

# Creatine Deficiency Syndromes

## TO EVALUATE PATIENTS WITH SUSPECTED CREATINE DEFICIENCY SYNDROMES

### Disease Overview

- Creatine is essential for intracellular energy metabolism and equilibration of ATP and ADP levels. The creatine system regenerates ATP from ADP at sites of energy requirement within the cell. Creatine is metabolized to creatinine and excreted in the urine.
- Creatine is synthesized from arginine and glycine through the actions of arginine: glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT). The creatine transporter SLC6A8 is responsible for creatine entry into the brain.
- Defects in creatine availability result from one of three conditions: GAMT deficiency, AGAT deficiency, and SLC6A8 deficiency, a creatine transporter defect.
- Symptoms of all three conditions can overlap, and typically include mental retardation and seizure disorder of variable severity, but may also include speech / language delays, movement disorders, and behavioral disorders such as autism, hyperactivity, and self-injury. Onset typically occurs in early childhood.
- Treatment can improve symptoms if initiated early in GAMT and AGAT deficiency:
  - GAMT deficiency is treated with oral creatine, ornithine, and restriction of arginine.
  - AGAT deficiency is treated with oral creatine supplementation.
  - SLC6A8 deficiency is treated with arginine and glycine supplements, although therapeutic effects are limited.
- Testing for creatine deficiency syndromes can involve:
  - Brain magnetic resonance spectroscopy to evaluate creatine content.
  - Evaluation of creatine and guanidinoacetate (GAA) in plasma and urine, as well as the creatine:creatinine ratio in urine.

### Epidemiology

- Incidence of creatine deficiency syndromes is unknown; more than 100 cases of SLC6A8 deficiency, several dozen cases of GAMT deficiency, and five cases of AGAT deficiency have been reported to date.
- It is estimated that approximately 1 percent of males with mental retardation of unknown etiology may have a creatine deficiency syndrome.

### Genetics

- Autosomal recessive inheritance for GAMT and AGAT deficiency.
- X-linked inheritance for SLC6A8 deficiency; approximately 50 percent of female carriers may have symptoms.

### Indications for Ordering

- For patients with a suspected creatine deficiency syndrome due to symptoms or decreased creatine on magnetic resonance spectroscopy, order [Creatine Disorders Panel, Urine \(ARUP test #2002333\)](#) and [Creatine Disorders Panel, Plasma or Serum \(ARUP test #2002328\)](#).
- For patients with suspected creatine transporter SLC6A8 deficiency, order [Creatine Transport, Fibroblasts \(ARUP test #2001875\)](#).

### Contraindications for Ordering

- Carrier testing
- Prenatal testing

### Interpretation

- Creatine Disorders Panel, Urine and Plasma/Serum:
  - Elevated plasma GAA with low creatine is suggestive of GAMT deficiency.
  - Decreased plasma GAA with low creatine is suggestive of AGAT deficiency.
  - Normal plasma GAA and normal creatine with an increased urine creatine:creatinine ratio is suggestive of SLC6A8 deficiency.
- Creatine Transport, Fibroblasts:
  - Decreased transport activity (below 10 percent of normal) is diagnostic for SLC6A8 creatine transporter deficiency.

### Methodology and Limitations

- For Creatine Disorder Panels: liquid chromatography followed by tandem mass spectrometry.
- For Creatine Transport, Fibroblasts: radioassay for creatine uptake.
- Analytical sensitivity and specificity are 99 percent.

### References

1. Gordon N. Guanidinoacetate methyltransferase deficiency (GAMT). *Brain & Development* 2010;32(2):79–81.
2. Creatine deficiency syndromes. In *Inborn metabolic diseases*, 4<sup>th</sup> ed. J Fernandes, et al, eds. 2006;Heidelberg, Germany:Springer.
3. Clark AJ. X-linked creatine transporter (SLC6A8) mutations in about 1% of males with mental retardation of unknown etiology. *Hum Genet* 2006;119(6):604–10.
4. Verhoeven NM. Laboratory diagnosis of defects of creatine biosynthesis and transport. *Clin Chim Acta* 2005;361(1–2):1–9.
5. Sykut-Cegielska J. Biochemical and clinical characteristics of creatine deficiency syndromes. *Acta Biochim Pol* 2004;51(4):875–82.

## Test Information

2002333	Creatine Disorders Panel, Urine
2002328	Creatine Disorders Panel, Plasma or Serum
2001875	Creatine Transport, Fibroblasts

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).