Concentration of interferon-inducible T cell chemoattractant and monocyte chemotactic protein-1 in serum and cerebrospinal fluid of patients with Lyme borreliosis

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Abstract

Purpose: Chronic inflammation in Lyme borreliosis may be sustained by aberrant inflammatory response, characterized by Th1 lymphocyte predominance, which in turn may be determined by chemokines synthesized in inflammatory focus. The aim of the study was to evaluate synthesis of chemokines: interferon-induced T cell chemoattractant (I-TAC – chemoattractant for Th1 lymphocytes), and monocyte chemotactic protein (MCP-1) in Lyme borreliosis.

Material and methods: Study group consisted of 13 patients with erythema migrans, 10 with Lyme arthritis and 6 with neuroborreliosis. Serum, as well as cerebrospinal fluid (CSF) in neuroborreliosis, was obtained before (examination 1) and during (examination 2) antibiotic treatment. Control serum was obtained from 8 healthy volunteers and control csf from 8 patients in whom meningitis and neuroborreliosis was excluded after diagnostic lumbar puncture. The samples were assayed for MCP-1 and I-TAC by ELISA.

Results: Serum mean I-TAC concentration in examination 1 was 73.0 pg/ml in erythema migrans, 78.9 pg/ml in Lyme arthritis and 87.3 pg/ml in neuroborreliosis (29.9 pg/ml in controls, difference significant for neuroborreliosis) and did not change significantly in examination 2. MCP-1 serum concentration was significantly increased to 497.5 pg/ml in neuroborreliosis in examination 2. I-TAC concentration in csf remained low, while MCP-1 concentration in examination 1 was increased to 589.1 pg/ml, significantly higher than simultaneously in serum.

Conclusions: I-TAC synthesis is increased in Lyme borreliosis and may be a factor favoring predominance of Th1 lymphocyte subset. MCP-1 creates chemotactic gradient towards central nervous system and may contribute to csf pleocytosis in neuroborreliosis.

Key words: Lyme borreliosis, meningitis, chemokines.

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Received 22.11.2004 Accepted 26.01.2005

Introduction

Lyme borreliosis is an infectious disease whose etiologic agent, Borrelia burgdorferi spirochete, is transmitted from animal reservoir to humans by Ixodes ticks. Three stages can be distinguished in course of the disease: localized infection, early disseminated infection and chronic infection (lasting for >12 months) [1]. Typically affected sites are skin (primary lesion – erythema migrans, EM), musculoskeletal system (Lyme arthritis, LA) and central (CNS) and peripheral nervous system (neuroborreliosis) [1]. Spirochetes found in affected tissues are innumerous related to the intensity of inflammatory and destructive processes, which suggests that functional disorders of the immune system and autoimmune processes take important part in the pathogenesis of this disease, especially in its chronic stage [2-4]. Consistently with that, clinical course of Lyme borreliosis is often prolonged and antibiotic treatment tends to be inefficient in chronic disease. The more profound understanding of the pathogenesis of inflammation in patients with chronic Lyme borreliosis could possibly lead to development of new therapeutic approaches, aimed at the aberrant and prolonged inflammatory response.

Chemokines are family of cytokines characterized by a potent chemotactic activity towards leukocytes and playing a vital role in the development of inflammatory reactions. According to amino acid sequence and spectrum of activity they are divided into CXC-chemokine family (including, among the others, interleukine 8; Il-8) and CC-chemokine family [5]. Synthesis

of chemokines is induced by proinflammatory cytokines (interleukine 1β – Il-1β, tumor necrosis factor alpha – TNF-α) and viral and bacterial antigens including surface lipoproteins of Borrelia burgdorferi, and takes place in leukocytes, fibroblasts, epithelial and endothelial cells [5-7]. The enhanced synthesis of chemokines has been observed in the inflammation site in course of various infectious diseases. In meningitides of viral and bacterial etiology increased concentrations of chemokines in cerebrospinal fluid (CSF) are observed [8-12]. A dominant role of endogenous chemotactic factors, including chemokines, in driving leukocytes into inflammatory infiltrates in Lyme borreliosis is very likely, especially that membrane components of Borrelia burgdorferi spirochetes themselves do not show chemotactic activity [13].

