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ADVANCES IN INVESTIGATIONS OF LYME BORRELIOSIS IN THE TERRITORY OF THE FORMER USSR

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Whereas late manifestations of Lyme borreliosis were described in Russia more than 100 years ago, early manifestations were described as different disease entities such as tick-borne erythema, etc. In 1985 Lyme borreliosis was first verified serologically and the agent was first identified in 1986. By the beginning of 1992 Lyme borreliosis was serologically confirmed in patients from the Baltics to the Far East.

Their geographical patterns in Russia are closely related to areas of the hard ticks *Ixodes persulcatus* and *Ixodes ricinus* which are also the main vectors of tick-borne encephalitis virus. As in the case of this infection, in the west of Russia there are "ricinus" natural foci of Lyme borreliosis, and to the east there are similar "persulcatus" foci; through large territories in the East Europe there are common foci for both species. Many *Borrelia burgdorferi* strains of tick origin have been isolated from various regions of Russia and neighbouring republics. Adult tick infection rates vary from several per cent to 30% in *I. ricinus* and up to 50-60% in *I. persulcatus*. Double infections of Lyme borreliosis spirochetes and tick-borne encephalitis virus have been recorded for ticks as well as for humans. Lyme borreliosis morbidity and its importance for the Russia territory are discussed.

INTRODUCTION

The history of etiological studies and the first steps in the investigations of Lyme borreliosis in the USA and some European countries have been described in detail in a number of special publications (2, 6, 8, 49). Analogous data with respect to the vast territory of the former USSR (12) are not yet complete. Late skin manifestations of Lyme disease were described by Russian dermatologists under different names as far back as the end of the last and the beginning of the present centuries (40, 42, 44, 45, 46). These publications appeared even before the widely known description of erythema migrans by Arvid Afzelius (1). In the 1950 a special comprehensive investigation was devoted to the clinical picture of atrophic acrodermatitis in the Leningrad region (37). Along with it, neuropathologists paid attention to illnesses that developed after bites of ixodid ticks and were characterized by vast annular erythemas, various neurological disturbances and the lack of serological evidence that would suggest tick-borne encephalitis (38, 43). It was suggested that these diseases represented erythematous forms of tick-borne encephalitis. However, some investigators clearly distinguished these diseases from tick-borne encephalitis and, long before the discovery of *Borrelia burgdorferi*, put forward correct hypotheses concerning their etiological independence (34, 50). In some regions patients with the above manifestations were given diagnoses of "tick-borne ring-shaped erythema". The subsequent thorough description of the clinical picture (10, 11, 48) and retrospective

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serologic investigations suggest that a considerable number of the cases should be regarded as Lyme borreliosis (15, 22, 29).

In 1984, investigations concerning this infection were launched in the territory of the former USSR by our Laboratory of Vectors of Infections in the Gamaleya Institute for Epidemiology and Microbiology in Moscow (31). In 1985 it was first serologically verified in the course of investigation using the indirect immunofluorescent test of blood sera of the patients (8, 24), and subsequently was demonstrated to be distributed in a number of regions (29). This served as a stimulus for work on the clinical manifestations of Lyme borreliosis, which was described in a number of special publications (2, 8, 9, 10, 11, 12, 13, 14, 15, 39). The investigations on etiology, epidemiology and epizootology set forth below, including the isolation of the agent from ticks and serological tests, were performed by us in the above mentioned laboratory the present paper is a review and its primary purpose is to acquaint occidental investigators with results that have been published at greater length in a number of papers in Russian. In the referenced publications the techniques have been described in detail. Taking into account the review nature of this paper, we only discuss the primary techniques.

METHODS

Borrelia isolation from *Ixodes persulcatus* and *I. ricinus* ticks was performed by means of tick dissection with subsequent incubation of the midgut in BSK medium. Resultant isolates were cultivated in the same medium in accordance with established techniques (4). Their identification was carried out by indirect immunofluorescent reaction (IIR) with a set of monoclonal antibodies kindly placed at our disposal by Prof. A. Barbour (Department of Microbiology, University of Texas, USA). Serologic studies were performed by IIR with antigen prepared from the Ip-21 strain, isolated by us from *I. persulcatus* ticks (Table 1).

