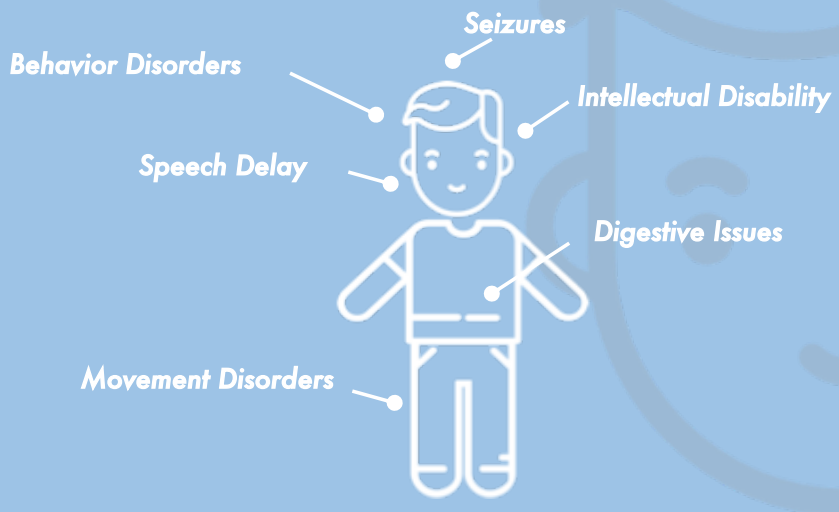
This document is intended as educational information for patients and their doctors. It does not replace a doctor's judgment or clinical diagnosis.

Learn more about CTD, AGAT and GAMT: The 3 CCDS.
Please visit www.ScreenCreatine.org

ScreenCreatine.org is a disease awareness program supported by Lumos Pharma, Inc.

What do CCDS look like ?

There are 3 Cerebral Creatine Deficiency Syndrome and they can look like many other pediatric neurodevelopmental diseases.



- GLOBAL DEVELOPMENTAL DELAY, OR GDD
  (Delay in meeting two or more developmental milestones, including body movements, large and small; speech and language; ability to think; social and personal skills; and daily life skills). GDD is a term applied to children under five years and typically predicts a future diagnosis of intellectual disability.

- INTELLECTUAL DISABILITY, OR ID
  (Marked by serious limitations in intellectual functioning and behaviors and skills needed to function in daily life). ID is a term applied to older children whose intelligence can be measured with an IQ test. It appears before age 18 years.

- SPEECH/LANGUAGE DEVELOPMENT DELAY

- SEIZURES
  Involving muscle stiffening and/or jerking

- BEHAVIOR DISORDERS
  Such as autism and attention deficit and/or hyperactivity disorders

- MOVEMENT DISORDERS
  Involving lack of coordination and delays in crawling, sitting, and walking

- VOMITING AND DIGESTIVE PROBLEMS

- FAILURE TO THRIVE

MY CCDS STORY

Here is a booklet to help you gather your loved one's symptoms and behaviors in one place. And lab results too! It will help you tell your CCDS Story.

Share this story, filled with valuable knowledge and information, with your doctor to help him/her diagnose, treat and manage your loved one.

For those still seeking a diagnosis, it may also help your doctor's team better understand if your loved one's signs and symptoms are related to CCDS. It can be especially helpful if you are referred out to other physicians and/or hospitals.

- ✓ WRITE IT DOWN
- ✓ ADD A VIDEO
- ✓ SHARE YOUR STORY TO YOUR PHYSICIAN AND THEIR TEAM

HELPFUL TIP 1

A picture is worth a thousand words and a video even more! One CCDS parent told a story about how showing a video of their toddlers/child's projectile vomiting made all the difference in explaining that it was not just regurgitation or normal vomiting! *

* Miller JS et al. Red Flags for Creatine Transporter Deficiency, and Potential Outcome Variables for the Severely Impaired. *Poster first presented at Society for Developmental Behavioral Pediatrics (SDBP) 2016 Annual Meeting Savannah, GA* September 2016.

My CCDS Story: Symptoms and Behavior Tracker

Use this tracker to help recount the story of your loved one as he/she is/was growing up and their current status.

Instructions: Take notes with or without video-documented experiences that relate to the following categories. Add "V" in the notes box to remind yourself to show relevant video footage to your physician.