Monocyte chemoattractant protein 1 (MCP-1) is a CC chemokine chemotactic for most of mononuclear cell populations [5,14]. Its receptor, CC-chemokine receptor 2 (CCR2), is expressed on Il-2-activated T lymphocytes, as well as on monocytes and basophils [5]. Borrelia burgdorferi and its surface lipoproteins induce MCP-1 synthesis in endothelial cells, fibroblasts and monocytes [6,7,15]. The capability of astrocytes and microglia to synthesize MCP-1 and its presence in CSF of patients with both viral and bacterial meningitis suggest that MCP-1 may be also synthesized within CNS in course of neuroborreliosis [11,16,17].

Interferon-induced T cell chemoattractant (I-TAC) is a CXC chemokine acting via a CXC-chemokine receptor 3 (CXCR3) (18,19). CXCR3 is expressed on T lymphocytes under stimulation with Il-2 and is present on active T lymphocytes and memory cells as well as, to a lesser extent, on NK cells and B lymphocytes [20-24]. I-TAC synthesis by monocytes and neutrophils may lead to recruitment of activated T lymphocytes to the inflammation site. I-TAC is also produced by astrocytes, which suggests its role in the inflammatory processes within CNS [20,21]. I-TAC synthesis is induced by IFN-γ and further enhanced by tumor necrosis factor alpha (TNF-α), Il-1 and lipopolisacharide (LPS), which, however, do not induce I-TAC expression on their own [18,20,21]. Il-4 and Il-10 suppress I-TAC synthesis, which may contribute to the regulation of the inflammatory response in vivo [20,21]. As far as its amino acid sequence and activity, I-TAC shows much similarity to IP-10 and Mig chemokines, which are also induced by IFN-γ and bind CXCR3, but with less affinity [19,20].

The purpose of our study was to evaluate the role of MCP-1 and I-TAC as factors possibly responsible for migration of mononuclear cells, especially activated T lymphocytes, into the inflammatory focus in Lyme borreliosis. To check for their increased synthesis in Lyme borreliosis in vivo and their role in creating chemotactic gradient, we measured MCP-1 and I-TAC concentration in serum of patients with different clinical forms of Lyme borreliosis, as well as in CSF of patients with neuroborreliosis.

Material and methods

The study included 29 patients with Lyme borreliosis (14 females and 15 males, age 21-68 years, mean 44.6) hospitalized in the Department of Infectious Diseases and Neuroinfections of the Medical University of Białystok or treated in the Outpatient Department of the Dłuski Regional Specialist Hospital in Białystok. Diagnosis was based on epidemiological data, anamnesis, physical examination and presence of anti-Borrelia burgdorferi antibodies in serum, and in neuroborreliosis also in CSF. Generally, diagnosis made by treating physician and recorded in medical documentation was a rationale for patients' inclusion into the study group. All Lyme borreliosis patients reported either tick bites or frequent exposure to ticks in endemic areas. The clinical forms of Lyme borreliosis were distinguished according to Åsbrink [1]. Diagnosis of EM was based on the presence of typical skin lesion at least 5 cm in diameter, developing within several days or weeks around the place of tick bite. Neuroborreliosis (NB) was diagnosed in patients either with lymphocytic meningitis or symptoms of chronic CNS involvement, antibodies against Borrelia burgdorferi detectable in serum and CSF and no indication of other probable etiology. Lyme arthritis (LA) was diagnosed in patients complaining of chronic or recurrent musculoskeletal pain, affecting mainly large joints of upper and lower extremities, who had IgG antibodies against Borrelia burgdorferi detectable in serum and no features of acute inflammation in basic laboratory tests (ESR, leukocyte and platelet count). Depending on clinical picture, other examinations were carried out (detection of rheumatoid factor by standard laboratory test, radiological examination of affected joints), which excluded other probable causes of musculoskeletal symptoms.

Patients were divided into three groups: with EM – 13 patients, 7 females and 6 males (21-68 years, mean – 45.5); with LA – 10 patients, 4 females and 6 males (24-64 years, mean – 44.5) and with NB – 6 patients, 3 females and 3 males (27-51 years, mean – 42.8). Typically, patients from different study groups represented consecutive stages of Lyme borreliosis. EM patients had short history of the disease, with symptoms lasting for days or weeks (early localized infection), NB patients presented with duration of illness from a few weeks (early disseminated infection) to 1-2 years while LA patients complained of chronic and/or recurrent symptoms (chronic infection). Control group (C) consisted of 16 people: serum samples were obtained from 8 healthy persons (blood donors from the Regional Blood Donation Center in Białystok) and CSF samples from 8 patients in whom meningitis and neuroborreliosis were excluded after performing diagnostic lumbar taps. Informed consent was obtained from the patients and the study design was approved by the Ethics Committee of the Medical Academy in Białystok.

