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InterRegioNovation is the International Association devoted to the transfer and exchange of knowledge and innovations at all regional levels (country, region, city, community etc.) between knowledge transfer professionals (business, research institutions, policy makers, government agencies, individuals, others) in all countries of the enlarged Europe, CIS countries and from other continents for stimulating and enhancing economic and social growth in the regions.

This is a policy and research association that brings together all knowledge transfer professionals who are interested in delivering efficient, flexible, innovative and cost-effective services across the private and public sectors. We work closely with business, research and educational institutions, government agencies, policy makers, NGOs, media, individuals and other stakeholders to promote the interests of their industries.

Our members understand the changing needs of the transfer and exchange of knowledge and innovations and through continuous professional development, marketing and networking opportunities offered in this association, we keep current with the latest knowledge trends and issues that challenge people in their work and life journey. We also offer expansive opportunities for partner connection through our networks.

Journal "Regional Innovations" is one of the Association's tools for innovators and everybody who is interested in any aspects of innovation development.



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About journal

On behalf of the Editorial Board, it gives us a great pleasure to welcome you to the forth issue of 2017 of the Regional Innovations Journal. This is a thematic special issue dedicated to broad aspects of **Medical Science and other innovative research areas** from basic research to clinical and experimental work.

This particular volume provides a platform for advances in basic, translational and clinical research and includes original papers on medical and clinical research, health care innovations, reviews, medical teaching, medical law, medical ethics, spirituality and medicine, policy environmental medicine and integrative general practice. Researchers in academic and clinical settings as well as health professionals are encouraged to publish their theoretical and experimental results in this journal, which aims to integrate expertise in different medical specialties.

This is an independent, peer-reviewed, Internet-based international journal devoted to publishing original research papers of highest quality, sharing ideas and discussing innovation sector within regional dimensions. The journal welcomes to submit research papers by exceptional innovators, leading universities, globally recognized business, government agencies, policy makers and political leaders.

We intend that our readers will be exposed to the most central and significant issues in innovations development. We wish to publish papers that exemplify the highest standards of clarity, and that promise to have significant impact on existing front-line debates or to lead to new ones. The journal explores key priorities of the knowledge and innovations transfer and exchange in terms of critical aspects of human life (economy, law, science, business, health, education, culture etc.). We therefore welcome submissions not only from established areas of research, but also from new and emerging fields and those which are less well represented in existing publications, e.g. engineering studies, biomedical research etc.

We also strive to ensure that being under expert evaluation, each submission will receive developmental and supportive comments to enhance the article. Our refereeing process will involve that each submission will be reviewed by one or more specialists in the relevant field. Articles will be added to the volumes and the journal audience will receive e-mails updates to encourage them to the new articles.

We are delighted with, and immensely grateful to the large numbers of colleagues, both members of the Associations InterRegioNovation and FranceXP (France), representatives from many universities in France, Latvia, UK, Azerbaijan, China, Nigeria, Belarus, Ukraine and other institutions, who have supported the editorial process. And we are very proud of the expertise that they collectively bring, which we believe is unsurpassed by any contemporary innovative journal.

We are immensely grateful to our colleagues for their support and advice through the process of setting the journal up, and for the confidence they have placed in us in supporting this initiative at a time of economic uncertainty.

In the development of the Regional Innovations to date, we would like to enlist the support of a number of organisations who wish to promote this online journal to their experts. To ensure its sustainability, we would also like to invite other organisations, networks, conferences and meetings to associate themselves with the Regional Innovations. We therefore aim for the Regional Innovations to become the leading online forum to globally disseminate outstanding research papers on innovation sector in regional dimensions. Being an online periodical, the Regional Innovations is also a forum for exchange of imaginative ideas readers wish to share. Contributions of articles on innovations sector and your comments about this issue are very welcome.

To this end, if you lead, represent, or are a member of any such organisation, please contact us to offer your support and commit to promoting the Regional Innovations as a publication outlet for research undertaken by your experts.

