MAYO CLINIC LABORATORIES

Test Definition: GSH

Glutathione, Blood

Overview

Useful For

Evaluation of neonatal hyperbilirubinemia, favism or chronic or episodic hemolysis or jaundice

Evaluation for gamma-glutamylcysteine synthetase deficiency

Evaluation for glutathione synthetase deficiency causing hemolytic anemia

Evaluation for generalized glutathione synthetase deficiency with 5-oxoprolinuria

Method Name

Kinetic Spectrophotometry (KS)

NY State Available

Yes

Specimen

Specimen Type

Whole Blood ACD-B

Specimen Required

Container/Tube:

Preferred: Yellow top (ACD solution B)

Specimen Volume: 6 mL

Collection Instructions: Send whole blood specimen in original tube. **Do not** transfer blood to other containers.

Forms

If not ordering electronically, complete, print, and send a Benign Hematology Test Request (T755) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

Gross hemolysis	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood ACD-B	Refrigerated	20 days	

Clinical & Interpretive

Clinical Information

Hemolytic anemia may be associated with deficiency of erythrocyte enzymes. Red blood cell (RBC) enzymes linked to hemolysis are those important in the energy generation of glycolysis or protection from oxidative stress such as the hexose monophosphate shunt.

The hexose monophosphate pathway depends primarily upon the glucose 6-phosphate dehydrogenase (G6PD) enzyme for the generation of reduced nicotinamide-adenine dinucleotide phosphate (NADPH) with 6-phosphogluconate dehydrogenase (6PGD) providing an additive effect. Both reactions require adequate levels of reduced glutathione (GSH). Because RBCs lack the citric acid cycle, this is an important source of NADPH, and a deficiency of G6PD or GSH results in the inability to neutralize oxidative insults. GSH is synthesized from amino acids by two enzymatic steps and is present in liver, kidney, brain, muscle, and RBCs. It plays widely versatile and important roles in the synthesis of proteins and DNA, the processing of medications and toxins, and other redox reactions.

Similar to G6PD deficiency, glutathione deficiency can have an episodic acute time course of hemolysis or jaundice, be triggered by fava beans, and cause neonatal hyperbilirubinemia. Five enzymes impact GSH availability and therefore are potential candidates for abnormalities leading to glutathione deficiency:
-Two enzymes, gamma-glutamylcysteine synthetase (GCLC) and glutathione synthetase (GSS), are required for GSH synthesis
-Two enzymes, glutathione reductase (GSR) and glutathione peroxidase (GPX1), are required for reduction-oxidation cycling of oxidized glutathione (GSSG) to reduced glutathione (GSH)
-A family of enzymes, glutathione S-transferases (GSTs), utilizes GSH in the detoxification and preparation of substances for excretion into the bile or urine

Enzyme deficiencies have been reported in all of these enzymes, albeit very rarely. The best characterized are GSS and GCLC deficiencies. GSS deficiency is associated with two clinical presentations; a mild form causing isolated chronic hemolytic anemia, and a more severe form marked by urinary excretion of 5-oxoproline, metabolic acidosis, hemolytic anemia, and central nervous system disorders (5-oxoprolinuria). GCLC deficiency is associated with moderate to severe chronic hemolytic anemia present from neonatal or early childhood, or compensated hemolysis with sporadic but recurrent anemia or jaundice. Some cases have shown learning disabilities, severe and progressive ataxia with myopathy and spinocerebellar degeneration. GSR deficiency has been confirmed in three siblings with favism (episodic hemolysis after fava bean ingestion) and cataracts in early adulthood, and an unrelated infant with marked neonatal hyperbilirubinemia. GSR activity can be decreased in riboflavin deficiency, but whether this results in hemolysis is not clear. Although patients have been reported with anemia in the context of decreased GPX1 activity and decreased GST activity was found in a person with hemolytic anemia, splenomegaly, hyperbilirubinemia, and cholelithiasis, neither have been characterized sufficiently as the definitive cause of hemolysis. All described cases have shown autosomal recessive inheritance pattern.

A deficiency of either of the synthetic enzymes, GCLC or GSS, results in GSH levels less than 25%, but many show a virtual absence of measurable GSH. Heterozygotes usually show normal GSH levels. Elevated concentrations of GSH are

found in patients with myelofibrosis and in those with pyrimidine-5'-nucleotidase deficiency.