For the purpose of the study we used serum samples obtained together with venous blood for routine laboratory examinations, before treatment (examination 1) and during or after antibiotic therapy with doxycycline or III generation cephalosporine (examination 2). In NB group, CSF obtained by spinal puncture performed for diagnostic purpose was also examined. All samples were stored at -80°C and tested simultaneously. In EM group the period between examination 1 and 2 was from 23 to 40 days (mean ± SD – 30.1 days ± 5.5), in LA group – from 5 to 52 days (14.6 days ± 13.6) and in NB group the period between taking serum samples was from 8 to 66 days (36.2 days ± 24.1); treatment-phase CSF samples were available

Table 1. **I-TAC concentrations in serum of patients with erythema migrans, Lyme arthritis and neuroborreliosis before treatment (examination 1) and during antibiotic therapy (examination 2) in comparison with the values observed in serum of controls (pg/ml)**

Group	Examination 1			Examination 2		
	min-max	$\bar{x}$	SD	min-max	$\bar{x}$	SD
EM (n=13)	2.79-173.16	73.00 ¶	54.18	2.03-379.48	88.66	112.16
LA (n=10)	5.14-440.31	78.87	132.51	3.93-630.63	90.26 ¥	191.43
NB (n=6)	46.00-149.73	87.25 **	38.58	70.56-137.93	96.76 ** ¥	28.82
C (n=8)	0.57-50.17	29.86	15.49	-	-	-

EM – erythema migrans; LA – Lyme arthritis; NB – neuroborreliosis; C – control group; min-max – the range of concentrations observed; $\bar{x}$ – mean; SD – standard deviation; ¶ – difference on the border of statistical significance in comparison with controls (p=0.0579); ** – statistically significant difference in comparison with controls (p< 0.01); ¥ – statistically significant difference between groups of patients with NB and with LA in examination 2 (p<0.05)

Table 2. **MCP-1 concentrations in serum of patients with erythema migrans, Lyme arthritis and neuroborreliosis before treatment (examination 1) and during antibiotic therapy (examination 2) in comparison with the values observed in serum of controls (pg/ml)**

Group	Examination 1			Examination 2		
	min-max	$\bar{x}$	SD	min-max	$\bar{x}$	SD
EM (n=13)	136.72-453.66	277.17	86.35	175.10-276.12	323.50	140.55
LA (n=10)	100.80-699.24	388.97	208.00	180.64-832.34	429.06¶	216.64
NB (n=6)	159.34-226.00	245.78 #§	78.24	226.00-775.74	497.47 * §	215.87
C (n=8)	152.32-314.60	253.71	55.25	-	-	-

EM – erythema migrans; LA – Lyme arthritis; NB – neuroborreliosis; C – control group; min-max – the range of concentrations observed; $\bar{x}$ – mean; SD – standard deviation; ¶ – difference on the border of statistical significance in comparison with controls (p=0.0506); * – statistically significant difference in comparison with controls (p<0.05); § – difference on the border of statistical significance between examination 1 and 2 in NB group (p=0.0796)

in 5 out of 6 NB patients and were obtained from 6 to 66 days after the first sample (32 days ±23.9).

IgM and IgG antibodies against Borrelia burgdorferi were detected with ELISA assay from Biomedica (Viena, Austria), according to manufacturer's instructions. Following Borrelia burgdorferi recombinant antigens were included in the assay: p21 (OspC), Borrelia garinii p41 and Borrelia afzelii p41 for IgM detection and p21, B. garinii p41, B. afzelii p41, p18 and p100 for IgG detection. Results were expressed as BBU/ml (Biomedica Borrelia units/ml) and >11 BBU/ml was considered positive. In case of borderline results (9-11 BBU/ml) sera were re-evaluated with Western blot assays Milenia Blot Borrelia IgM and IgG (DPC Bierman GmbH, Germany). Patients with symptoms of meningitis were examined for presence of antibodies against tick-borne encephalitis virus in class IgM and IgG in serum and CSF with ELISA assay from Virion/Serion (Würzburg, Germany). The CSF protein concentration and pleocytosis were measured on the day of CSF collection, with standard laboratory techniques. MCP-1 and I-TAC concentrations were measured in serum and CSF samples by ELISA assay with reagents from R&D Systems (USA), following the manufacturer's instructions.

