Malignant Lymphomas

The diagnostic value of cerebrospinal fluid pleocytosis and protein in the detection of lymphomatous meningitis in primary central nervous system lymphomas

The exact rate of lymphomatous meningitis in primary central nervous system lymphomas (PCNSL) is uncertain. In this prospective multicenter study, cerebrospinal fluid (CSF) from 116 immunocompetent patients with newly diagnosed PCNSL was evaluated. Lymphoma cells were found in 18.1%, protein elevation (>45 mg/dL) in 65%, and CSF pleocytosis (>5/μL) in 36% of patients. Pleocytosis correlated with positive cytology, whereas CSF protein did not (specificity cell count vs. protein 74% vs. 34% [*p*<0.001], sensitivity 86% vs. 62% [*p*=0.18]).

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Lymphomatous meningitis (LM) may have prognostic and therapeutic impacts in primary central nervous system lymphomas (PCNSL).[1,2] The exact rate of meningeal disease in PCNSL is not known due to limitations of the diagnostic tools. Cerebrospinal fluid (CSF) cytology is still the gold standard for detecting malignant leptomeningeal infiltration.[3] Radiographic findings are not specific and their sensitivity for demonstrating LM is low compared to that for solid tumors.[4,5] The contribution of additional biochemical parameters remains controversial. From January 2000 to October 2003, we evaluated CSF samples from patients participating in a prospective multicenter therapy trial with newly diagnosed, histologically confirmed, non-AIDS-associated PCNSL for leptomeningeal spread by cytomorphology and for the diagnostic significance of CSF pleocytosis and protein levels.

CSF was obtained by lumbar puncture more than 1 week after stereotactic or open brain biopsy and before commencing therapy. Samples were processed immediately: cell count and protein levels were determined, and cytospin preparations were examined by an experienced hematopathologist at the treating institution. A CSF cell count of >5/μL and protein levels of >45mg/dL were considered abnormal. CSF cytology was deemed positive in the case of lymphoma cells being unequivocally present. Negative cytology included suspicious or reactive lymphocytes and truly negative specimens. The sensitivity and specificity of CSF pleocytosis and protein were determined using the given cut-off values and compared using the McNemar test. CSF from 116 of 145 patients registered for the therapy trial was analyzed. In 29 patients CSF data were incomplete or lumbar puncture was refused by the patient. The most important prognostic factors were identical in analyzed and excluded patients (median age: 62 years, median Karnofsky index: 70). Seventy-one patients were receiving dexamethasone (4-24 mg/day) at the time of CSF collection, 20 did not receive corticosteroids, and in 25 patients this information was lacking. Lymphoma cells were found in 21 cases (18.1%). The median CSF cell count was 4.0/μL (range 0-121.3/μL) and was elevated in 43 samples (37%). The median CSF protein level was 55mg/dL (range 10-1641

Table 1. Overview of results.

	Cytology positive (n=21)	*Cytology negative (n=95)*
CSF protein ≤ 45mg/dL (n=40)	8 (38%, CI 18-62%)	32 (34%, CI 24-44%)
CSF protein > 45mg/dL (n=76)	13 (62%, CI 38-82%)	63 (66%, CI 56-76%)
CSF cells ≤ 5/μL (n=73)	3 (14%, CI 3-36%)	70 (74%, CI 64-82%)
CSF cells > 5/μL (n=43)	18 (86%, CI 64-97%)	25 (26%, CI 18-36%)

CI: 95% confidence interval; CSF protein/cytology p=0.8; CSF cells/cytology p<0.0001.

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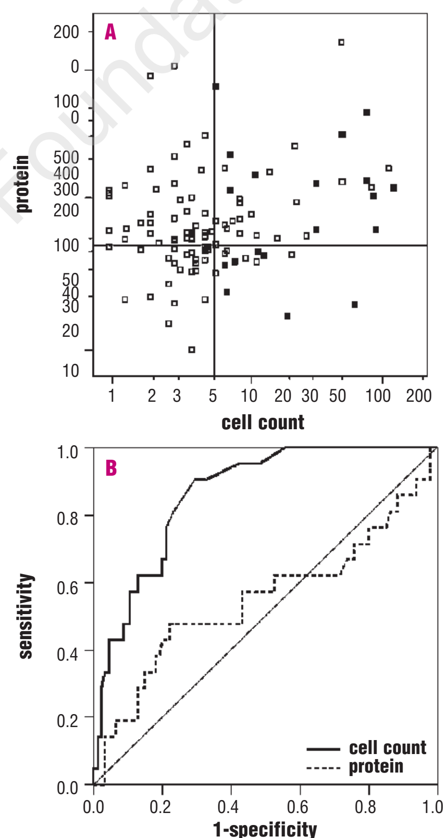

