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CHEMOKINE CXCL13 CONCENTRATION IN CEREBROSPINAL FLUID IN PATIENTS WITH NEUROBORRELIOSIS – OWN OBSERVATIONS

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ABSTRACT

THE AIM of the study was to evaluate the usefulness of cerebrospinal fluid chemokine CXCL13 concentration assay in diagnostics of neuroborreliosis in adults.
MATERIAL AND METHODS. Investigations were carried out in 22 patients treated for neuroborreliosis , manifested as lymphocytic meningitis, at the Department of Infectious Diseases, Medical University of Silesia, in Bytom between 2011-2013. Based on the presence or absence of anti-borrelial antibodies in the cerebrospinal fluid, the examined individuals were divided into two groups on the day of admission: group I – patients with antiborrelial antibodies in the cerebrospinal fluid (confirmed diagnosis of neuroborreliosis), group II – patients without antiborrelial antibodies in the cerebrospinal fluid (possible diagnosis of neuroborreliosis). In all patients the cerebrospinal fluid CXCL13 level was assessed on the first day of hospitalization. Control tests were performed in both groups after 14 days of therapy with antibiotics.
RESULTS. Mean cerebrospinal fluid CXCL13 concentration in group I on the 1 st day was 4123 pg/mL, and in group II – 3422 pg/mL. Differences in mean concentrations of this chemokine were statistically insignificant. No correlations between examined mean CXCL13 concentrations and other cerebrospinal fluid inflammatory parameters were revealed. The control tests showed the evident decrease of CXCL13 level in cerebrospinal fluid in both groups. Besides, in individuals of group II anti-*Borrelia burgdorferi* antibodies appeared in cerebrospinal fluid, whereas in group I, the control results of this parameter were similar to preliminary values.
CONCLUSION. The obtained results indicate a kind of usefulness of estimation of cerebrospinal fluid chemokine CXCL13 concentration in diagnostics of early, acute neuroborreliosis, manifested as lymphocytic meningitis, especially in case of anti-borrelia antibodies absence in cerebrospinal fluid. Changes in this chemokine concentrations, opposite to cerebrospinal fluid levels of anti-borrelia antibodies, may be prognostic in acute, early neuroborreliosis.

Key words: *Lyme neuroborreliosis, chemokine CXCL13, cerebrospinal fluid*

INTRODUCTION

Borreliosis, also referred to as Lyme disease, is the most prevalent tick condition, recognized in Poland and worldwide. The disease affects several organs and systems, including the central and peripheral nervous system (neuroborreliosis). Diagnosis of neuroborreliosis bases upon the history taken, the clinical image , results of cerebrospinal fluid test (CSF) as well as serological investigations (fluid presence of *Borrelia burgdorferi* antibodies proving their intrameningeal synthesis (1,2).

In many cases, patients fails to report the tick bite or the skin lesions of erythema migrans (EM) nature. The clinical image of early neuroborreliosis may appear similar to other neurological conditions, including the viral, lymphocytic cerebrospinal meningitis. Most investigations of the cerebrospinal fluid during early neuroborreliosis showed increased pleocytosis with the dominance of lymphocytes and elevated protein concentration, while the fluid could show no presence of specific *Borrelia burgdorferi* antibodies. It appears quite frequent that routine evaluation of CSF parameters

(pleocytosis and cytogram, protein, glucose and lactic acid concentration) fails to provide certain diagnosis of neuroborreliosis at the early stage of the disease. Therefore, new cerebrospinal fluid parameters are looked for to enhance diagnostics of early neuroborreliosis, manifesting as lymphocytic cerebrospinal meningitis (2,3).

The aim of the study was to evaluate CSF concentration of CXCL13 chemokine in patients with acute early neuroborreliosis and to show possible advantages of determination of such parameter in early diagnostics and monitoring of the disease.

MATERIALS AND METHODS

Enrolled in the study were 22 patients admitted to the Clinical Ward of Infectious Diseases, Medical University of Silesia, throughout the years 2011 –2013. The group included 14 men (63.6%) and 8 women (36.4%). The youngest patient was 19. The and the oldest – 69, with the median age of 38.6 years.

All the patients were admitted to the Ward for the suspicion of neuroborreliosis. Each of them reported tick bites, often multiple ones, during the past 1 – 3 months. The erythema migrans was observed in 10 patients (45.45%). On admission all the patients reported headaches, nausea, vomiting, photofobia and subfebrile or febrile temperatures. Some patients reported also root pains of the lumbar-sacral spine (7 patients). The examination performed showed meningeal symptoms in all the patients, while 5 patients (27.73%) showed symptoms of unilateral or bilateral facial palsy (n. VII).