Affected Area	Symptom Questions	Age of child you first noticed or yes/no response	Notes about certain episodes or Comments
 Language Issues	When did you notice little to no babbling or vocalizing?		
	When did you notice delayed or very limited speech?		
	When did you think this was a problem/symptom of something not right?		
	How many words can he/she speak now?		
	Is your child involved with speech therapy?		
 Digestive Issues	Did/Does your baby (especially in months 0-12) vomit or"spit up" often and forcefully?Could digestive problems be referred to as projectile vomiting?		
	Have physicians described your baby as "failure to thrive"? Failure to thrive means that it is difficult to gain and keep weight.		
	Is your child/adult child often constipated?		
	Does your child/adult child have a feeding tube?		
	Is your child a very picky eater?		

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Affected Area	Symptom Questions	Age of child you first noticed/or yes/no response	Notes about certain episodes or Comments
 Movement Disorders	When did your baby roll over?		
	When did your baby sit up?		
	When did your toddler start to crawl?		
	When did your toddler start to walk?		
	Would you describe your child's walking as clumsy?		
	Has your doctor ever told you that your child has a "low muscle tone" ?		
	Does your child tire easily?		
 Seizures Epilepsy	Has your child experienced any seizures (epilepsy) ?		
	Has your child experienced episodes that look like they are holding their breath?		
	If seizures have been diagnosed, are they controlled with medication?		
 Behavioral Issues	Is your child overly active?		
	Is your child very "clingy" ?		
	Does your child exhibit any self-harm behaviors (e.g., hand-biting)?		
	Does your child engage in behaviors commonly associated with autism?		
	At what age was your child potty-trained?		

What Tests Are Used to Diagnose CCDS?

Although urine and blood are the simplest and most economical tests, sometimes doctors might not order these specific creatine tests when they are doing an initial workup for an individual.

Other diagnostic options that can help involve imaging tests called MRS (magnetic resonance spectroscopy) and DNA/genetic tests.

IF CCDS ARE SUSPECTED, THESE TESTS SHOULD BE ORDERED:

- A simple urine test to look for creatine/creatinine levels
- A simple blood test to look at GAA*/creatine levels.

*guanidinoacetate acid

HELPFUL TIP 2

If you are a caretaker/parent of a child/adult with intellectual disability without a specific diagnosis, also referred to by healthcare professionals as Intellectual Disability due to Unknown Etiology you might want to check with your physician if lab tests were performed relating to creatine/creatinine and GAA/creatine levels.

HELPFUL TIP 3

Remember CCDS are diseases that prevent creatine from getting into brain cells. A regular MRI ***WILL NOT*** show creatine levels in the brain.

There is a special type of MRI that can show the presence/absence of creatine in the brain, called a MRI with spectroscopy, also known as MRS.

What Should I Know About DNA/Genetic Tests?

DNA tests are looking for changes in genes.

There are relatively new ways to help doctors either confirm a diagnosis or help them find ***disease-causing genetic mutations*** that could be the reason for your loved one's signs and symptoms.

DNA/genetic tests are helpful to identify many known neurodevelopmental disorders.

Neurodevelopmental disorders can involve:

- Global Developmental Delay
- Intellectual Disability
- Autism Spectrum Disorders
- Epilepsy/Seizure Disorders

Fortunately, the genes for the 3 CCDS have been identified and many genetic labs are already testing and analyzing them.

These are the genes associated with these CCDS:

- GATM- AGAT Deficiency
- GAMT- GAMT Deficiency
- SLC6A8-Creatine Transporter Deficiency

There are many types of genetic testing choices that your doctor can order. Here is a sample listing of tests that might be considered.

- Single gene tests
- Panel gene tests
- WES (Whole Exome Sequencing)
- WGS (Whole Genome Sequencing)

Genetic testing is most often done using a blood or saliva sample. The sample is sent overnight by your doctor or genetic counselor in a special kit that the genetic testing lab has provided.