Statistical analysis was performed by means of SSST software. The Mann-Whitney test was used for comparisons of the chemokine concentrations between groups and between serum and CSF. The levels in examination 1 and 2 were compared by means of Wilcoxon's paired test. Pearson's linear correlation coefficient was used to estimate correlations between variables. The value of $p < 0.05$ was considered statistically significant.

Results

I-TAC concentration in patients' serum together with statistical interpretation is shown in *Tab. 1*. Mean I-TAC concentration was significantly increased in NB group both before and after treatment, while in EM in examination 1 it was increased with borderline significance.

MCP-1 concentrations are presented in *Tab. 2*. Significant increase of MCP-1 concentration in comparison with control serum was observed in NB group in examination 2 and borderline increase – in LA in examination 2. In NB group there was also increase of MCP-1 concentration between examination 1 and 2.

The mean chemokine concentrations in CSF are shown in *Tab. 3*. I-TAC concentration was significantly increased in comparison with control CSF both before and after treatment, but it remained lower than simultaneous concentration of I-TAC in serum. Concentration of MCP-1 before treatment showed only a borderline tendency to increase when compared with control CSF, but was significantly higher than concentration observed at the same time in serum; this difference was no longer present in examination 2.

CSF of all patients with NB presented with changes characteristic of lymphocytic meningitis, except for one patient whose CFS parameters were within the normal range (<5 cells/mm^3 and protein concentration <45 mg/dl). The mean CSF pleocytosis was $\bar{x}$=153/mm^3 (from 1 to 343) in examination 1, whereas, in examination 2, it improved to $\bar{x}$=17/mm^3 (from 12 to 23), with percentage of mononuclear cells in both examinations

Table 3. **I-TAC and MCP-1 concentrations in cerebrospinal fluid of patients with neuroborreliosis before treatment (examination 1) and during antibiotic therapy (examination 2) in comparison with the values observed in serum of these patients and in control cerebrospinal fluid (pg/ml)**

Chemokine	Examination 1			Examination 2			C		
	min-max	$\bar{x}$	SD	min-max	$\bar{x}$	SD	min-max	$\bar{x}$	SD
I-TAC	25.63-55.42	36.69 ** †	13.12	28.72-58.41	44.84 ** †	11.70	16.79-26.75	23.23	3.38
MCP-1	306.36-872.16	589.11 ¶ ‡	235.11	214.40-940.82	510.95	253.17	306.13-400.50	356.01	36.94

C – control group; min-max – the range of concentrations observed; $\bar{x}$ – mean; SD – standard deviation; ¶ – difference on the border of statistical significance in comparison with controls ($p=0.0528$); ** – statistically significant difference in comparison with controls with $p<0.01$; † – significantly lower levels than observed simultaneously in serum ($p<0.05$); ‡ – significantly higher levels than observed simultaneously in serum ($p<0.05$)

ranging from 80 to 100%. The mean protein concentration was $\bar{x}=76.5$ mg/dl (44.3-145.4 mg/dl) in examination 1 and $\bar{x}=59.25$ mg/dl in examination 2.

The serum and CSF concentrations of chemokines were not significantly correlated with CSF inflammatory parameters (data not shown). In case of MCP-1 there was a tendency for positive correlation of its CSF concentration with CSF parameters (protein level, and total, mononuclear and polynuclear cell count), which, however, did not reach statistical significance.

