Clinical Problem: A 50 year old man has neurological symptoms and a known primary non-CNS cancer. A lumbar puncture is performed and CSF is obtained. What is the meaning of a negative CSF cytological analysis?

Clinical Question: What is the specificity and sensitivity of CSF analysis for leptomeningeal metastases (LM)?

SUMSearch: “cerebrospinal fluid” [MESH] AND “leptomeningeal” [MESH] (Focus: DIAGNOSIS, ages: all, subjects: HUMAN) resulted in many articles. Pubmed “cerebrospinal fluid” [MESH] AND “leptomeningeal” [MESH] AND focus DIAGNOSIS resulted in 357 articles. The three articles reviewed were chosen amongst them. There were no good, large studies available. A neuro-oncologist was consulted for aid in locating other studies but none were found. The three studies chosen were some of the largest and Study 1 & 2 did attempt to determine sensitivity of CSF cytological analysis.

Clinical Bottom Lines:

1. CSF cytology for leptomeningeal metastases is positive in 44-58% of suspected cases on the 1st CSF cytological analysis but rose to 57-84% with the 2nd CSF analysis.
2. As no gold standard exists, sensitivity and specificity of CSF analysis for diagnosing leptomeningeal metastases cannot be determined.
3. The highest rate of positive CSF cytology was seen in the study that included only solid tumours without any haematological malignancies.
4. Specificity could not be calculated based on these studies.

The Evidence:
Study 1:

Retrospective study of all cancer patients at one Cancer Center from 1992–1995 and in whom the clinical diagnosis of leptomeningeal metastases was considered. All inpatients and outpatients who had undergone both CSF cytology and Gd MRI were included. Patients with a primary brain tumor and those with known brain metastasis were excluded. Cytological results were classified as either positive or negative for LM according to a cytopathologist at the time of the lumbar puncture. MRI comprised at least imaging of the symptomatic area followed by Gd enhancement of the same area. All MRI scans were reevaluated by 1 neuroradiologist who was informed that all patients had cancer but was not aware of clinical details, nor did he know the CSF findings. The features used to evaluate MRI: leptomeningeal enhancement, dural enhancement, cranial nerve enhancement, superficial cerebral metastasis, hydrocephalus, subependymal enhancement, and/or enhancement of subarachnoid noduli. Data was combined with data from a previous study and exact maximum likelihood calculation of sensitivity, specificity and prior probability.

Study 2:

Retrospective study of all patients in one center seen from 1992-1993 in whom LM was considered as a possible diagnosis. Results from CSF analysis and MRI were reviewed. MRI scans were read as positive, suggestive or negative. Leptomeningeal and subependymal enhancement were categorized as positive, dural enhancement, cranial nerve enhancement, superficial cerebral metastasis, hydrocephalus, and/or enhancement of subarachnoid noduli were categorized as suggestive.

Study 3:

Retrospective study of 90 patients with LM from solid tumors seen in one center from 1975-80. Patients had either typical clinical findings of meningeal carcinomatosis or conclusive laboratory evidence supporting diagnosis i.e. CSF positive, tumor nodules on nerve roots on myelography or Ct evidence of leptomeningeal tumor.

-------------------------------------------------------------------------------------------------------------------------------

Study 1:

Data:
124 patients total: 61 patients had CSF analysis + MRI with Gadolinium

MRI results: First MRI was positive for Leptomeningeal Mets in 30/61 = 49%  
Second MRI increased the yield to 38/61 = 62%

CSF cytology: First CSF analysis was positive for Leptomeningeal Mets in 27/61 = 44%  
Second CSF analysis increased the yield to 35/61 = 57%  
Third CSF analysis increased the yield to 36/61 = 59%

<table>
<thead>
<tr>
<th>MRI Results</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF Results</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

Sensitivity and Specificity were calculated from this table, although there was no gold standard.

Study 2:

Data:
137 patients with possible LM but only 106 patients had both CSF analysis and MRI.

<table>
<thead>
<tr>
<th>MRI results for LM disease</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF cytology</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Positive</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>Negative</td>
<td>21</td>
<td>36</td>
</tr>
</tbody>
</table>

**Study 3**  

**Data:**  
90 patients with LM from solid tumors seen in one center from 1975-80. Patients had either typical clinical findings of meningeal carcinomatosis or conclusive laboratory evidence supporting diagnosis i.e. CSF positive, tumor nodules on nerve roots on myelography or CT evidence of leptomeningeal tumor.

CSF cytology: First CSF analysis was positive for Leptomeningeal Mets in 49/90 = 54%  
Second CSF analysis increased the yield to 76/90 = 84%

**Comments:**
1. All are Retrospective studies.
2. No gold standard available for leptomeningeal disease.
3. Unclear how specificity and sensitivity were calculated in Study 1 (Straathof, CSM, el. J Neurol (1999) 246:810–814.)
4. None of the studies included patients without tumors.
5. CSF collection method (volume, cytofix, time interval for analysis, etc). not well described in any of the studies. In addition, no details on cytological analysis of CSF.
6. In Study 2, it is unclear if the radiologist was blinded.
7. No information on cancer stage.

**References:**

**Key Words:** Leptomeningeal metastases, cerebrospinal fluid, cytology

**Appraiser:** Carmela Tartaglia and the UWO Evidence Based Neurology Group

**Date Appraised:** April 24, 2007
EXACT MAXIMUM LIKELIHOOD CALCULATION:

Used to evaluate the accuracy of a new diagnostic test against a standard test with unknown error rates. If the two tests are applied simultaneously to the same individuals from two populations with different disease prevalences, then assuming conditional independence of the errors of the two tests, the error rates of both tests and the true prevalences in both populations can be estimated by a maximum likelihood procedure. Generalizations to several tests applied in several populations are also possible.