

Overview

Useful For

Aiding in the diagnosis and differentiation of type 1 narcolepsy from other causes of hypersomnolence

This assay is **not intended** for use as a screening test.

Highlights

Orexin-A (hypocretin-1) is a neuropeptide involved in the sleep/wake cycle in humans. An abnormally low concentration of orexin-A (hypocretin-1) in cerebrospinal fluid (CSF) indicates type I narcolepsy.

CSF concentrations have been found to almost always be above 200 pg/mL in healthy individuals and those with non-type 1-narcoleptic sleep disorders, such as narcolepsy type 2 and idiopathic hypersomnia.

Method Name

Radioimmunoassay (RIA)

NY State Available

Yes

Specimen

Specimen Type

CSF

Ordering Guidance

Orexin-A (hypocretin-1) deficiency is the hallmark of narcolepsy type 1. The diagnostic criteria for type 1 narcolepsy include the presence of cataplexy and/or measured cerebrospinal fluid orexin-A/hypocretin-1 concentrations less than or equal to 110 pg/mL. Alternative testing for narcolepsy type 1 includes mean latency of 8 minutes in the clinical multiple sleep latency test, with evidence of sleep-onset rapid eye movement periods and cataplexy.

Specimen Required

Patient Preparation: Patient **should not** have recently received radioisotopes, either therapeutically or diagnostically, due to potential assay interference.

Collection Container/Tube: Sterile vial

Submission Container/Tube: Plain vial with no additives

Specimen Volume: 1.5 mL

Pediatric Volume: 0.5 mL minimum volume

Collection Instructions:

1. Obtain aliquot from second collection vial (preferred, not required).
2. Hemolyzed specimens will give false-positive results. Specimens should be centrifuged to remove any red cells prior to

shipping.

Forms

If not ordering electronically, complete, print, and send a [Neurology Specialty Testing Client Test Request](#) (T732) with the specimen.

Specimen Minimum Volume

0.5 mL

Reject Due To

Gross hemolysis	Reject
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Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
CSF	Frozen	120 days	

Clinical & Interpretive**Clinical Information**

Narcolepsy affects 0.02% to 0.05% of the population and the onset of symptoms often occurs in adolescence. Orexin (also known as orexin-A or hypocretin-1) is a neuropeptide produced in the hypothalamus and is involved in the sleep/wake cycle in humans. Impairment of orexin production and orexin-modulated neurotransmission is associated with narcolepsy with cataplexy (episodes of muscle weakness in response to emotional stimuli). An abnormally low concentration of orexin-A/hypocretin-1 in cerebrospinal fluid (CSF) is indicative of what is termed type 1 narcolepsy.

Survey of the literature reveals that approximately 85% to 95% of randomly selected individuals with type 1 narcolepsy and typical cataplexy, exhibit low (<110 pg/mL) CSF orexin (hypocretin-1) concentrations.(1) In one large study, the sensitivity of this cutoff was found to be 87% with a specificity of 99%.(2) Orexin deficiency and type 1 narcolepsy are closely associated with HLA (human leukocyte antigen) complex *DQB1 *0602*. It is estimated that only 1 in 500 HLA *DQB1 *0602*-negative individuals exhibit low CSF orexin concentrations. CSF concentrations have been found to almost always be above 200 pg/mL in healthy individuals and those with non-type 1-narcoleptic sleep disorders such as narcolepsy type 2 and idiopathic hypersomnia.

Reference Values

Normal individuals should be >200 pg/mL

Previous literature has defined cerebrospinal fluid orexin-A/hypocretin-1 concentrations of 110 pg/mL or below as being consistent with narcolepsy type 1-(Mignot E: Arch Neurol 2002;59:1553-1562). Concentrations between 111 to 200 pg/mL are considered intermediate and have limited diagnostic utility for narcolepsy, as they may be representative of other neurological disorders. Concentrations above 200 pg/mL are considered normal.

Interpretation

The diagnostic criteria for type 1 narcolepsy in the International Classification of Sleep Disorders (3) include the presence of hypersomnia, cataplexy (episodes of muscle weakness in response to emotional stimuli) and measured cerebrospinal fluid (CSF) orexin (hypocretin-1) concentrations less than or equal to 110 pg/mL.