Figure 1. A. Scatter plot for cell count, protein and cytology: an abnormal cell count differentiates well between positive and negative cytology whereas there is a relatively even distribution of CSF protein values for positive and negative cytology. (x axis: CSF cell count /μL, y axis: CSF protein in mg/dL, log. scale for both axes, horizontal and vertical lines: cut-off values for protein and cell count; □: negative cytology; ■: positive cytology). **B.** Receiver operating characteristic (ROC) curve: the value of CSF cell count as a diagnostic marker for meningeal involvement in PCNSL. Sensitivity (0.0 to 1.0) and 1 – specificity (0.0 to 1.0) of CSF protein and cell count for detecting LM are plotted. The diagonal reflects the characteristics of a test with no discriminatory power.

mg/dL) and was elevated in 76 (65%) (Table 1). Statistical analysis showed an association of positive cytology with CSF pleocytosis, but no association with elevated protein levels (Figure 1A and B). The specificity of CSF pleocytosis was significantly higher than that of protein (74% vs. 34%, $p<0.001$), whereas the higher sensitivity of pleocytosis over protein was not statistically significant (86% vs. 62%, $p=0.18$). The frequency of LM in PCNSL has been reported to be between 0 and 70%, depending on the detection method applied. More detailed examination has been reported in only three larger studies, two of which were retrospective.[1,6,7] LM diagnosed by CSF cytology was found in 12-21%,[6,8,9] corresponding to our findings. Corticosteroid pretreatment was not reported. Elevated levels of CSF protein, reported in 60% of PCNSL patients, have been considered an indicator for LM by some authors,[1,9] while others have not found such a correlation.[6] Elevated levels of CSf protein may simply reflect a large tumor burden[6] and a different degree of blood-brain barrier disruption or may be caused by preceding brain biopsy. According to our data, an elevated level of CSF protein cannot be considered an indicator for LM. In contrast, we found a strong correlation between pleocytosis and positive cytology, which is not obvious since pleocytosis is often caused by reactive T cells. CSF pleocytosis had a significantly higher specificity and a non-significantly higher sensitivity than had protein levels in our study. Setting higher cell counts as the threshold further increased the likelihood of positive cytology (Figure 1B) but drastically reduced the sensitivity of this marker.

A limitation of our study is the possible influence of false negatives in CSF cytology, especially when the cell count was low.[3] This might have contributed to the correlation of low numbers of CSF cells with negative cytology. Moreover, LM cannot always be detected by CSF sampling.[1,9] Therefore, neither a normal cell count nor negative cytology excludes LM. The majority of our patients received corticosteroids which might have biased our results. Corticosteroids are lymphocytotoxic and known to hamper the histological examination in PCNSL. Thus, the rate of positive cytology and pleocytosis could be falsely low in our series. When patients with and without corticosteroids were compared, the frequency of positive cytology was not significantly different; however, the sizes of the groups were not well balanced (13/71 and 3/20, respectively; $p=1.0$).

In conclusion, CSF pleocytosis, in contrast to CSF protein levels, may be an indicator of LM in PCNSL. Considering the methodological limitations, this parameter alone should not influence the therapeutic approach in patients with negative cytology, but should prompt the clinician to look for further signs of meningeal lymphoma spread.

Lars Fischer,+ Kristoph Jahnke,*+ Peter Martus,°*
Michael Weller,# Eckhard Thiel, Agnieszka Korfel**

**Department of Hematology, Oncology and Transfusion Medicine; °Department of Medical Informatics, Biometry and Epidemiology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Germany; #Department of Neurology, University of Tübingen Medical School, Germany*

+Lars Fischer and Kristoph Jahnke contributed equally to this work.

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Correspondence: Lars Fischer, Department of Hematology, Oncology and Transfusion Medicine, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany. Phone: international +49-30.84452337. Fax: international +49.30.84454468. E-mail: lars.fischer@charite.de

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