We do hope you enjoy and benefit from the Regional Innovations! And many thanks for staying with us in 2017!

Jean-François Devemy
Editor-in-Chief

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REGIONAL AND CLINICAL-EPIDEMIOLOGICAL PECULIARITIES OF BABESIOSIS IN UKRAINE



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Abstract

In this article the authors presented generalized data about the regional, clinical and epidemiological features of babesiosis in Ukraine. The authors of the article substantiated the factors of danger of this parasitosis, which are related to the geo-climatic features of the prevalence of pathogens of the disease and their carriers in Ukrainian regions, the high susceptibility of the human organism to this parasitic invasion, certain clinical polymorphism of the disease. On the example of the detection of new types of Babesia the analysis of the resources, capabilities and prospects of modern diagnostic methods taking into account regional specifics were carried out. The material about the clinical and epidemiological features of the babesiosis development was described in detail, the conclusions were confirmed by digital material.

Key words: babesiosis, Ukraine, clinical and epidemiological features.

Introduction. Human babesiosis (B60.0 Babesiosis, Babesia invasion – BI, ICD-10) is an emergent obligate transmissible protozoan disease caused by protozoans of the genus *Babesia*. The causative agents of babesiosis are characterized by their ability to invade and parasitize in erythrocytes and haemopoietic organs and initiate an infectious process whose clinical course may vary from asymptomatic subclinical mild flu-like forms to a severe flash-like progressing disease (the fulminant form) with lethal outcomes.

Babesiae are a group of protozoan unicellular haemoparasites united into the genus *Babesia*, which together with the genera *Piroplasma* and *Fransaiella* are included into the family Babesiidae, the order Piroplasmida, the type Apicomplexa (or Sporozoa), the superphylum Alveolata, the subkingdom Animalia, the domain Eukaryota [4]. By today they have been recognized as the blood parasites, which are the most widespread in the world and dangerous for people, by the number of cases of their invasion these parasites being inferior only to trypanosomes (causative agents of African trypanosomiasis and Chagas disease). Specialists point out that babesiae are characterized by certain epidemiological and epizootic specificity, unpredictability of the clinical course and some difficulties in the ways of their diagnosis and prevention [14]. It is in view of the last feature and clear urgency of in-depth studies of the regional specificity of babesiosis spreading in Ukraine and its clinical-epidemic aspects of development that the present research began [1; 4].

Problem statement. The danger of babesiosis is based on the spread of causative agents of this disease, their carriers and, as it is known now, a rather high vulnerability of the human organism to parasitic invasions. Today we know more than 100 species of the genus *Babesia*, which infect many varieties of mammals and a number of birds [1; 4; 10; 15]. The number of *Babesia* species is continuously increasing owing to discovery of their new representatives. The use of resources of the molecular-biological (phylogenetic) classification of *Babesia* species in Ukraine and their grouping by evolutionary relationship [4; 6] have made it possible to confirm existence of 5 different groups (clades) of the causative agents. The 1st group consists of *B. microti*, including such species as *B. rodhaini*, *B. felis*, *B. leo*, the species *B. microti* itself and *B. microti*-like parasites, before KO-1, ovine Babesia-like. By the way, this group is characterized by a broad spectrum of warm-blooded hosts (small rodents, the Felidae, the Canidae, birds). The 2nd group unites such species as *B. duncani* (WA-1,2, the causative agent of babesiosis in dogs), *B. duncani*-like (before CA1-6, its natural reservoir is unknown), *B. conradae* (the aetiological factor of the disease of dogs in southern regions of the State of California, the USA). The 3rd group is made up of *Theileria*, which cause invasions in cattle. The 4th

group is formed by the “true” (*sensu stricto*) *Babesia* spp. with the species *B. canis* and *B. gibsoni* (isolated from representatives of the genus *Canida*), as well as *B. divergens*, *B. divergens*-like (before MO-1), *B. venatorum* (before EU-1) and *B. odocoilei* (haemoparasites of domestic and wild artiodactyles, cattle, deer, roe deer). The 5th group, also of the “true” *Babesia* spp., unites a considerable number of haemoparasites, mostly causative agents of invasions in hoofed animals: *B. caballi* (horses), *B. ovis* (sheep), *B. bovis* and *B. bigemina* (cattle).