On admission, the lumbar puncture and cerebrospinal fluid (CSF) examination were carried out in all patients to evaluate pleocytosis and cytogram as well as protein, glucose, lactic acid and CXCL13 chemokine concentration. CXCL13 concentration was measured by the immunoenzymatic method with the use of *Quantikine human CXCL13/BLC/BCA-1* kits (*R&D Systems, Minneapolis, MN, USA*).

Serum and CSF concentrations of *Borrelia burgdorferi* antibodies were measured by ELISA method with positive or questionable results confirmed by the Western blot test (kits by BIOMEDICA, Poland). Should such antibodies be observed in the cerebrospinal fluid, the so-called antibody index, CSF/serum, was calculated to prove their intrameningeal synthesis.

Based on EFNS (2) criteria, the patients were divided into two groups:

- group I – patients with established diagnosis of neuroborreliosis (CSF presence of *Borrelia burgdorferi* antibodies) – 14 patients (63,.64%),
- group II – patients with tentative diagnosis of neuroborreliosis (no CSF presence of *Borrelia burgdorferi* antibodies) – 8 patients (36.36%)

IV treatment with antibiotics was commenced in all the patients: ceftriaxone (20 patients; 90.91%) or doxycycline (2 patients; 9.09%) along with the symptomatic treatment. None of the patients received any antibiotic prior to hospitalization.

On the 14th day of treatment, the control examination of the cerebrospinal fluid was performed in all the patients to measure all the aforementioned parameters.

The mean values of pleocytosis and concentrations of protein, glucose, lactic acid and CXCL13 chemokine between the evaluated patient groups were determined with the use of t Student test. Evaluation comprised also correlations between CSF parameters in both groups, using Pearson correlation coefficient.

In all cases, informed written consent was obtained from the patient to perform the investigations. The study and its assumptions were approved of by the Bioethical Committee of the Silesian Academy of Medicine (at present: The Medical University of Silesia) in Katowice (NN-6501-126/06).

RESULTS

Results of the cerebrospinal fluid tests performed on admission to the Ward, are presented in Table I.

In group I the mean pleocytosis was 114 cells in 1 mm^3, the cytogram was dominated by lymphocytes (56 – 92%), the mean concentration of protein was – 0.9 g/L, glucose – 2.5 mmol/L, lactic acid – 2.9 mmol/L and CXCL13 cytokine concentration was 4123 pg/mL. In this group the presence of *Borrelia burgdorferi* antibodies was observed in IgM class in serum of all the patients, with the mean titre of 132 RU/mL, and in IgG class in 4 patients with the mean titre of 88 RU/mL. *Borrelia burgdorferi* antibodies were also present in the cerebrospinal fluid: IgM with the mean titre of 69 RU/mL in 14 patients and IgG with the mean titre of 54 RU/mL in 4 patients. In all cases, the calculated

Table I. The results of CSF examination on the day of admission to the ward

Group	Pleocytosis (cell/mm^3)	Protein (g/L)	Glucose (mmol/L)	Lactic acid (mmol/L)	CXCL!3 (pg/mL)
I	114 (20-291)	0.9 (0.5-1,8)	2.5 (1.9-3,3)	2.9 (1.9-4.0)	4123 (1138-9040)
II	99 (17-240)	0,8 (0.5-1,6)	2,7 (1.7-3.8)	2,6 (2.0-4.8)	3422 (904-6711)

Table II. Follow-up CSF assay after 14 days of therapy

Group	Pleocytosis (cell/mm^3)	Protein (g/L)	Glucose (mmol/L)	Lactic acid (mmol/L)	CXCL!3 (pg/mL)
I	39 (13-53)	0,7 (0.4-1,6)	2,6 (2.0-2.9)	2,2 (1.3-3.0)	741 (163-1957)
II	53 (12-81)	0.6 (0,3-1,1)	2.4 (1,8-2,5)	2.1 (1,1-2,9)	531 (139-891)

antibody ratio CSF/serum confirmed the intrameningeal synthesis.

In group II the mean pleocytosis was 99 cells in 1 mm^3 , the lymphocytes sharing from 65 to 94% and concentration of the remaining CSF parameters scoring as follows: protein 0.8 g/L, glucose 2.7 mmol/L, lactic acid 2.6 mmol/L and the mean concentration of CXCL13 – 3422 pg/mL. The mean serum concentrations of *Borrelia burgdorferi* antibodies was about 180 RU/mL in IgM class and about 74 RU/mL in IgG class where they were observed in all patients. On the other hand, none of the patients showed the *Borrelia burgdorferi* antibodies in the cerebrospinal fluid.