TABLE 1. - Origins and monoclonal reactivities of spirochetal isolates in IIR tests by Kryuchechnikov V.N. *et al.* (32, 33, with additions).

ISOLATE	REGION	MONOCLONAL ANTIBODIES				
		H 9724	H 5332	H 3 TS	H 605	H 4825
Ip-3*	Leningrad reg., Russia	+	+	–	nd*	nd
Ip-21	----	+	+	±	+	–
Ip-86	Khabarovsk Terr., Russia	+	+	–	nd	nd
Ip-87	----	+	+	–	nd	nd
Ip-89	----	+	+	–	nd	nd
Ip-90	----	+	–	–	+	–
Ip-91	----	+	+	–	nd	nd
Ir-148*	Lithuania	+	+	–	+	–
Ir-208	Leningrad reg., Russia	+	+	–	+	–
Ir-210	----	+	+	–	+	–
Ir-211	----	+	+	–	+	–
Ir-215	----	+	+	–	+	–
Ir-228	Crimea	+	+	–	+	–
Ip-245	Kirgizstan	+	+	–	+	–
Ip-248	----	+	+	+	+	–
Ip-305	Ekatherinbourg reg., Russia	+	+	–	+	–
Ip-308	----	+	+	–	+	–
Ip-318	Sakhalin reg., Russia	+	±	–	+	–
CONTROLS						
F-1	Sweden	+	–	–	+	–
ACA-1	----	+	+	–	+	–
ECMA-3	----	+	+	–	+	–
B-31	USA	+	+	+	+	–
HB-19	----	+	+	+	+	–
14 (*B. persica*)	Khorezm reg., Uzbekistan	+	–	–	nd	nd
B. recurrentis	unknown	+	–	–	nd	nd

* Ip = *I. persulcatus*; Ir = *I. ricinus*; nd = no data.

The efficiency of this antigen was confirmed by special interlaboratory investigations (36). The cases developed typical erythema migrans after a tick bite and were considered serologically confirmed if there was a minimum fourfold rise in IgM-specific antibodies during the first month of the disease (Fig. 1). Tick infections by borrelia were revealed by darkfield microscopy of tick midgut contents, which were accompanied by spot checks for borrelia indentification in IIR with positive patient sera and monoclonals. References to pertinent publications with detailed descriptions of proper techniques are cited in the text below. In 1986-1991 about 7500 ticks were tested.

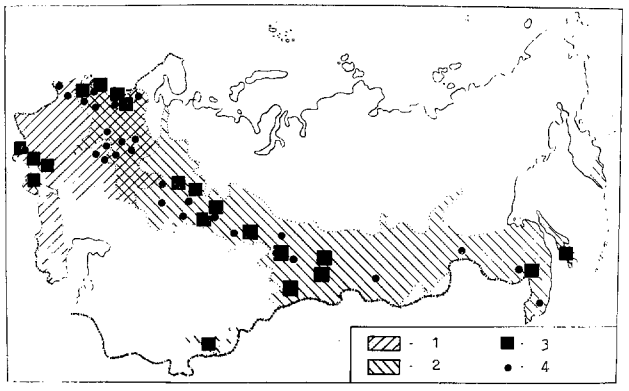

Figure 1. - Distribution of Lyme borreliosis in the territory of the former USSR (according to data through 1991).

1 - *I. ricinus* tick area;
2 - *I. persulcatus* tick area;
3 - points of isolation of the agent;
4 - points of human seropositive findings.