Geographical specificity of causative agents and carriers. Different geographical territories, which have natural foci of spreading of certain varieties of babesiae, are associated with the habitat of absolutely concrete species of ixodid tics. In Ukraine, *Ixodes ricinus*, *Dermacentor reticulatus* and *Ixodes persulcatus* are definitive hosts of *Babesia* spp. [11; 12]. Recent large-scale researches have shown that the *Babesia* invasiveness level reaches 4.6 % (including the parasite species *B. microti*, *B. venatorum* and *B. divergens*, which are pathogenic for people – 2.8, 1.2 and 0.2 % respectively) for the tics *I. ricinus* and 2.7 % for the tics *D. reticulatus* (*B. microti* were revealed in 2.1 % of this species of tics) [12]. Currently in Ukraine the contamination of the tics *I. ricinus* and *D. reticulatus* with *B. microti* reaches, respectively, 7.1 % and 7.8 %, and with other species of babesiae 18.9 % and 17.9 % [3; 4]. Vertebrate (chiefly warm-blooded) animals, whose list today includes more than 30 species of mammals and 10 species of birds, act as the intermediate host of babesiae [3; 6]. Earlier a viewpoint prevailed among scientists that there were strict borders of the “specific linkage” of each species of babesiae to the concrete species of their intermediate host. But, as results of researches conducted during past decades showed, typical for many representatives of this group of haemoparasites is their rather high plasticity in adaptation for existence in different species of intermediate hosts (e.g. *B. microti* are able to cause invasions in 10 species of mammals and 4 species of birds).

Usually people are an accidental intermediate link in the life cycle of the development of these parasites, while the main natural intermediate hosts of *Babesia* species pathogenic for people are as follows: small myomorph rodents (for *B. microti* and *B. microti*-like – voles, shrews, wood mice, etc.), domestic and wild hoofed animals (for *B. divergens*, *B. venatorum* and *B. divergens*-like – cattle, deer, roe deer, etc.) as well as maybe the Canidae (for *B. duncani* and *B. duncani*-like) [13]. The level of contamination of myomorph rodents with babesiae in Ukraine remains unclear, while on Poland territories adjacent to Ukraine the contamination of voles with *B. microti* ranges from 7.7 % to 50.0 % (depending upon the species of animals and their

habitat), that of other varieties of myomorphic rodents being about 2.0 %. By the level of contamination of cattle with babesiae the enzootic foci include territories of Volyn, Zhytomyr, Kyiv, Cherkasy and Chernigiv Regions, where contamination of cattle with causative agents of babesiosis is within 2.8-55.5 %, while other areas of Ukraine are recognized as menacing foci (with irregular sporadic cases of the disease or where no purposeful studies were conducted) [3]. As for other domestic hoofed animals, significant outbreaks of babesiosis are observed in sheep of the Autonomous Republic of Crimea, Kherson and Zaporizhzhya Regions as well as the steppe area of Kharkiv Region, where the infection rate among the livestock ranges from 2.0 % to over 20.0 %. Besides, cases of babesiosis in domestic dogs are constantly registered actually on the whole territory of Ukraine (annually about 6.0 % of animals fall ill), the peaks of the disease incidence (up to 30.0 % of the whole number of dogs) occurring in May-June and September-October [12].

Unfortunately, almost all researches in diagnosis of babesiosis in animals conducted in Ukraine were not accompanied with an exact identification of causative agents with help of modern molecular-biological methods, thereby making it impossible to reveal the spread of the species of Babesia that are pathogenic for people. Nevertheless the above scientific data completely substantiate the conclusion about presence and intense cooperation of some definitive and intermediate hosts of these haemoparasites on the territory of Ukraine, thereby providing reproduction of the life cycle of these parasites and spread of Babesia invasions.

