

## CXCL13 and CXCL12 in Central Nervous System Lymphoma Patients

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**Abstract Purpose:** Homing of malignant lymphocytes to the central nervous system (CNS) may play a role in the pathogenesis of CNS lymphoma. In this study, we evaluated the chemokines CXCL12 and CXCL13 in the cerebrospinal fluid (CSF) and serum of patients with CNS lymphoma.

**Experimental Design:** Samples from 30 patients with CNS lymphoma (23 with primary and 7 with secondary CNS lymphoma; all B-cell lymphoma) and 40 controls (10 patients with other CNS malignancies and 30 without a malignant CNS disease) were examined. CXCL12 and CXCL13 concentrations were measured using enzyme-linked immunosorbent assays. The grade of blood-brain barrier disruption was estimated by the CSF/serum albumin ratio.

**Results:** CNS lymphoma patients and controls did not differ in CXCL12 serum and CSF levels. Serum levels of CXCL13 were generally low. CXCL13 CSF levels, however, were significantly higher in CNS lymphoma patients as compared with controls ( $P < 0.0001$ ). Chemokine levels in CSF and serum did not correlate. In CNS lymphoma, CXCL13 concentration in CSF correlated with the degree of blood-brain barrier disruption ( $R = 0.66$ ;  $P = 0.003$ ). Elevated CSF levels of CXCL12 and CXCL13 measured in seven CNS lymphoma patients during therapy decreased in five patients who responded to chemotherapy and increased in two with lymphoma progression.

**Conclusions:** Our results suggest a production of CXCL13 within the CNS of CNS lymphoma patients, which decreases with response to therapy. Thus, CXCL13 may represent a marker for further diagnostic and prognostic studies. (Clin Cancer Res 2009;15(19):5968–73)

Primary central nervous system (CNS) lymphoma is rare subtype of extranodal non-Hodgkin's lymphoma, mostly diffuse large B-cell lymphoma, confined to the CNS in the absence of systemic disease (1). Mechanisms leading to lymphoma development in the CNS normally devoid of a lymphatic system are still unclear. Lymphocyte homing to the CNS regulated by chemokines may play an important role in the pathogenesis of this disease.

CXCL12 and CXCL13 are important chemokines mediating germinal center organization in lymphoid tissue (2). CXCR5 is the prime receptor for CXCL13, which causes homing of B-helper cells and a subset of T-helper cells to the lymphoid follicle. Follicular dendritic cells located in the germinal centers

of lymphoid follicles are considered the main source of CXCL13. CXCL13 expression was shown in several B-cell lymphomas, some with extranodal location such as gastric or ocular adnexal lymphomas (3–6).

CXCR4, the receptor for CXCL12, is physiologically expressed on B and T cells, bone marrow stroma cells, and other hematopoietic cells. Expression of CXCR4 on malignant cells has been reported for a variety of tumors such as glioblastoma, breast cancer, and B- and T-cell lymphoma. CXCL12 is expressed by a wide variety of tissues and plays a key role in the trafficking of hematopoietic cells but is also involved in tumor growth and metastasis (7–10).

Recently, the expression of CXCR4 and CXCR5, as well as their chemokine ligands, CXCL12 and CXCL13, has been shown on malignant lymphocytes in primary CNS lymphoma (11–14). These findings suggest a role for chemokines in the pathogenesis of primary CNS lymphoma.

We studied the levels of both chemokines in the cerebrospinal fluid (CSF) and serum of patients with CNS lymphoma before and during therapy and compared the results to controls with other CNS malignancies and nonmalignant CNS diseases.

### Materials and Methods

**Patients and samples.** CSF samples obtained by lumbar puncture and serum samples were collected from patients with newly diagnosed or relapsed primary or secondary CNS lymphoma. All had B-cell non-Hodgkin's lymphoma, confirmed either by brain biopsy or CSF

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Received 1/17/09; revised 5/14/09; accepted 5/26/09; published OnlineFirst 9/22/09.

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doi:10.1158/1078-0432.CCR-09-0108

## Translational Relevance

Chemokines are suspected to play a role in the pathogenesis of central nervous system (CNS) lymphoma. The chemokines CXCL13 and CXCL12, as well as their respective chemokine receptors, CXCR4 and CXCR5, are expressed on primary CNS lymphoma tumor cells. We studied cerebrospinal fluid (CSF) and serum samples of 30 CNS lymphoma patients and 40 controls to find a unique pattern in CNS lymphoma. CXCL13 was significantly raised in the CSF of CNS lymphoma patients correlating with the degree of blood-brain barrier disruption and decreased after lymphoma response to chemotherapy. Thus, we believe that CXCL13 levels in CSF represent tumor burden in CNS lymphoma patients and may serve as a marker for further diagnostic and prognostic studies.

immunocytology. Pretherapeutic sampling was done before chemotherapy was started. Corticosteroid pretreatment was allowed.

