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Expression of Fas receptor on human T lymphocytes under stimulation with Borrelia burgdorferi sensu lato – preliminary results

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ABSTRACT

Purpose: Apoptosis of activated T lymphocytes is essential to immunoregulation and its abnormalities have been observed in immune system disorders and persistent infections. To asses Borrelia burgdorferi influence on the susceptibility of T lymphocytes to apoptosis, we have measured expression of the Fas death receptor on these cells after incubation with live B. burgdorferi.

Material and Methods: Peripheral blood mononuclear cells from 23 LD patients (18 with Lyme arthritis, 5 with neuroborreliosis) and 13 healthy controls (C) were incubated for 48 hours with and without live B. burgdorferi spirochetes: B. afzelii, B. garinii or B. burgdorferi sensu stricto. After incubation, Fas expression on CD3+ cells was measured cytometrically with FITC-labeled monoclonal antibody.

Results: Median fraction of Fas-expressing T lymphocytes increased under incubation with B. burgdorferi, with more cells expressing Fas after incubation with B. burgdorferi sensu stricto than with B. garinii. There was a tendency for a higher expression of Fas on T lymphocytes from LD patients then from controls, both in unstimulated and B. burgdorferi-stimulated cultures, but it did not reach a level of statistical significance.

Conclusions: B. burgdorferi seems to increase Fas expression on CD3+ T lymphocytes, which may render these cells more susceptible to apoptosis. This effect is stronger for B. burgdorferi s.s. than for B. garinii genospecies.

Key words: Lyme borreliosis, Lyme arthritis, neuroborreliosis, apoptosis, T lymphocytes

INTRODUCTION

The Lyme disease (LD) is caused by the tick-borne spirochete Borrelia burgdorferi sensu lato (B. burgdorferi), which invades skin, musculoskeletal and nervous system, causing a wide range of clinical symptoms. LD symptoms are often self-limited and typically resolve after a proper antibiotic treatment, but in some cases chronic neurologic or osteoarticular symptoms develop, sometimes leading to persistent sequelae. The disease presents with a wide spectrum of clinical forms and symptoms and many elements of its pathogenesis remain controversial [1-4].

Geographic variability of B. burgdorferi, which is represented solely by B. burgdorferi sensu stricto (B. burgdorferi s.s.) genospecies in North America and several genospecies with prevalence of B. afzelii and B. garinii in Europe, is reflected by a variability in the clinical picture of LD. There is a well established relationship of the three main B. burgdorferi genospecies with different clinical forms of the disease: B. burgdorferi s.s. with arthritis, B. garinii with neuroborreliosis and B. afzelii with chronic skin lesion (acrodermatits chronica atrophicans) [5,6]. The characteristic of individual clinical manifestations is also dependent on genospecies. The primary localized infection (erythema migrans) is larger, spreading faster and is more often accompanied by general symptoms

and seropositivity in patients infected with B. burgdorferi s.s. than in those infected with B. afzelii [7,8]. The manifestations of the disseminated infection by different genospecies have not been compared systematically, but the natural course of both Lyme arthritis and neuroborreliosis seems to differ between the North American and European patients [3,9]. Thus, the pathogenic potential of the three main B. burgdorferi genospecies vary, seemingly dependent on their immunogenic and inflammatory properties, with a tendency for greater invasiveness and stronger response to B. burgdorferi s.s. than to the main European genospecies [8-10].

Apoptosis of activated T lymphocytes triggered by the activation of the surface Fas receptor is essential in regulation and timely resolution of the inflammatory/immune response to infection [11,12]. Impairment of T lymphocyte apoptosis results in lymphoproliferation and tendency to autoimmunity, while increased apoptosis of T lymphocytes could facilitate pathogen survival and contribute to the chronic and persistent character of the infection, so the process must be tightly regulated [13,14]. The Fas expression and resultant apoptosis is an important element of the inflammatory/immune response, on which very little study has been performed in LD, and which could have impact on the disease pathogenesis and possibly on the differences in the response to different B. burgdorferi genospecies.