Discussion

Our study revealed a consistent tendency for increased concentrations of I-TAC and MCP-1 in serum of patients with Lyme borreliosis. The role of I-TAC in Lyme borreliosis has not been evaluated so far. In our study we found mean concentration of I-TAC to be from 2.4 to 3.2 – fold higher in patients with different forms of Lyme borreliosis in comparison with controls, which, however, was statistically significant only in neuroborreliosis. The important role of MCP-1 in Lyme borreliosis was already suggested by results of in vitro studies by Sprenger's et al., who found that MCP-1 synthesis was most effectively stimulated by a small number of Borrelia burgdorferi cells (1 bacterial cell per 10 monocytes) [6]. In the same setting, Il-8 was produced most effectively at the spirochete to monocytes ratio of 1:1 and MIP-1α at 10:1 [6]. This suggests that production of MCP-1 in vivo may be initiated by a relatively small number of invading spirochetes [6]. In the study of Gergel et al. MCP-1 appeared to be a factor responsible for T lymphocyte migration across cultured human endothelium incubated with B. burgdorferi [25]. However, in contrast with in vitro data, in the study of Pashenkov et al. no elevated levels of MCP-1 were detected in serum and CSF of patients with Lyme meningitis [26]. In our study, MCP-1 levels were not significantly increased in serum of patients before treatment, but reached significantly increased values in examination 2 in neuroborreliosis (and of borderline significance in LA group).

I-TAC concentration remained significantly lower in CSF of patients with neuroborreliosis than in serum, arguing against its role in causing CSF pleocytosis. In contrast with that, the mean MCP-1 concentration before treatment, as well as individual concentrations in all studied patients, were higher in CSF than in serum, which suggests that MCP-1 may participate in stimulating migration of mononuclear cells to CSF in neuroborreliosis. So far, similar chemotactic gradient towards CSF in neuroborreliosis was observed for Il-8, however, it was present only in 10 out of 20 patients examined and in the whole studied group there was no difference between mean Il-8 concentration in CSF and serum [27]. MCP-1 is present in CSF of patients with viral and purulent meningitis, where it seems to be the main factor responsible for the migration of monocytes/macrophages to CSF and contributing to the migration of T lymphocytes [8,11,17]. Concentrations of MCP-1 in CSF were generally higher (3-6 ng/ml) and concentration gradient between CSF and serum was more evident in patients with viral and purulent meningitides than in patients with neuroborreliosis included in our study [8,11]. More similar to values we noted in neuroborreliosis was mean concentration of MCP-1 observed by Mastroianni et al. in patients with tuberculous meningitis (808 pg/ml), a condition which differs from neuroborreliosis in terms of severity but resembles it with its prolonged and subacute clinical course [8]. Lack of significant correlation between CSF pleocytosis and MCP-1 concentration does not exclude pathogenetic significance of this chemokine, as any correlation of this kind must be weakened by multiplicity of factors contributing to the inflammatory state within CSF. Other studies in which chemokine concentrations were measured in CSF of patients with meningitis showed either no correlation at all or only limited to certain forms of meningitis and certain leukocyte populations [6,8,9].

There was no decline in chemokine concentrations between examination 1 and 2, and even a weak tendency for increase could be observed, which reached the borderline significance in case of MCP-1 in patients with neuroborreliosis. Of note, the examination 2 was often carried out before completion of treatment, which typically lasted four weeks. However, this result is in contrast with our previous study, in which concentrations of Il-8 and β-chemokines: macrophage inflammatory protein-1α and 1β (MIP-1α and MIP-1β) in serum and CSF of patients with Lyme borreliosis fell several-fold during two weeks of treatment [27]. It may suggest the long-term maintenance of the synthesis of MCP-1 and I-TAC in patients with Lyme borreliosis and possibly their involvement in some form of protracted inflammatory reaction, which is sustained in spite of antibiotic therapy and spirochete elimination. Conversely, it could be hypothesized that the increased synthesis of I-TAC and/or MCP-1 at this time point is somehow related to the resolution of the inflammatory

condition. Further studies serially measuring concentrations of MCP-1 and I-TAC in larger groups of patients and relating them to other markers of inflammation and clinical course and outcome of the disease could possibly clarify that issue.