Table II presents results of CSF follow-up after 14 day antibiotic therapy.

In group I the mean pleocytosis was 39 cells in 1 mm^3, the cytogram showing lymphocytes, the mean concentration of protein was 0.7 g/L, glucose – 2.6 mmol/L, lactic acid – 2.2 mmol/L and CXCL13 cytokine concentration was 741 pg/mL. The mean concentrations of *Borrelia burgdorferi* antibodies were as follows: serum IgM – 108 RU/mL, IgG – 110 RU/mL, while for CSF: IgM – 56 RU/mL, IgG – 65 RU/mL. Serum *Borrelia burgdorferi* antibodies were present in all the assessed patients in both classes.

In group II the mean pleocytosis was 53 cells in 1 mm^3, the cytogram showing lymphocytes and concentration of the remaining CSF parameters scoring as follows: protein 0.6 g/L, glucose 2.4 mmol/L, lactic acid 2.1 mmol/L and the mean concentration of CXCL13 – 531 pg/mL. The mean concentration of *Borrelia burgdorferi* antibodies were as follows: serum IgM – 160 RU/mL, IgG – 134 RU/mL; for CSF, IgM – 41 RU/mL, IgG – 72 RU/mL. The antibodies were present in all the patients, both in serum and in the cerebrospinal fluid.

Differences in mean values of pleocytosis and concentrations of protein, glucose, lactic acid as well as CXCL13 chemokine in the cerebrospinal fluid, observed between the evaluated groups were statistically insignificant.

DISCUSSION

Neuroborreliosis, referred to as the form of Lyme borreliosis, is manifested by the central and peripheral nervous system symptoms. The pathological process may be localized in any area of the nervous system which accounts for the extensive and complex symptomatology of neuroborreliosis. The nervous system may become affected immediately on infection with *Borrelia burgdorferi* as well as months or years following such infection. In some patients, the neurological symptoms may be preceded by other manifestations of borreliosis (e.g. erythema migrans) which brings about some major diagnostic difficulties (1-3).

Most authors have distinguished among the early (acute) neuroborreliosis and the late (chronic) one. Among other conditions, early neuroborreliosis includes the lymphocytic cerebrospinal meningitis, cranial neuropathies and acute painful radiculopathies. The lymphocytic cerebrospinal meningitis, occurring during early neuroborreliosis, may bring certain diagnostic obstacles, as it demands differentiation from viral meningitis. This has been true especially in those patients who deliver no evident history of a tick bite, show no erythema migrans preceding the neurological symptoms and, first of all, those in whom *Borrelia burgdorferi* antibodies are not yet observed in the cerebrospinal fluid (1-3).

Pathogenesis of neuroborreliosis is a complex process and in spite of extensive studies, has not been fully recognized. The central nervous system (CNS) is invaded by *Borrelia burgdorferi* Treponema during the early stage of infection. The damage of the central nervous system may effect directly from the treponema invasion, showing the experimentally proved neurotropism. Interaction of the treponema with the nervous cells causes their damage and triggers the immunological response against the bacteria. Once penetrating the CNS, *Borrelia burgdorferi* induces expression of inflammatory mediators (cytokines and chemokines), responsible for the inflammatory condition within the CNS. Only later the specific antibodies are intrameningeally synthesized against *Borrelia burgdorferi* (4-8).

Found among numerous chemokines having their role in inflammatory processes within the central nervous system is chemokine CXCL13. Member of the family of CXC chemokines, it is a selective chemoattractant of lymphocytes B and T helper B cells, acting through their specific receptor CXCR5. It is responsible for migration of B cells through the cerebral endothelial cells. CXCL13 has a role in innate immunity. It is the first immunology line of defence, earlier than

the acquired immunity characterized by synthesis of antibodies (9-13).

Numerous authors pointed to the role of CXCL13 chemokine in differrent neurological conditions. This very chemokine has also a role in pathogenesis of multiple sclerosis (14-16), in primary lymphoma of the CNS as well as tick-borne encephalitis (18).

Experiments showed participation of CXCL13 chemokine in pathogenesis of borreliosis, in particular the neuroborreliosis. The chemokine is expressed in the cerebrospinal fluid by monocytes/macrophages and the dendritic cells. Such process is the effect of induction by *Borrelia burgdorferi* cell membrane lipoproteins of CXCL13 expression in those cells , through TLR-2 (*Toll-like receptor-2)* signaling pathway. CXCL13 is responsible for attraction of B cells (leukocytes typical in acute, early neuroborreliosis) to the cerebrospinal fluid. This process precedes the humoral immunological response in the CNS, comprising synthesis of specific *Borrelia burgdorferi* antibodies (19-21).