For the control group, patients undergoing diagnostic lumbar punctures at our hemato-oncology and neurology departments were enrolled. All patients gave written informed consent for the analyses.

CSF drawn by lumbar puncture was processed immediately at room temperature. CSF protein and albumin were measured by nephelometry, and total CSF cells were enumerated in a counting chamber. For chemokine measurements, CSF cells were pelleted by centrifugation (4 min; 4,000 rpm), and supernatants were stored at  $-80^{\circ}\text{C}$ . Paired serum samples were also collected and stored at  $-80^{\circ}\text{C}$ . For determination of blood-brain barrier disruption, the ratio of albumin in CSF and serum ( $Q_{\text{alb}}$ ) was calculated (15). The extent of blood-brain barrier disruption was graded according to the  $Q_{\text{alb}}$  value as none ( $\leq 7.4 \times 10^{-3}$ ), slight ( $>7.4$  and  $\leq 10 \times 10^{-3}$ ), moderate ( $>10$  and  $\leq 20 \times 10^{-3}$ ), and severe ( $>20 \times 10^{-3}$ ).

**Enzyme-linked immunosorbent assay.** For enzyme-linked immunosorbent assays of CSF supernatants and serum samples, the Quantikine Human CXCL13/BLC/BCA-1 and the Quantikine Human CXCL12/SDF-1 $\alpha$  immunoassay kits were purchased from R and D Systems and were used according to the manufacturer's instructions. The minimum detectable chemokine doses were 0.4 pg/mL CXCL13 and 1.0 pg/mL CXCL12.

**Statistical analyses.** Descriptive and explorative data analyses of all parameters were done. Quantitative parameters were tested for normal distribution. To detect significant differences, the Kruskal-Wallis and Mann-Whitney  $U$  tests were used for quantitative parameters and the  $\chi^2$  square test for nonquantitative parameters.

For bivariate correlations, the Spearman's  $r$  was calculated. All tests were two-sided, with a  $P$  value of  $<0.05$  indicating a significant difference. For all statistical analyses, the SPSS software package for Windows, release 15.0.1, was used.

## Results

**Patients' characteristics.** Included were 23 patients with primary CNS lymphoma and 7 patients with secondary CNS lymphoma. CNS histology was diffuse large B-cell lymphoma in 28 patients, including three patients with Richter's transformation of a systemic indolent B-cell lymphoma. Two patients had an indolent CNS B-cell lymphoma, one of which was secondary. Four patients had leptomeningeal lymphoma spread in addition to their brain parenchyma manifestations, and none had intraocular involvement as controlled by slit lamp examination. All lymphoma patients were HIV negative.

There were 2 control groups: 10 patients with CNS involvement of cancer (7 with meningeal or brain metastases of solid tumors and 3 with glioblastoma) and 30 patients without CNS malignancy (6 lymphoma and 3 cancer patients without CNS involvement, 12 with normal pressure hydrocephalus, 4 with dementia, and 4 who had exclusion of inflammatory CNS disease).

CNS lymphoma patients were more often male compared with the control groups, CSF cell count and  $Q_{\text{alb}}$  were the highest in CNS lymphoma patients and lowest in no-CNS cancer controls, and total protein was higher in CNS lymphoma and cancer patients compared with no-CNS cancer controls. Moderate or severe blood-brain barrier disruption was significantly more frequent in the CNS lymphoma group as compared with the no-CNS cancer group (76% versus 26% of patients, respectively; Table 1).

**Chemokine levels in CNS lymphoma patients and controls.** CXCL12 serum levels were high both in CNS lymphoma patients and controls, without a significant difference between the groups (Table 2). There was a trend toward higher levels in

**Table 1.** Characteristics of patients and control subjects

	CNS lymphoma	Controls (CNS cancer)	Controls (no CNS cancer)	P
No. of patients	30	10	30	
CSF samples	29	9	25	
Age, y	52-86 (67)	54-76 (63)	25-83 (62)	0.39
Sex, male/female	19/11	4/6	9/21	0.032
CSF, cells/ $\mu\text{L}$	0-81 (9.0)	1-40 (6.0)	0-26 (1.0)	0.0003
CSF protein, mg/dL	16-376 (98)	44-136 (100)	24-129 (52)	0.014
$Q_{\text{alb}}, \times 10^{-3}$	3.4-62.7 (19.2)	7.3-24.4 (13.7)	2.8-25 (6.7)	0.001
BBB disruption	(n = 21)	(n = 7)	(n = 19)	
None	3	1	13	
Slight	2	2	1	
Moderate	6	3	4	
Severe	10	1	1	0.0007

NOTE: Median values are in parentheses.  
Abbreviation: BBB, blood-brain barrier.