The tendency to predominance of inflammatory response dependent on lymphocytes of either Th1 (with increased synthesis of IFN-γ) or Th2 (synthesis of Il-4, Il-5 and Il-10) subset in different infections can vary individually and condition the host's capability to eliminate various pathogens [28]. According to Gergel et al., human endothelium incubated with B. burgdorferi promotes a selective migration of IFN-γ secreting T lymphocytes and may recruit them into inflammatory lesion, which suggests that Th1 response to B. burgdorferi typically dominates [25]. However, in Lyme borreliosis predominance of cytokines released by Th2 lymphocytes over the cytokines produced by Th1 cells may be associated with milder inflammatory reaction and better prognosis [29,30]. Th1 predominance was suggested to be associated with the prevailing cellular response, which may not be fully effective in Borrelia burgdorferi elimination and lead to prolonged infection, tissue damage and even autoimmunity [2,29]. The experiments on mice suggest an unfavorable effect of IFN-γ and favorable of Il-4 on symptoms of Lyme arthritis [30]. An increased IFN-γ and a decreased Il-4 expression was observed in the joints of patients with chronic LA, which may indicate that this type of response promotes a clinical manifestation of the disease in humans [29]. Also in neuroborreliosis IFN-γ synthesis in peripheral blood and CSF lymphocytes dominates over Il-4 synthesis [31].

According to the study of Sallusto et al., the predominance of Th1 or Th2 cells in inflammatory focus may depend on a spectrum of produced chemokines, which determine the selective migration and accumulation of different populations of T lymphocytes at the site of an inflammation [24]. Studies on I-TAC synthesis indicate its dependence on IFN-γ and inhibition by Il-4 and Il-10 [19-21]. According to Burns et al. synthesis of MPC-1 by the endothelium incubated with Borrelia burgdorferi was inhibited by Il-10 [15]. This may suggest the connection of both chemokines with the Th1 type response and suppression of their synthesis in the case of the Th2 response predominance. The receptor for I-TAC (CXCR3) is exposed on Th1 in several-fold higher quantities than on Th2 lymphocytes, which is reflected by stronger chemotactic effect of I-TAC on Th1 than on Th2 cells [22-24]. According to Quin et al., CXCR3 is found on practically all T cells forming inflammatory infiltrates in rheumatoid arthritis – a chronic inflammatory condition with a marked predominance of Th1 response [23]. Moreover, I-TAC and, to a lesser extent, related chemokines Mig and IP-10, act antagonistically on the chemokine receptor CCR3, expressed on eosinophils and Th2 lymphocytes, but not on Th1 cells [23,24,32]. This may allow I-TAC to inhibit Th2 cell migration stimulated through CCR3 and their accumulation in an inflammatory focus [32]. I-TAC seems to be connected by a positive feedback with Th1 cell activity, as it favors Th1 lymphocyte selective accumulation in inflammation site, while its synthesis is stimulated by Th1-related cytokines. As I-TAC demonstrates so evident association with the Th1 cytokine profile, the increase of its concentration in Lyme borreliosis seems consistent with the present knowledge about the cytokine patterns in this disease and may be considered another element of inflammatory processes unfavorable for its clinical course.

As for MCP-1, its relation to the specific cytokine profile in not explicit. The MCP-1 receptor is found on both main subsets of Th lymphocytes, but its expression is higher on Th1 cells; in vitro this chemokine attracts both Th1 and Th2 lymphocytes [23]. In the study of Gergel et al. migration of T lymphocytes across B. burgdorferi-stimulated endothelium driven by MCP-1 lead to selective enrichment in IFN-γ secreting cells [25]. However, some data from animal models suggest the connection between MCP-1 and Th2 type response [33,34]. In murine endotoxemia MCP-1 plays a protective role, enhancing the expression of Il-10 [33]. The differentiation of T lymphocytes towards Th2 phenotype due to MCP-1 was observed in mice, probably through the stimulation of Il-4 synthesis by MCP-1 [34]. Interestingly in this context, our study demonstrated significant increase of MCP-1 levels in serum, but not in CSF, of patients with Lyme borreliosis during the antibiotic treatment, suggesting its systemic synthesis being increased during the resolution phase of the inflammation caused by Borrelia burgdorferi.

Our study has shown the increased synthesis of chemokines acting on mononuclear cells, including activated T lymphocytes, MCP-1 and I-TAC, in patients with Lyme borreliosis. The increase in serum concentrations was more pronounced for I-TAC, and this chemokine, which is connected with Th1 profile of cytokine expression, may be one of the important pro-inflammatory factors in Lyme borreliosis and possibly promote its unfavorable clinical course. MCP-1 is present in CSF in neuroborreliosis and creates a chemotactic gradient between CSF and serum. It is likely that MCP-1 plays, next to Il-8, certain role in stimulating the inflow of leukocytes to CSF in course of neuroborreliosis.

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