Clinical-epidemiological regularities of babesiosis. The main epidemiological regularities of human babesiosis in Ukraine in general are similar to those described in Europe and the USA. The principal differences of these diseases are as follows: an overwhelming majority of cases (about 80.0 %) was diagnosed in asplenic patients and cases with other types of the pronounced immunocompromised state; severe forms of the disease course dominate with the lethality level among the patients (even hospitalized in due time and treated in compliance with proper protocols for giving medical aid) reaching 50.0 %; *B. divergens* is the chief species of the causative agent (more than 70.0 %) [7; 9]. It is important to note that for a long period of time the species *B. divergens* was regarded as the only causative agent of human babesiosis in Ukraine (according to our data, in countries of the Old World too). But beginning from 2003 it became clear that a considerable number of cases of the disease in people were caused by the species *B. microti* and *B. venatorum*. The latter species of babesiae is characterized by a substantial level of similarity to *B. divergens*, therefore at the initial stage of study *B. venatorum* was regarded as a representative

of the variety *B. divergens*-like with the previous name *Babesia* sp. EU1 [6].

Results of our studies, carried out in 2015 on blood serum samples from people and animals that suffered from tick bites, confirmed the presence of invasions on the territory of Ukraine, these invasions being caused by different species of Babesia pathogenic for people: *B. microti* in 2.3 %, *B. divergens* and similar babesiae in 5.4 %. Clinical manifestations of babesiosis develop in people, when the level of erythrocytes infected with the causative agent reaches 3.0-5.0 %, severe forms in the course of the disease are registered after achievement of parasitaemia > 10.0 %, while levels of parasitaemia up to 1.0-2.0 % reveal, as a rule, asymptomatic invasion [7; 11].

The clinical picture of babesiosis is characterized by a broad spectrum of manifestations and varies from asymptomatic to severe and fulminant forms; the above depends upon the immune status and genetically caused patient's predisposition to the disease, the species of the causative agent and the infecting dose, the mechanism of contamination, the presence of concomitant diseases and other factors [2; 5; 11].

The incubation period lasts: most frequently 1-4 weeks (more seldom up to 6 weeks) after a tick bite and 1-9 weeks (sometimes up to 3-6 months) after transfusion of infected blood or its components. Neonatal babesiosis results from transplacental (about 60.0 %), transplacental (about 20.0 %) and transplacental (about 20.0 %) transmission of the causative agent. In the latter case manifestations of babesiosis can be revealed as early as during the prenatal period (spleno- and hepatomegaly, haemolytic anaemia, hyperbilirubinaemia, etc.) and in newborns immediately after the birth or during the first two weeks of their life [11].

According to conclusions of the specialists, who carried out long-term observations of patients with detected babesiosis, the clinical course of the above disease manifests itself in three leading forms: asymptomatic parasitic invasion, mild/moderate and severe invasion (in some cases – fulminant manifestation with a flash-like course, development of a chronic recurrent disease or even the lethal outcome) [11].

Asymptomatic forms of babesiosis are diagnosed in about 30.0-40.0 % of the population (in 19.0-25.0 % of adults and 40.0-50.0 % of children) that lives in endemic regions and almost in 6.0 % of the people who live in the regions which are "safe" as for this parasitosis [9; 11]. Scientists consider even the above high values of detection of Babesia invasion lowered and its real level of spread significantly higher. Asymptomatic parasitaemia in people can last for several months and even years. During all this time the

invaded persons feel clinically healthy, but preserve an increased risk of activation and development of the disease in case of a reduced resistance of their organism as well as can be the source of infection in cases of provision of donor blood and transmission of pathogens to other people and animals by means of subsequent tick bites [11].