**Table 2.** Chemokine levels in the CSF and serum

	CXCL13		CXCL12	
	CSF	Serum	CSF	Serum
CNS lymphoma patients, pg/mL				
Median	468	77	880	2,088
Range	41-1,384	36-657	144-3,537	692-2,944
Controls (CNS cancer), pg/mL				
Median	6	94	934	1,987
Range	0-601	21-363	111-2,040	1,643-2,345
Controls (no CNS cancer), pg/mL				
Median	8	65	785	1,352
Range	0-187	28-170	139-2,442	851-2,566
<i>P</i>	0.000000047	0.57	0.48	0.091

CNS lymphoma compared with all controls (median values 2,088 and 1,500 pg/mL;  $P = 0.059$ ). CXCL12 CSF levels were lower than serum levels in all groups and did not differ between CNS lymphoma patients and controls (Fig. 1).

CXCL13 serum levels were, unlike CXCL12, low in all patients (median, <100 pg/mL). In patients without CNS lymphoma also, CXCL13 CSF levels were very low. Only CNS lymphoma patients had high CXCL13 CSF levels; the difference to CNS cancer and noncancer controls was highly significant (Fig. 1).

**Blood-brain barrier function and chemokine levels in CNS lymphoma.** Serum and CSF chemokine levels were correlated in CNS lymphoma patients to exclude a possible impact of high systemic chemokine levels on CSF levels in the presence of a disrupted blood-brain barrier. No correlation of CXCL12 and CXCL13 levels in CSF and serum was found with  $r$ 's of 0.14 ( $P = 0.62$ ) for CXCL13 and 0.13 ( $P = 0.67$ ) for CXCL12, respectively. The lack of correlation persisted when all control patients were included into the analysis.

CSF CXCL13 levels in CNS lymphoma patients were significantly associated with  $Q_{alb}$  ( $R = 0.66$ ;  $P = 0.003$ ), whereas no such association was found for CSF CXCL12 levels. There was neither a correlation of both chemokines with the number of CSF cells per microliter nor with the presence of lymphoma

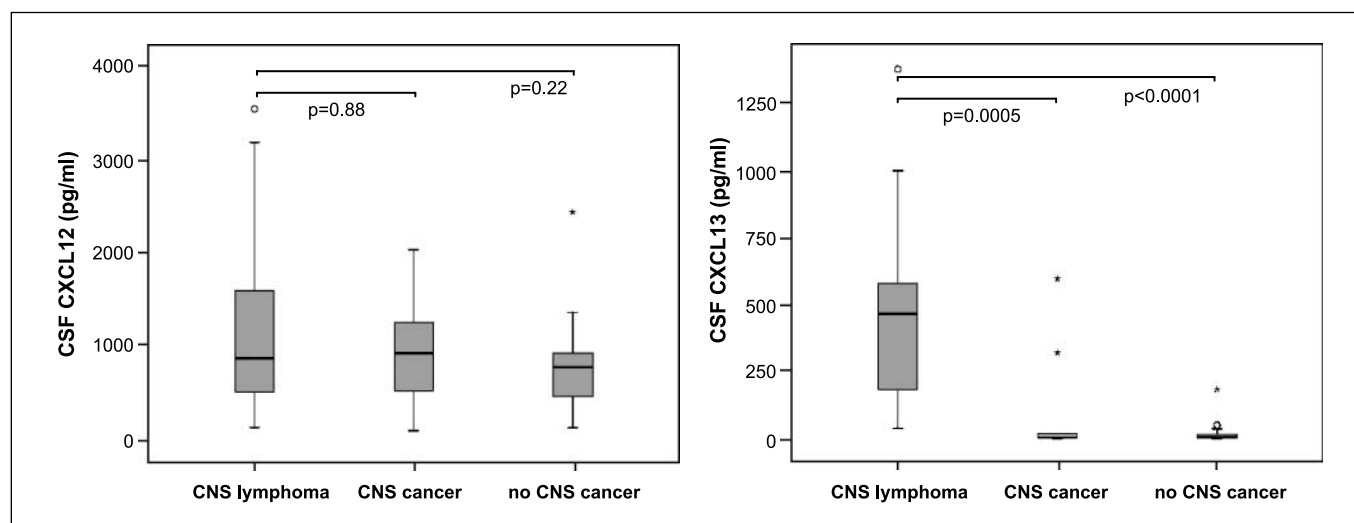
cells in the CSF (detected either by cytomorphology or immunocytology).

