MAYO CLINIC LABORATORIES

Test Definition: MMAP

Methylmalonic Acid, QN, P

Overview

Useful For

Evaluating children with signs and symptoms of methylmalonic acidemia using plasma specimens

Evaluating individuals with signs and symptoms associated with a variety of causes of vitamin B12 (cobalamin) deficiency

Method Name

LiquidChromatography-TandemMassSpectrometry(LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Plasma

Specimen Required

Collection Container/Tube:

Preferred: Green top (sodium heparin)

Acceptable: Lavender top (EDTA)

Submission Container/Tube: Plastic vial

Specimen Volume: 1.5 mL

Forms

If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

-Benign Hematology Test Request (T755)

-Biochemical Genetics Test Request (T798)

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK
Gross icterus	OK

Specimen Minimum Volume

0.5 mL

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Plasma	Refrigerated (preferred)	48 days	
	Ambient	48 days	
	Frozen	48 days	

Clinical & Interpretive

Clinical Information

Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 (cobalamin) or its downstream metabolites. Acquired deficiencies of vitamin B12 are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Older adult patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as kidney insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria.

MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin.

Since the first reports of this disorder in 1967, thousands of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, including plasma and urine MMA levels.

Several studies have suggested that the determination of plasma or urinary methylmalonic acid could be a more reliable marker of vitamin B12 deficiency than direct vitamin B12 determination.

Reference Values

< or =0.40 nmol/mL

Interpretation

In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed.

In adults, moderately elevated values indicate a likely vitamin B12 (cobalamin) deficiency.

Cautions

Diet, nutritional status, and age should be considered in the evaluation of plasma or urine methylmalonic acid level.

Clinical Reference

1. Fenton WA, Gravel RA, Rosenblatt DS: Disorders of propionate and methylmalonate metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill, 2019. Accessed October 6, 2021. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225086103&bookid=2709

2. Klee GG: Cobalamin and folate evaluation measurement of methylmalonic acid and homocysteine vs vitamin B12 and folate. Clin Chem 2000 Aug:46(8):1277-1283

3. Watkins D, Rosenblatt DS: Inherited disorders of folate and cobalamin transport and metabolism. In: Valle D, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. The Online Metabolic and Molecular Basis of Inherited Disease. McGraw-Hill, 2019. Accessed October 6, 2021. Available at https://ommbid.mhmedical.com/content.aspx?sectionid=225548307&bookid=2709

4. Vashi P, Edwin P, Popiel B, et al. Methylmalonic acid and homocysteine as indicators of vitamin B-12 deficiency in cancer. PLoS One. 2016 Jan 25;11(1):e0147843

Performance

Method Description

Methylmalonic acid (MMA) is determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) stable isotope dilution analysis. The specimen is mixed with an internal standard (methyl-d3-malonic acid). MMA and d3-MMA are isolated by solid phase extraction. LC-MS/MS is performed using mobile phases and a short column (C18, 50 mm x 4.6 mm, 5 micron) to separate MMA and d3-MMA from the bulk of the specimen matrix. The MS/MS is operated in the multiple reaction monitoring (MRM) negative mode to follow the precursor to product species transitions. Separation of MMA/d3-MMA from the more physiologically abundant succinic acid is accomplished by the careful selection of MRM transitions and optimization of the LC separation. The ratios of the extracted peak areas of MMA to d3-MMA determined by LC-MS/MS are used to calculate the concentration of MMA present in the sample.(Unpublished Mayo method)

PDF Report

No

Specimen Retention Time

1 week

Performing Laboratory Location

Rochester

Fees & Codes

Test Classification

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

CPT Code Information

83921