MAYO CLINIC LABORATORIES

Test Definition: NMHR1

N-Methylhistamine, Random

Overview

Useful For

Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions as a part of a random urine collection profile
Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

Method Name

Only orderable as part of a profile. For more information see:
NMHR / *N*-Methylhistamine, Random, Urine
Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Urine

Ordering Guidance

Patients with chronic mast cell activation often have chronically elevated N-methylhistamine (NMH) levels and will sometimes have intermittent NMH elevations.In these cases, a 24-hour urine collection is preferred. See NMH24 / *N*-Methylhistamine, 24 Hour, Urine.

Specimen Required

Only orderable as part of a profile. For more information see: NMHR / *N*-Methylhistamine, Random, Urine
Supplies: Aliquot Tube, 5 mL (T465)
Container/Tube: Plastic, 5-mL tube
Specimen Volume: 5 mL
Collection Instructions:
1. Collect a random urine specimen.
2. No preservative.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Urine	Refrigerated (preferred)	28 days	
	Ambient	28 days	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, in particular mastocytosis.

Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most but not all adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP.(1,3) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock.

Diagnosis of mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPG / 2,3-Dinor-11Beta-Prostaglandin F2 Alpha, Urine), and alpha or beta tryptase (TRYPT / Tryptase, Serum).

Reference Values

Only orderable as part of a profile. For more information see:

NMHR / *N*-Methylhistamine, Random, Urine

0-5 years: 120-510 mcg/g creatinine

6-16 years: 70-330 mcg/g creatinine

>16 years: 30-200 mcg/g creatinine

Interpretation

Increased concentrations of urinary *N*-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal.

The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease.

Up to 25% variability in random-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results.

Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

Cautions

While an average North American diet has no effect on urinary *N*-methylhistamine (NMH) levels, mild elevations (around 30%) may be observed on very histamine-rich diets. This problem is more pronounced in random-urine specimens especially when it is collected following a histamine-rich meal.

NMH levels may be depressed in individuals who have an alteration in the histamine-N-methyltransferase gene (*HNMT*), which encodes the enzyme that catalyzes NMH formation. This alternation results in an amino acid change that

decreases the rate of NMH synthesis.
When N-acetylcysteine is administered at levels sufficient to act as an antidote for the treatment of acetaminophen overdose, it may lead to falsely decreased creatinine results.

Clinical Reference

1. Roberts LJ II, Oates JA: Disorders of vasodilator hormones: the carcinoid syndrome and mastocytosis. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. 8th ed. WB Saunders Company;1992:1625-1634
2. Akin C, Metcalfe DD: Mastocytosis. In: Leung DYM, Greaves MW, eds. Allergic Skin Disease: A Multidisciplinary Approach. Marcel Dekker, Inc.:2000:337-352
3. Keyzer JJ, de Monchy JG, van Doormaal JJ, van Voorst Vader PC: Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. N Engl J Med. 1983;309(26):1603-1605
4. Heide R, Riezebos P, van Toorenbergen AW, et al: Predictive value of urinary N-methylhistamine for bone marrow involvement in mastocytosis. J Invest Dermatol. 2000;115(3):587
5. Van Gysel D, Oranje AP, Vermeiden I, et al: Value of urinary N-methylhistamine measurements in childhood mastocytosis. J Am Acad Derm. 1996;35(4):556-558
6. Divekar R, Butterfield J: Urinary 11b-PGF2a and N-methyl histamine correlate with bone marrow biopsy findings in mast cell disorders. Allergy. 2015 Oct;70(10):1230-8. doi: 10.1111/all.12668

Performance

Method Description

N-methylhistamine (NMH) is extracted from urine using solid-phase extraction. The elute is analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and quantified using a stable isotope labeled internal standard.(Martens-Lobenhoffer J, Neumann HJ: Determination of 1-methylhistamine and 1-methylimidazole acetic acid in human urine as a tool for the diagnosis of mastocytosis. J Chromatogr B Biomed Sci Appl 1999;721[1]:135-140; Lueke AJ, Meeusen JW, Donato LJ, et al: Analytical and clinical validation of an LC–MS/MS method for urine leukotriene E4: A marker of systemic mastocytosis. Clin Biochem. 2016 Sep;49(13-14):979-82. doi: 10.1016/j.clinbiochem.2016.02.007)

PDF Report

No

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

82542