Test Definition: ORXNA
Orexin-A/Hypocretin-1, CSF

Overview

Useful For
Aiding in the diagnosis and differentiation of type 1 narcolepsy from other causes of hypersomnia

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.

The diagnostic criteria for type 1 narcolepsy in the third edition of the International Classification of Sleep Disorders (2014) include the presence of hypersomnia, cataplexy (episodes of muscle weakness in response to emotional stimuli) and/or measured CSF orexin (hypocretin-1) concentrations less than or equal to 110 pg/mL.

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

Advisory Information
Orexin-A (hypocretin-1) deficiency is the hallmark of narcolepsy type 1. The diagnostic criteria for type 1 narcolepsy includes the presence of cataplexy and/or measured cerebrospinal fluid (CSF) 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: CSF in 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 Neurorlogy Specialty Testing Client Test Request (T732) with the specimen.

**Specimen Minimum Volume**
0.5 mL

**Reject Due To**

<table>
<thead>
<tr>
<th>Gross hemolysis</th>
<th>Reject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thawing**</td>
<td>Cold OK; Warm OK</td>
</tr>
</tbody>
</table>

**Specimen Stability Information**

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>Frozen</td>
<td>120 days</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical and 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 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 CSF orexin-A/hypocretin-1 concentrations of < or = 110 pg/mL 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 of >200 pg/mL are considered normal.
Test Definition: ORXNA
Orexin-A/Hypocretin-1, CSF

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/or 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 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 and/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 in this assay (mean value of <50 pg/mL).

Clinical Reference


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 I(125) 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. (Package Insert: Orexin A/Hypocretin-1 [Human, Rat, Mouse, Porcine, Ovine, Bovine]-RIA kit, Phoenix Pharmaceuticals, Burlingame, CA. 2018)

PDF Report

No

Day(s) and Time(s) Test Performed

Third Tuesday of every month; 8 a.m.

Analytic Time

3 days

Maximum Laboratory Time

28 days

Specimen Retention Time

90 days

Performing Laboratory Location

Rochester

Fees and 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 Regional Manager. 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 U.S. Food and Drug Administration.

CPT Code Information

83519

LOINC® Information
<table>
<thead>
<tr>
<th>Test ID</th>
<th>Test Order Name</th>
<th>Order LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORXNA</td>
<td>Orexin-A/Hypocretin-1, CSF</td>
<td>91670-0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result ID</th>
<th>Test Result Name</th>
<th>Result LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>604230</td>
<td>Orexin-A/Hypocretin-1, CSF</td>
<td>91670-0</td>
</tr>
</tbody>
</table>