**Corticosteroid pretreatment.** Data on corticosteroid pretreatment were recorded in 26 of 30 CNS lymphoma patients: 20 patients received 3 to 24 mg of systemic dexamethasone per day, and 6 patients had not been pretreated with corticosteroids before sampling.

Serum and CSF chemokine levels were not significantly different in patients with and without corticosteroid pretreatment, although there was a trend toward lower CXCL12 serum levels in patients on corticosteroids (Table 3).

**Serum chemokine levels in systemic lymphoma.** CXCL12 and CXCL13 serum levels in 9 patients with systemic B-cell lymphoma (5 with diffuse large B-cell lymphoma and 4 with indolent B-cell lymphoma, including 5 with secondary CNS involvement) and 19 patients without lymphoma were compared. Median CXCL12 serum levels were 2,059 pg/mL in systemic lymphoma patients and 1,357 pg/mL in patients without lymphoma ( $P = 0.069$ ); median CXCL13 levels were 105 and 65 pg/mL ( $P = 0.039$ ), respectively (Fig. 2).

**Chemokines and therapy in CNS lymphoma.** Serial CSF measurements before, during, or after chemotherapy were done for CXCL12 in five and for CXCL13 in six patients, including

**Fig. 1.** Chemokine levels in the CSF.

**Table 3.** Chemokines and corticosteroid pretreatment in CNS lymphoma

	CSF		Serum	
	CXCL12	CXCL13	CXCL12	CXCL13
Corticosteroid pretreatment ( <i>n</i> = 20), pg/mL	888	457	1,860	55
No corticosteroid pretreatment ( <i>n</i> = 6), pg/mL	556	584	2,620	65
<i>P</i>	0.24	0.27	0.06	1.0

NOTE: Median chemokine levels are presented.

one patient each with a progressive lymphoma. All other patients responded to therapy (partial or complete remission). Chemotherapy consisted of high-dose methotrexate (4 g/m<sup>2</sup> i.v. over 4 hours; day 1) and ifosfamide (1,5 g/m<sup>2</sup> i.v. per day; days 3-5) in all patients.

During chemotherapy CSF chemokine levels decreased 1.1 to 10.1 times (mean, 3.8) in all responding patients and increased in both patients with progressive disease (Fig. 3). Very low CSF CXCL12 and CXCL13 levels were detectable in one patient in complete remission, in whom relevant pretreatment specimens were not available.

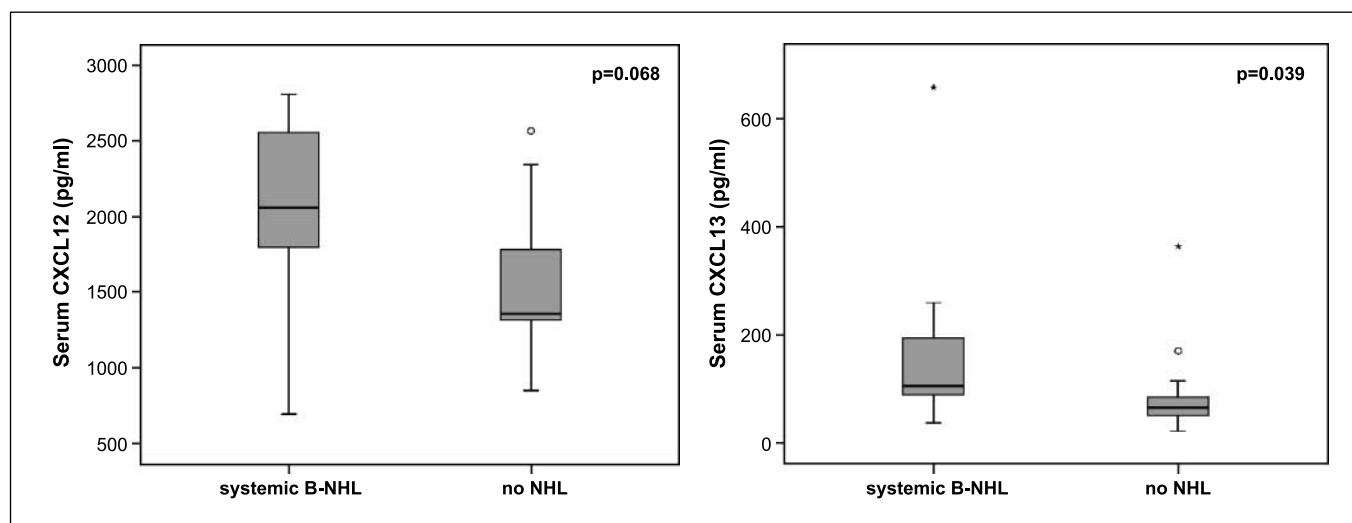
In patients responding to therapy, CXCL13 levels dropped to values comparable with those measured in controls (<100 pg/mL) in all but one patient with a complete resolution of an intracerebral lesion and a persistence of the concomitant meningeal involvement on therapy. In one patient who had complete surgical removal of primary CNS lymphoma, a low CXCL13 level was found before chemotherapy.