RESULTS

By the beginning of 1990 Lyme disease was serologically confirmed in patients in Estonia, Latvia, Lithuania, Moldova and Russia. Within Russia there were patients from 27 large administrative territories (Fig. 1). In the near future a list of endemic regions will undoubtedly be completed for those regions which have not yet been investigated. Nevertheless, observations available so far support our suggestions (23, 29) that Lyme borreliosis is widely distributed in the forest zone of Eastern Europe and North Asia, from the Baltics to the Far East. It indicates that a considerable part of the world-wide nosoarea of Lyme borreliosis is situated within this territory. Its geographical patterns are closely associated to the hard ticks *Ixodes ricinus* and *I. persulcatus*, which are also the main vectors of tick-borne encephalitis virus. As in the case of this infection, in the west of the former USSR there are "*ricinus*" natural foci of Lyme borreliosis (41, 47) and to the east there are similar foci with *I. persulcatus* (30); across the large territories of Eastern Europe there are foci with *I. ricinus* and *I. persulcatus* occurring simultaneously (20, 22, 29). These postulations have been verified by the isolation of *B. burgdorferi* strains from *I. ricinus* and *I. persulcatus* ticks from Estonia, Lithuania, Moldova, the Nikolaev and Odessa regions of Ukraine, Crimea, Kirgizstan and also Leningrad, Perm, Ekatherinebourg, Tyumen, Omsk, Kurgan, Novosibirsk and South Sakhalin regions as well as Krasnoyarsk, Altai and Khabarovsk Territories of Russia (Fig. 1). Thus, *I. persulcatus* has been identified as a new vector of *B. burgodorferi*, and is also the primary vector in the vast area (23, 25, 32), as supported by other investigators as well (7, 17, 52).

Two human isolates were obtained in the Perm region from peripheries of erythema migrans lesions but they were lost during further cultivation because of contamination.

Based on their response to monoclonal antibodies, the strains isolated both from *I. ricinus* (Ir) and *I. persulcatus* (Ip) appear to be similar to the European strains rather than to those of American origin (Table 1).

It was demonstrated that in their electrophoretic protein patterns strains Ip3 and Ip21 were found to be practically identical to those isolated from patients in Sweden (16). A. Barbour (5) studied some of our isolates in PAGE. The Ip90 strain, in contrast to Ip3 and Ip21 strains, as well as certain strains from Sweden, Austria and Germany had a major protein in the 20-22 kD range that most likely corresponded to "pC" proteins described by B. Wilske *et al.* (51). The strains isolated by us should certainly undergo more detailed studies. However, the present data support the suggestion that *B. burgdorferi* spirochetes are characterized by a considerable antigenic and serologic polimorphism. The vast area of the agents' distribution as well as different biocenotic structures of parasitic systems in which it circulates are contributing factors. In this connection one may suppose that in the vast territory of Eastern Europe and North Asia there is great etiologic diversity of circulating borrelia. It may well be that the term "Lyme borreliosis" refers to a whole group of etiologically distinct borrelioses.

One should also remember that the genus *Borrelia* includes *B. recurrentis* as well as a number of spirochetes widely distributed in the southern republics of the former USSR, and many other countries, and is carried by argasid ticks. The taxonomy of the genus *Borrelia* needs a detailed investigation to clarify the question concerning the number of nosological forms of borreliosis in the world. It will also facilitate a solution to the problem of the evolution of borrelia, their ecological relationships with various arthropods and the paleogenesis of borreliosis. As a means to resolve these problems, our laboratory created a depository of isolates which includes over 130 cultures of *B. burgdorferi* from Eastern Europe and North Asia, Austria, Czechoslovakia, France, Germany, Japan, Sweden, Switzerland and USA as well as strains of *B. persica* and *B. recurentis.*

Infection rates of adult ticks with borrelia in various regions, natural foci and even in different sites of the same focus vary up to 30% in *I. ricinus* and 50-60% in *I. persulcatus* (18, 21, 22, 30, 41). Spirochetes have not been found in *Dermacentor reticulatus* from the Kaliningrad region (47) nor in *Haemaphysalis concinna* from the Far East (30) at this point. Possible changes in infection rates among ticks and variation in tick abundance were studied in the Leningrad region during 1986-1989 (21). It was revealed that in natural populations the *I. ricinus* and *I. persulcatus* infection rates did not undergo great annual fluctuations and they did not depend on annual changes in tick abundance. But the rate of intensity of infection (*i.e.* the number of borrelia found to be present in one tick) differed greatly (18). The vector population may be characterized not only by general infection rate but also by the ratio between the specimens having different quantities of the agent. This ratio reflects general numbers of the agent population and seems to be of significant epizootic and epidemic importance.