Keeping Track Of CCDS Tests And Their Results

Biochemical Tests (Blood and Urine)

guanidinoacetate acid (GAA) and creatine (Cr)		Blood Results	Blood Results	Blood Results	Blood Results	Blood Results	Blood Results
	Plasma/Serum (Blood) Reference values	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
AGAT deficiency (L-arginine:glycine amidinotransferase)	↓ GAA ↓ Cr						
GAMT deficiency (guanidinoacetate methyltransferase)	↑ GAA ↓ Cr						
CTD (creatine transporter deficiency)	Normal						

creatine/creatinine ratio (Cr/Crt)		Urine Results	Urine Results	Urine Results	Urine Results	Urine Results	Urine Results
	Urine Reference values	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
AGAT deficiency (L-arginine:glycine amidinotransferase)	Normal						
GAMT deficiency (guanidinoacetate methyltransferase)	Normal						
CTD (creatine transporter deficiency)	↑ Cr/Crt *						

References

ARUP Laboratories - Additional Technical Information Sheet http://ltd.aruplab.com/Tests/Pdf/179

Mercimek-Mahmutoglu S, Stöckler-Ipsiroglu S, Salomons GS. Creatine Deficiency Syndromes. 2009 Jan 15 [Updated 2011 Aug 18]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015 (www.ncbi.nlm.nih.gov/ books/NBK3794/)

Keeping Track Of CCDS Tests And Their Results

Genetic Testing

Sequencing and Deletion/ Duplication Tests	Inheritance Pattern	Variants Unknown Clinical Significance (VUS) detected Yes/No	Mutation detected Yes/No	Name of the mutation	De novo mutation? Yes/No (means that this is the first person in the family to have this mutation)
AGAT deficiency ***(gene tested GATM*)***	Autosomal Recessive				
GAMT deficiency ***(gene tested GAMT)****	Autosomal Recessive				
CTD ***(gene tested SLC6A8)****	X-Linked				

Below Explanation Guide From ARUP Laboratories

http://ltd.aruplab.com/Tests/Pdf/179

GATM Sequencing (AGAT Deficiency)

- Two pathogenic GATM mutations on opposite chromosomes predicts AGAT deficiency
- One pathogenic GATM mutation indicates individual is at least a carrier for AGAT deficiency
- If no mutations are detected, AGAT deficiency less likely but not excluded

GAMT Sequencing (GAMT Deficiency)

- Two pathogenic GAMT mutations on opposite chromosomes predicts GAMT deficiency
- One pathogenic GAMT mutation indicates individual is at least a carrier for GAMT deficiency
- If no mutations are detected, GAMT deficiency less likely but not excluded

SLC6A8 Gene Sequencing and Deletion/Duplication

- Presence of a pathogenic gene mutation in males confirms creatine transporter deficiency
- Female carriers of a pathogenic gene mutation have variable presentation that ranges from asymptomatic to classic disease
- If no mutation is detected, creatine transporter deficiency is less likely but not excluded

Finding a Doctor Who Is Familiar with CCDS

If your current doctor isn't familiar with CCDS or how to diagnose it, you can always see other doctors who *are* familiar with CCDS, including specialists. Specialists are vital for people with rare neurodevelopmental diseases.

Ask your doctor for the name of a specialist or doctor who might be familiar with CCDS.

Specialists that are involved with CCDS diagnosis/treatment and/or symptom management include:

- Geneticists
- Pediatric neurologists
- Some adult neurologists
- Epileptologists
- Speech therapists
- Occupational therapists

HELPFUL TIP 4

Finding suitable specialists can take time and patience. It's OK to ask doctors all your important questions and telling your CCDS Story will help to streamline the process.

- You are your loved one's health advocate.
- Tell their CCDS Story: Being prepared and organized with their information will help them and your family.
- Contacting CCDS patient organizations in your area can also be helpful in learning about specific specialists and other resource information.
  - Association for Creatine Deficiencies - creatineinfo.org
  - Xtraordinaire – xtraordinaire.org

Notes, Notes, Notes.....the more the better! Write away!

HELPFUL TIP 5

Join the efforts of your nearby CCDS Patient Organizations! Patient organizations often offer patient and family support and resource links, encourage and spur scientific and medical research, and are a vital outlet for families to share and get advice, resources and a listening ear.

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TELL YOUR CCDS STORY!

Your photos, your video with data and information in this booklet will help you and your medical team care for your CCDS loved one and understand their unfolding story.

Did you know that CCDS Awareness Day is February 1st ?

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