## Discussion

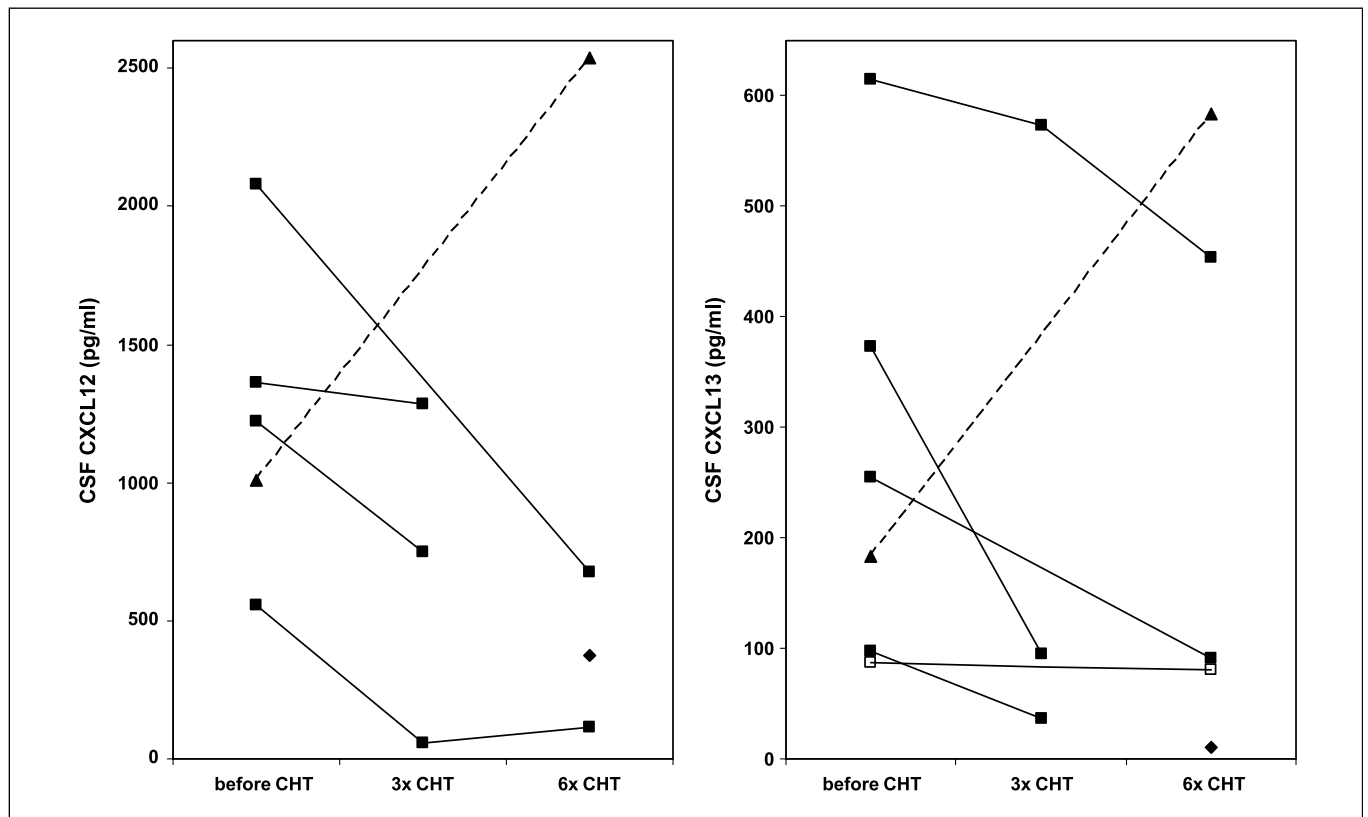
In our study, we detected high concentrations of CXCL12 and CXCL13 in the CSF of CNS lymphoma patients, with a significant difference for CXCL13 as compared with control patients, whereas no difference was found for CSF CXCL12. It seems likely that these findings reflect the role of the chemokines in the pathogenesis, homing, and survival of malignant lymphoma cells in the CNS (16). Both chemokines are known as homing