Any suspicion of neuroborreliosis should assume CSF test as an important element of the diagnostic procedure. In acute (early) neuroborreliosis, manifested as lymphocytic cerebrospinal meningitis, CSF shows elevated pleocytosis with lymphocytes dominating the cytogram as well as increased protein concentration, reflecting dysfunction of the blood-cerebrospinal fluid barrier . Many authors pointed to the CSF absence of specific *Borrelia burgdorferi* antibodies throughout the early stage of the disease (25,26).

In our patients, CSF investigations also showed pleocytosis dominated by lymphocytes in the cytogram, elevated protein concentration, normal glucose and in some patients. Insignificantly elevated concentration of the lactic acid. The presence of *Borrelia burgdorferi* antibodies in the cerebrospinal fluid was observed in 63.64% of patients (group I). In those patients tick bites took place earlier before the admission date than in group II patients.

The absence of *Borrelia burgdorferi* antibodies in CSF may hamper or even make it impossible to deliver a final diagnosis of acute, early neuroborreliosis. The neurological symptoms manifested at this stage of neuroborreliosis may hinder explicit interpretation as in many cases they resemble symptoms of lymphocytic meningitis of different etiology, e.g. viral. Therefore, many authors have looked for additional CSF parameters to improve diagnostics of early neuroborreliosis. The investigations carried out pointed to the role of chemokine CXCL13 in pathogenesis of this disease (20-21). *Rupprecht et al.* confirmed the intrameningeal synthesis of this chemokinę in patients with neuroborreliosis (27).

The clinical studied pointed to high concentration of CXCL13 in cerebrospinal fluid of patient with acute, early neuroborreliosis, both children and adults (27-33).

Most of the authors have emphasizes the usefulness of measurements of this chemokine in the CSF in diagnostics of acute (early) neuroborreliosis, manifested as the lymphocytic meningitis, accepting CXCL13 as an early CSF marker of acute neuroborreliosis, in particular with the absence of *Borrelia burgdorferi* antibodies in the cerebrospinal fluid (28-30,32,33).

Van Burgel et al. Showed correlation between the level of CXCL13 and the range of lymphocytic pleocytosis (34) while other authors observed no correlation between concentration of this chemokine and with the range of pleocytosis or the titre of *Borrelia burgdorferi* antibodies in the CSF (33).

Our patients showed high concentrations of CXCL13 2 chemokine in the cerebrospinal fluid in both, group I and II. On the other hand, no correlation was observed between the concentrations and the range of pleocytosis in both patient groups or the titre of *Borrelia burgdorferi* antibodies in patients included in group I.

Interestingly, many authors observed rapid decrease of chemokine CXCL13 concentration on the cerebrospinal fluid resulting from implementation of the adequate and effective antibiotic therapy (27-29,31,34,35).

Our studies also showed significantly decreased concentration of this chemokine during the CSF test performed after 14 days of antibiotic therapy in both patient groups. On the other hand, the patients included in group I showed no clear effect of the therapy on the titre of *Borrelia burgdorferi* antibodies during the CSF follow-up, as compared to the preliminary results.

Such results seem to point to particular usefulness of chemokine CXCL13 assays in the cerebrospinal fluid, especially in the clinically uncommon cases of acute, early neuroborreliosis when tests of intrameningeal specific *Borrelia burgdorferi* antibodies prove still negative, when differentiating between the active and the past infection, as well as an element differentiating neuroborreliosis among other neurological conditions (34,35).

CONCLUSIONS

Chemokine CXCL13 is a significant element of pathogenesis of neuroborreliosis. Elevated concentrations of the chemokine in the cerebrospinal fluid is observed in early, acute neuroborreliosis, manifested as lymphocytic cerebrospinal meningitis where the causative therapy (antibiotic therapy) results in rapid decrease of its CSF concentration. There are reasons to accept chemokine CXCL13 as a possible diagnostic marker and the therapy response marker in acute neu-

roborreliosis. A relatively scarce number of patients evaluated prevents any further conclusions, however the results obtained seem to justify further studies enrolling more patients. It is worth recalling that EFNS recommendations regarding diagnosis and treatment of neuroborreliosis in Europe consider the present data insufficient to accept chemokine CXCL13 assays in CSF as a recommended routine diagnostic test or a method to monitor effectiveness of treatment, however, in line with the same recommendations, the growing number of reports points to the need for further studies in this area (2).

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