We measured expression of the Fas receptor on the peripheral blood T CD3+ lymphocytes from healthy persons and LD patients under the stimulation with the live B. burgdorferi cells. Fas was chosen as an easily measurable marker of both activation and susceptibility to apoptosis of CD3+ cells, giving insight into their functional state in the presence of B. burgdorferi.

MATERIAL AND METHODS

Study group consisted of 23 patients with chronic symptoms of LD (mean age 54,0 ± 7,6 years), including 18 with Lyme arthritis (patients 1-18; LA, 54,3 ± 6,4 years) and 5 with neuroborreliosis (patients 19-23, NB, 52,8 ± 11,9 years) diagnosed on the basis of epidemiologic, clinical and serologic data. The diagnosis of Lyme disease was primarily made by treating physician who recommended patient for a study and who decided about the panel of examinations performed for the purpose of differential diagnosis. The selection of the study group was aimed at choosing patients with a long history of borrelial infection before treatment and chronic and/or persistent symptoms, as this meant long exposition of the immune system to B. burgdorferi, which could be reflected in PBMC response to stimulation. All LD patients came from the highly endemic area, had a history of a tick bite or multiple bites and were frequently exposed to tick during work or recreational activities. All patients included into LA group had musculoskeletal pain, involving primarily large joints, with pain on motion and palpation of affected joints. Four patients had overt arthritis: wrist effusion in one, knee effusions in two and effusion and reddening of both knee and elbow joints in one; one patient with no abnormality on physical examination had a knee effusions detected ultrasonografically. One patient with a knee inflammation had an accompanying skin focus of acrodermatitis chronica athrophicans. Routinely, LA patients had undergone basic laboratory examinations and radiologic examinations of the affected joints; other examinations were carried out depending on the clinical picture and need for differential diagnosis. Patients with any other diagnosed or probable inflammatory disease of the musculoskeletal system, elevated inflammatory parameters (leucocytosis, C-reactive protein, highly elevated erythrocyte sedimentation rate), radiologic changes consistent with osteoarthrosis of the affected joints and any other examinations results pointing to other etiology (e.g. with detectable rheumatoid factor) or other infectious disease were excluded.

NB symptoms involved protracted meningoencephalomyelitis with spastic lower paresis in one patients, hearing impairment and tinnitus in one and limb paresthesia in 3 patients, in one of them accompanied by mild flaccid paresis of left arm and leg. All the patients were consulted by a neurologist or directed to our Department from neurology wards after exclusion of other possible causes of the neurologic abnormalities.

The symptoms persisted or recurred for a median of 24 months (30 months in LA and 11 months in NB) and lasted for > 6 months in all patients except one in NB group, thus qualifying as late Lyme disease.

Most patients, with exception of one in LA and one in NB group had undergone some previous antibiotic treatment without full resolution of their symptoms or with the recurrence of symptoms after an interval of several months up to 4 years. Five LA and two NB patients had been treated with standard courses of oral antibiotics (amoxycylline or doxycycline) from 2 months to about a year before admission. Four patients had been treated 2-3 years earlier with currently not recommended regimens: intravenous cefotaxime for 2-4 weeks in a dose of 2g/day (3 patients in LA group), or combination of 2 weeks ceftriaxone followed by oral metronidazole (one NB patient). Seven LA patients had been treated either with intravenous III generation cephalosporin or oral doxycycline from over a year to 5 years before with a good original response, but reported the reappearance of symptoms. One patient with osteoarticular symptoms had a few attempts of short-term treatment with frequently changed oral antibiotics in the last 18 months. The patient with meningoencephalomyelitis had been treated with intravenous ceftriaxone for 30 days previously and referred to the Department after 5 months for assessment of the residual focal neurologic symptoms. The reasons for the clinically ineffective treatment were probably variable. In some patients active infection could have persisted after ineffective treatment, possibly because of non-optimal treatment scheme or poor adherence. Re-infection could be a more likely