factors for B cells, but it remains unclear whether B cells undergo a malignant transformation before or after homing to the CNS. CXCL13 expression has not been detected in healthy CNS but in malignant B cells in primary CNS lymphoma, as shown by *in situ* hybridization for CXCL13 mRNA (13). Follicular dendritic cells are the only proven physiologic source of CXCL13; however, normal CNS lacks the formation of germinal centers. However, the formation of ectopic germinal centers within the meninges and intra-CNS production of CXCL13 has been shown in inflammatory CNS diseases such as neuroborreliosis and multiple sclerosis (17-22). An inflammatory CNS lesion initiating B-cell homing to the CNS may represent a first step in the pathogenesis of CNS lymphoma. CXCL12 expression on vascular endothelia facilitating the crossing of lymphocytes through the blood-brain barrier (11, 14) and the prevention of apoptosis (as shown for CXCL13 in B-cell chronic lymphatic leukemia and for CXCL12 in malignant glioma) may additionally contribute to the malignant lymphoma pathogenesis (10, 23).

Because primary CNS lymphoma tumor cells express both chemokines and their corresponding receptors, their role in supporting tumor growth and survival by autocrine mechanisms seems possible. Because follicular dendritic cells are not normally present in CNS lymphoma, one can assume that CXCL13 measured in the CSF directly represents its production by lymphoma cells. This is also indicated by higher serum CXCL13 levels in patients with systemic B-cell lymphoma. The sources of CXCL12 in the CSF are probably manifold. CXCL12 is considerably smaller than albumin (89 versus 584 amino acids). Because



**Fig. 2.** Serum chemokine levels in the presence of systemic B-cell non-Hodgkin's lymphoma (NHL).



**Fig. 3.** CSF chemokines in CNS lymphoma patients during chemotherapy. Solid squares, patients responding to chemotherapy. Triangles, patients with progressive disease. Diamonds, patients in complete remission; no pretherapeutic measurements. Open squares, patients with complete tumor resection. CHT, chemotherapy.

serum CXCL12 levels were higher than CSF levels, it cannot be ruled out that CSF CXCL12 was derived from serum, particularly in the presence of a disrupted blood-brain barrier. However, we found neither a correlation of serum and CSF levels nor a correlation of CXCL12 CSF levels and the degree of blood-brain barrier disruption so that a production of CXCL12 within the CNS can also be assumed. Apart from lymphoma cells, endothelial cells of tumor vessels and reactive glia are other potential sources of this chemokine within the CNS (24).

The decrease of CSF chemokine levels parallel to lymphoma response to therapy in CNS lymphoma patients suggests a correlation with tumor burden. This assumption is supported by the significant correlation of CXCL13 with the grade of blood-brain barrier disruption because large tumors have a stronger impact on the blood-brain barrier, and a disrupted blood-brain barrier reconstitutes during successful chemotherapy. Thus, in particular, CXCL13 CSF levels might have a prognostic value in primary CNS lymphoma similar to CSF protein,

which also correlates with blood-brain barrier disruption and has been shown to predict outcome in this disease (25).

Corticosteroid application in primary CNS lymphoma patients might have biased our results because of the down-regulation of chemokine expression (26, 27). However, we did not find an impact of corticosteroid pretreatment on CSF chemokines levels. Serum CXCL12 levels were somewhat lower in corticosteroid pretreated patients, which possibly reflects the anti-inflammatory properties of corticosteroids.

According to our results, CXCL13 rather than CXCL12 seems to reflect the tumor burden and thus may represent a promising diagnostic and prognostic marker in CNS lymphoma warranting further studies. The potential role of both chemokines in the pathogenesis of CNS lymphoma should be evaluated.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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