Reference Values

> or =12 months: 46.9-90.1 mg/dL RBC
Reference values have not been established for patients who are younger12 months of age.

Interpretation

Measurement of reduced glutathione (GSH) is used as a surrogate for the activity of the enzymes that contribute to normal levels of GSH within the red blood cell. GSH is associated with less than 25% of mean normal in individuals with deficiencies of gamma-glutamyl cysteine synthetase or glutathione synthetase.

Elevated concentrations of GSH are of uncertain significance. This finding can be nonspecific and is seen in normal neonates, pyrimidine-5’-nucleotidase deficiency, lead poisoning, dyserythropoietic disorders (inherited and acquired), myelofibrosis (possibly due to chromosome 8 duplication), or riboflavin supplementation. Consistently elevated glutathione levels have been reported in a family with mild hemolytic anemia of uncertain cause (1); however, whether this was causative or incidental was not determined.

Cautions

Samples with white blood cell counts greater than 20x10(9)/L have been shown to falsely increase the glutathione level by as much as 25%. Results in the normal or elevated range should be interpreted with caution if high white blood cell count is noted.

Recent transfusion may mask the patient's intrinsic enzyme activity and cause unreliable results.

Clinical Reference

1. Valentine WN, Paglia DE: Syndromes with increased red cell glutathione (GSH). Hemoglobin. 1980;4(5-6):799-804. doi:10.3109/03630268008997748
2. Manu Pereira M, Gelbart T, Ristoff E, et al. Chronic non-spherocytic hemolytic anemia associated with severe neurological disease due to gamma-glutamylcysteine synthetase deficiency in a patient of Moroccan origin. Haematologica. 2007;92(11). doi:10.3324/haematol.11238
3. Ristoff E, Mayatepek E, Larsson A. Long-term clinical outcome in patients with glutathione synthetase deficiency. J Pediatr. 2001;139(1):79-84. doi:10.1067/mpd.2001.114480
4. Konrad PN, Richards F, Valentin WN, et al. Gamma glutamyl cysteine synthetase deficiency. N Engl J Med. 1972;286:557
5. Mehta A, Mason PJ, Vulliamy TJ. Glucose-6-phosphate dehydrogenase deficiency. Baillieres Best Pract Res Clin Haematol. 2000;13(1):21-38
6. Beutler E, Dunning D, Dabe IB, Forman L. Erythrocyte glutathione S-transferase deficiency and hemolytic anemia. Blood. 1988;72:73-77
7. Kamerbeek NM, van Zwieten R, de Boer M, et al. Molecular basis of glutathione reductase deficiency in human blood cells. Blood. 2007;109(8):3560-3566. doi:10.1182/blood-2006-08-042531
8. Tomoda A, Noble NA, Lachant NA, Tanaka KR. Hemolytic anemia in hereditary pyrimidine 5'-nucleotidase deficiency: nucleotide inhibition of G6PD and the pentose phosphate shunt. Blood. 1982;60(5):1212-1218
9. van Solinge WW, van Wijk. Enzymes of the red blood cell. In: Rifai N, Horvath AR, Wittwer CT: eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6th ed. Elsevier; 2018:chap 30

Performance

Method Description

Virtually all of the non-protein sulfhydryl of red cells is in the form of reduced glutathione (GSH). 5,5'-dithiobis (2-nitrobenzoic acid) is a disulfide compound, which is readily reduced by sulfhydryl compounds, forming a highly colored yellow anion. The absorbance of this resultant yellow substance is measured by 412 nm and compared to that of a known standard.(Beutler E: Red cell metabolism. In: A Manual of Biochemical Methods. 2nd ed. Grune and Stratton, 1984; Alisik M, Neselioglu S, Erel O. A colorimetric method to measure oxidized, reduced and total glutathione levels in erythrocytes, J Lab Med. 2019:43(5), 269-277. doi:10.1515/labmed-2019-0098)

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

10 to 13 days

Specimen Retention Time

28 days

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

82978

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
GSH	Glutathione, B	2383-8

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Test Definition: GSH

Glutathione, Blood

Result ID	Test Result Name	Result LOINC® Value
608409	Glutathione, B	2383-8