

Glutaryl carnitine Quantitation for Glutaric Acidemia Type I

BIOCHEMICAL TESTING TO EVALUATE NEWBORNS FOR GLUTARIC ACIDEMIA TYPE 1 AFTER AN ABNORMAL NEWBORN SCREEN

Disease Overview

- Glutaric acidemia type I (GA1) is caused by deficiency of the enzyme glutaryl-CoA dehydrogenase, which metabolizes glutaryl-CoA to crotonyl-CoA as part of the catabolism pathway for lysine and tryptophan. Deficiency of this enzyme causes elevations of glutaric acid and related metabolites, one of which is glutarylcarnitine (C5DC). Glutaric acid is neurotoxic.
- Affected patients typically present with macrocephaly at birth or shortly thereafter, and may otherwise be asymptomatic. Neurologic deterioration frequently occurs at 6–18 months of age after febrile illness and is characterized by frontotemporal atrophy with widening of the sylvian fissures, dystonia, and athetosis due to striatal neurotoxicity. Cognitive function is generally preserved despite neuronal damage, although speech and motor skills can be impaired due to severe spasticity.
- Without treatment, the vast majority of patients develop severe neurological disability. However, when treated presymptomatically, neurologic deterioration can be prevented in up to 90 percent of cases. Treatment typically includes carnitine supplementation, protein-restricted diet with supplementation of lysine-free formula, and aggressive treatment of illness.
- GA1 is one of the conditions routinely evaluated by state newborn screening programs. In affected patients, confirmatory testing after an abnormal newborn screen typically shows elevations of glutaric acid and 3-OH glutaric acid in urine organic acids, as well as elevations of C5DC in plasma acylcarnitines.
- After an abnormal newborn screen, some affected patients (low excretors) may have normal urine organic acids and plasma acylcarnitines. However, C5DC in urine is virtually always elevated in affected patients not being treated. Urine evaluation of C5DC can help identify patients who should have further diagnostic testing for GA1.

Epidemiology

- Incidence is approximately one in 30,000–50,000 in the United States based on newborn screening data.
- Incidence is higher among the Old Order Amish community in Pennsylvania, the Lumbee in North Carolina, Irish Travellers, and the North American Ojibway-Cree in Canada.

Genetics

- Autosomal recessive inheritance.

- No genotype-phenotype correlations are known; affected siblings can have widely varying phenotypes.

Indications for Ordering

- For patients with an abnormal newborn screen indicative of possible GA1.
- This test can be ordered concurrently with urine organic acids and plasma acylcarnitines, or following ambiguous results on urine organic acids and plasma acylcarnitines.

Contraindications for Ordering

- Carrier testing.
- Prenatal testing.

Additional Ordering Notes

This test should never be ordered as the only confirmatory test for GA1.

Interpretation

- Elevated C5DC in urine is consistent with a possible diagnosis of GA1. Diagnostic testing by DNA analysis or enzyme studies in fibroblasts should be considered to confirm the diagnosis.
- Normal levels of C5DC in urine greatly reduce the chance that the patient is affected with GA1.

Methodology and Limitations

- Separation by liquid chromatography followed by identification with tandem mass spectrometry.
- Analytical sensitivity and specificity are 99 percent.
- Urine acylcarnitine species other than glutarylcarnitine (C5DC) will not be assessed.

Related Tests

- Acylcarnitine Quantitative Profile, Plasma (0040033)
- Organic Acids, Urine (0098389)

References

1. Kölker S et al. Diagnosis and management of glutaric aciduria type I—revised recommendations. *J Inherit Metab Dis* 2011;34(3):677–94.
2. Hedlund GL. Glutaric acidemia type 1. *Am J Med Genet C Semin Med Genet* 2006 15;142C(2):86–94.
3. Tortorelli S. The urinary excretion of glutarylcarnitine is an informative tool in the biochemical diagnosis of glutaric acidemia type I. *Mol Genet Metab* 2005;84(2):137–43.
4. Glutaric aciduria (type I). In *Atlas of metabolic diseases*, 2nd ed. WN Nyhan, BA Barshop, PT Ozand, eds. 2005; London: Hodder Education.

Test Information

2001510 Glutarylcarnitine Quantitative, Urine

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

AUTHORS

Nicola Longo, MD, PhD

Marzia Pasquali, PhD