Orexin (hypocretin-1) CSF concentrations have been classified into 3 categories in the literature. They include low (< or =110 pg/mL), which is indicative of type 1 narcolepsy; intermediate (ranges between 111-200 pg/mL); and normal (>200 pg/mL). Previous studies have shown that 106 of 113 patients with clinically defined type 1 narcolepsy exhibited low (<110 pg/mL) orexin concentrations. In another study, all 48 healthy individuals exhibited orexin (hypocretin-1) CSF concentrations above 200 pg/mL.

In the periodic hypersomnia disorder of Kleine-Levin syndrome, the CSF orexin levels may be low during the sleepy periods, with return to normal when individuals are not sleepy.

Cautions

Several factors contribute in the decision to measure orexin in cerebrospinal fluid (CSF). Orexin deficiency in HLA (human leukocyte antigen) *DQB1*0602*-negative patients is rare. This test may be considered for the diagnosis of narcolepsy type 1, after HLA positivity is shown, if a clinical multiple sleep latency test is negative or unavailable due to potential confounding circumstances. It may also be considered if there is suspicion that cataplexy is of psychogenic origin.

Orexin (hypocretin-1) concentrations between 111 to 200 pg/mL are considered intermediate and have limited diagnostic utility for type 1 narcolepsy, as they may be representative of other neurological disorders.

This test should not be requested in patients who have recently received radioisotopes, therapeutically or diagnostically, because of potential assay interference. A recommended time period before collection cannot be made because it will depend on the isotope administered, the dose given, and the clearance rate in the individual patient.

Some patients who have been exposed to animal antigens, either in the environment or as part of treatment or imaging procedures, may have circulating anti-animal antibodies present. These antibodies may interfere with the assay reagents to produce unreliable results.

Supportive Data

In an in-house Mayo Clinic study utilizing this assay on cerebrospinal fluid (CSF) from 100 individuals without type 1 narcolepsy, all samples (100%) exhibited orexin (hypocretin-1) concentrations higher than the 200 pg/mL normal threshold (mean value of 531pg/mL + or - 89). Additionally, all 6 out of 6 patients with confirmed type 1 narcolepsy had measured CSF concentrations below 110 ng/mL by this assay (mean value of <50 pg/mL).

Clinical Reference

1. Bourgin P, Zeitzer JM, Mignot E: CSF hypocretin-1 assessment in sleep and neurological disorders. *Lancet Neurol*. 2008 Jul;7(7):649-662. doi: 10.1016/S1474-4422(08)70140-6
2. Mignot E, Lammers GJ, Ripley B, et al: The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol*. 2002 Oct;59(10):155-162. doi: 10.1001/archneur.59.10.1553
3. Sateia MJ: International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014 Nov;146(5):1387-1394. doi: 10.1378/chest.14-0970
4. Dauvilliers Y, Arnulf I, Mignot E: Narcolepsy with cataplexy. *Lancet*. 2007 Feb;369(9560):499-511. doi: 10.1016/S0140-6736(07)60237-2
5. Ripley B, Overeem S, Fujiki N, et al: CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. *Neurology*. 2001 Dec 26;57(12):2253-2258. doi: 10.1212/wnl.57.12.2253

Performance

Method Description

The orexin-A (hypocretin-1) cerebrospinal fluid assay is a competitive radioimmunoassay. Orexin-A (hypocretin-1) in the patient sample competes with labeled (125)I orexin-A/hypocretin-1 for a limited number of primary antibody binding sites during a 24-hour incubation. Antibody-bound orexin-A/hypocretin-1 is separated from the unbound portion by a goat-anti-rabbit secondary antibody. Centrifugation brings down the heavy antibody complexes while unbound antigen remains in solution and is discarded. The competitive binding to the anti-peptide between endogenous orexin-A/hypocretin-1 and labeled peptide allows for the determination of orexin-A/hypocretin-1 concentration. This is done by measuring bound labeled peptide as a function of orexin-A/hypocretin-1 concentration in a prepared calibration curve. (Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Twice monthly (Second and fourth Monday)

Report Available

3 to 32 days

Specimen Retention Time

90 days

Performing Laboratory Location

Rochester

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. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

83519

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
ORXNA	Orexin-A/Hypocretin-1, CSF	91670-0

Result ID	Test Result Name	Result LOINC® Value
604230	Orexin-A/Hypocretin-1, CSF	91670-0