CSF hypocretin-1 levels may be useful as a confirmatory test for clinically suspected narcolepsy.

Clinical Problem: A 39 year old man presents with a clinical history suspicious for narcolepsy.

Clinical Question: Are hypocretin CSF levels useful to confirm a diagnosis of narcolepsy?

Search Strategy:
SUMSearch:
Keywords: hypocretin and narcolepsy. Limits: diagnosis, human, english. Results: Practice Guidelines: none, Systematic reviews: none, Original research: 34 documents, DARE (includes Cochrane abstracts): none.
PubMed:
Serach terms: narcolepsy (MeSH), subheading: cerebrospinal fluid. Limits: adults, english, clinical trials, human. One article identified (see reference below)

Clinical Bottom Lines:
1. A low CSF hypocretin level (≤ 110 pg/ml) was 62% sensitive and 98% specific for narcolepsy (see comments below)
2. A low CSF hypocretin level significantly increased the probability of narcolepsy (+LR=31, 95% CI 16.8, 74.3)
3. Normal CSF hypocretin levels (> 110 pg/ml) did not rule out the diagnosis of narcolepsy.

The Evidence:
CSF hypocretin levels were measured in 274 patients with various sleep disorders and 296 control patients with various other neurological disorders. Sleep disorders were diagnosed by clinical assessment and sleep studies, and classified according to the International Classification of Sleep Disorders (ICSD; see appendix below for narcolepsy criteria). Examiners were blinded to CSF hypocretin level results. Using a QROC analysis, a CSF hypocretin threshold value of 110 pg/ml was found to best distinguish patients with narcolepsy from all other subjects in the study.

Data:

<table>
<thead>
<tr>
<th>CSF hypocretin-1 level</th>
<th>Narcolepsy</th>
<th>No narcolepsy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 110 pg/ml</td>
<td>106</td>
<td>7</td>
<td>113</td>
</tr>
<tr>
<td>&gt; 110 pg/ml</td>
<td>65</td>
<td>392</td>
<td>457</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>399</td>
<td>570</td>
</tr>
</tbody>
</table>

Sensitivity = 106/(106+65)x100 = 62%
Specificity = 392/(392+7)x100 = 98%
+LR = 0.62/(1-0.98) = 31 (95% CI 16.8, 74.3)
-LR = (1-0.62)/0.98 = 0.39 (95% CI 0.32, 0.47)

Comments:
1. This study was an exploratory analysis of CSF hypocretin levels in patients with various sleep disorders and other neurological conditions, and not truly a study designed to evaluate the utility of a diagnostic test.
2. Patients without any suspicion of having narcolepsy (‘control’ patients with other neurological disorders) were included in the analysis. Inclusion of these patients spuriously inflates the specificity and makes the sensitivity unreliable.
3. This test and these results need to be confirmed in a more appropriate patient population i.e. patients presenting with symptoms suggestive of narcolepsy.

Reference:

Key Words: narcolepsy, hypocretin, diagnosis

Appraiser: Abdullah Alajmi and the UWO Evidence Based Neurology Group

Date Appraised: September 2004

Appendix
ICSD Diagnostic Criteria for Narcolepsy

Minimal Criteria: B plus C, or A plus D plus E plus G.
A. The patient has a complaint of excessive sleepiness or sudden muscle weakness.
B. Recurrent daytime naps or lapses into sleep occur almost daily for at least 3 months.
C. Sudden bilateral loss of postural muscle tone occurs in association with intense emotion (cataplexy).
D. Associated features include:
   1. Sleep paralysis
   2. Hypnagogic hallucinations
   3. Automatic behaviors
   4. Disrupted major sleep episode
E. Polysomnography demonstrates one or more of the following:
   1. Sleep latency less than 10 minutes
   2. REM sleep latency less than 20 minutes
   3. An MSLT that demonstrates a mean sleep latency of less than 5 minutes
   4. Two or more sleep-onset REM periods
F. HLA typing demonstrates DQB1*0602 or DR2 positivity.
G. No medical or mental disorder accounts for the symptoms.
H. Other sleep disorders (e.g., periodic limb movement disorder or central sleep apnea syndrome) may be present but are not the primary cause of the symptoms.