Most cases of human babesiosis, diagnosed in the world, are attributed to mild and moderately severe forms. These are characterized by a gradual onset of indisposition and one or several following signs and symptoms, which are revealed in patients with different frequency: intermittent fever (from 85.0 to 91.0 %), tiredness (from 79.0 to 91.0 %), chills (from 63.0 to 77.0 %), hidrosis (from 53.0 to 69.0 %), headache (in 39.0 %), myalgia (in 33.0 %), anorexia (in 24.0 %), coughing (in 22.0 %), arthralgia (in 18.0 %), nausea (in 16.0 %) [5; 7; 11]. More seldom the patients pay attention to pains in their throat and abdomen, suffer from vomiting, loss of their body weight, congestion of the conjunctiva and photophobia, paleness of the facial skin and eruptions on the body (fingers, hands, region of the abdomen and waist), skin hyperesthesiae, emotional impatience and depression [8; 11].

An objective examination of the patients often reveals only minimum manifestations of the disease in the form of fever with an elevated body temperature from 37.5 to 39.5° C. Moderately manifested splenomegaly and/or hepatomegaly are observed in 10.0-25.0 % of patients; erythema of the pharynx, skin icterus, retinopathies with punctate haemorrhages and retinal infarctions, petechial eruptions on the body (extensive eruptions and haemorrhages are more typical for severe forms of babesiosis) occur less often [11]. The duration of the disease, as a rule, is from a few weeks to several months with gradual recovery and restoration of the organism that may last up to one year and more. In such cases parasitaemia quite often persists even if the patient feels well. A severe, including fulminant (flash-like with the lethal outcome), chronic recurrent (lasting for three months and more, and sometimes up to one year) course of babesiosis is observed in patients with immunocompromised states, which are most commonly caused by: splenectomy (asplenia/hyposplenia), HIV infection, malignant tumours, taking of immunosuppressive drugs [8]. It should be noted that the first case of babesiosis, revealed in Ukraine in a 6-year-old boy (Kyiv, 2011), proved to be endemic. The fact of the disease was diagnosed posthumously by specialists from the USA. This tragic case was covered in media resources ("The first case of babesiosis is

registered in Ukraine": Topmost news of ICTV channel, FACTS OF THE WEEK, 2013-05-19; "The killer tick": The Observer, May 17, 2013). Also, patients at the age of 50 and over are more inclined to a severe course of babesiosis, though such data are still more frequently attributed to genetically determined higher sensitivity of certain people to haemoparasites [11].

Besides, a more severe course of the disease can be caused by mixed tick infections, when babesiosis is combined in 10.0-30.0 % of diagnosed cases with boreliosis (Lyme disease) and/or human granulocytic anaplasmosis, monocytic ehrlichiosis, bartonellosis, rickettsioses, haemorrhagic fevers, leptospirosis and other diseases, the above combination being a rule rather than an exception for this group of infections [8; 11].

Conclusions. The danger of babesiosis is based on the spread of causative agents of this disease, their carriers and a rather high vulnerability of the human organism to parasitic invasions. The number of *Babesia* species is continuously increasing owing to discovery of their new representatives. The use of resources of the molecular-biological (phylogenetic) classification of *Babesia* species in Ukraine and their grouping by evolutionary relationship have made it possible to confirm existence of 5 different groups (clades) of the causative agents. Scientific data completely substantiate the conclusion about presence and intense cooperation of some definitive and intermediate hosts of these haemoparasites on the territory of Ukraine, thereby providing reproduction of the life cycle of these parasites and spread of *Babesia* invasions.

The main epidemiological regularities of human babesiosis in Ukraine in general are similar to those described in Europe and the USA. The principal differences of these diseases are as follows: an overwhelming majority of cases (about 80.0 %) was diagnosed in asplenic patients and cases with other types of the pronounced immunocompromised state. Results of our studies, confirmed the presence of invasions on the territory of Ukraine, these invasions being caused by different species of *Babesia* pathogenic for people: *B. microti* in 2.3 %, *B. divergens* and similar babesiae in 5.4 %. Clinical manifestations of babesiosis develop in people, when the level of erythrocytes infected with the causative agent reaches 3.0-5.0 %, severe forms in the course of the disease are registered after achievement of parasitaemia > 10.0 %, while levels of parasitaemia up to 1.0-2.0 % reveal, as a rule, asymptomatic invasion.

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