The vertical transmission of *B. burgdorferi* through *I. persulcatus* nymphs to adults still takes place without additional infective feeding of nymphs (28). However, this means of transmission does not bring the rates of adult infection commensurable to the levels in nature. Apparently in nature nymphs are infected significantly during the process of bloodsucking. Our supposition coincides with recent views of American investigators (35) on the Lyme disease agent - vector - host interrelations. Since the nymphs of *I. ricinus* and *I. persulcatus* have a wide range of hosts, we suggest that in various natural foci of the forest zone of Palearctics the epizootic process is supported by numerous vertebrate species.

One of the major preconditions for epidemic manifestations of natural foci is intensive interaction between the human population and forest. Thus, during seroepidemiological screening of the rural population in an endemic area of the Leningrad region, nearly 90% of the people stated that they had visited the surrounding forests for various purposes such as walks, gathering mushrooms, berries etc. In all age groups this index was practically the same. Over 66% of the investigated persons (from 53-60% in older ages to 77-87% among people less than 20 years of age) visited the forest during the last spring or summer, *i.e.*, during the last season of tick activity. In fact, during the last season nearly 12% of the persons under investigation reported tick bites. The number of persons accustomed to removing ticks from their body in any of the previous years was, of course, considerably higher, ranging from 20-30% in the younger age groups to 35-50% in the older groups. Overall, nearly 9% of persons tested serologically revealed antibodies in titers above the cut-off level (19). In Lithuania (41) and the Kaliningrad region up to 16% and 20%, respectively, of forest workers proved to be seropositive.

A general route of transmission and the main vectors of the Lyme disease agent *B. burgdorferi* are similar to the tick-borne encephalitis virus in Russia. Therefore, the main epidemiological features of these infections (the seasonal character of the cases, the reasons for and intensity of contact with the foci determine the professional and age composition of those infected, the patterns of their distribution about places of infection, etc.) are practically identical. In the Leningrad region, for instance, new cases of Lyme disease are registered from May to September, with the infection rate being the highest (nearly 50%) in June. Most cases occur in adults, although more than 16% are registered in pre-school and school age children (26). Infection rates among the citizens are rather high.

According to incomplete data on the Leningrad region, in 1986-1989 the morbidity index ranged from 3.9 to 7.0 cases per one hundred thousand people. These figures are 2.5-3 times as high as the morbidity index for tick-borne encephalitis for the same period. Considering our data on the distribution and epidemiology of borreliosis, the prevalence of infected ticks as well as the frequency of tick-borne encephalitis cases, we suggest that the annual number of primary cases of Lyme disease in Russia may be at least 6000-11,000. Compared with morbidity rates of other infections, Lyme borreliosis appears to be the most prevalent tick-borne infection and one of the main zoonoses with natural foci in Russia.

DISCUSSION

Tick-borne encephalitis is widely distributed in the Russian territory and the differential diagnosis of this disease and Lyme spirochetosis present a problem. Mixed infection in humans have already been detected serologically (22, 39). Their level in the Leningrad region is about 1.5% for both Lyme borreliosis and tick-borne encephalitis. Individual virological and bacteriological investigations of adult *I. persulcatus* from Khabarovsk Territory have revealed mixed infections in the same tick. The data (27) indicated that the presence of *B. burgdorferi* in the tick seems to be of no importance with respect to the presence of tick-borne encephalitis virus in its organism, and the virus seems to show no significant effect on borrelia. Calculations based on the established infection rate with the virus and borrelia among ticks indicate that the frequency of mixed infection among *Ixodes ricinus* and *I. persulcatus* in various regions varies from a small fraction of a percent, to several percent in some territories reaching 5-10%. In this light the problems of the frequency of mixed infections in people in the various regions, their early and late manifestations and the most efficient treatments arise.

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