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NEOEHRlichiosis – A NEW TICK-BORNE DISEASE – IS THERE A THREAT IN POLAND?

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ABSTRACT

Recently in a few European countries a new pathogen transmitted by ticks *Ixodes ricinus* - *Candidatus* Neoehrlichia mikurensis was identified. It is a Gram negative intracellular bacterium belonging to the *Anaplasmataceae* family. Worldwide 23 cases were described, among which 16 in Europe. Infection with *Candidatus* Neoehrlichia mikurensis in humans runs mainly with fever, headache, nausea, arthralgia, thrombotic or haemorrhagic lesions, subcutaneous haemorrhages, haemorrhagic rash, general malaise, weight loss. The course of infection may be acute or chronic. The diagnosis is based on TaqMan real-time PCR, which allows for the detection of the gene coding for 16S rRNA and a blood smear. The drug of choice is doxycycline. Due to the fact that the *Ixodes ricinus* ticks are common in Poland, there is a probability of infection with *Candidatus* Neoehrlichia mikurensis among patients bitten by ticks. The possibility of non-symptomatic human infection *Candidatus* Neoehrlichia mikurensis in north-eastern Poland was shown, confirming the necessity to conduct research on a larger scale. Moreover, awareness of physicians about the possibility of infection in patients with non-specific symptoms after tick bite should be increased.

Key words: *Candidatus* Neoehrlichia mikurensis, *Ixodes ricinus*, Poland

INTRODUCTION

Common tick: *Ixodes ricinus* is the most important vector responsible for the spread of tick-borne diseases such as Lyme disease, tick-borne encephalitis (TBE), anaplasmosis and babesiosis in Europe, Asia and North America. Recently in several European countries, eg. in Sweden, Germany and Russia new pathogen transmitted by ticks *Ixodes ricinus* *Candidatus* Neoehrlichia mikurensis was identified (1,2,3). It is a Gram negative intracellular bacterium belonging to the family *Anaplasmataceae*.

Candidatus Neoehrlichia mikurensis species was recently recognized in Europe as pathogenic for humans and seems to be second to *Borrelia afzelii* most commonly transmitted by *I. ricinus* ticks pathogen in Central Europe. The presence of the bacteria was confirmed in various species of rodents in Europe and Asia (4,5).

I. ricinus ticks become infected by sucking the blood of rodents, which developed symptomatic infection. The frequency of *Candidatus* Neoehrlichia mikurensis detection in *I. ricinus* collected in Germany was 8.1%, the Czech Republic 10%, France 1.7%, Sweden 6.1%,

in Denmark 0.95%, in the Netherlands 7.9% and in Austria even 23.5% (1,6,7,8).

Infection of *I. ricinus* ticks, with this little-known pathogen was observed in Hungary (9) and Slovakia - 2.39% (10). In Poland, infection rate varies from 0.4% in the center of the country to 1.5% in the north-east (11).

Richter and *Matuschka* studied ticks removed from the skin of people and found that 8.1% of *I. ricinus* ticks were infected with *Candidatus* Neoehrlichia mikurensis, including 9.0% of nymphs and 4.5% of the adults. They also proved coinfection of *Candidatus* Neoehrlichia mikurensis, *Borrelia burgdorferi* sensu stricto and *B. afzelii* (6). *Lommano* et al. found that 3.3% of ticks removed from birds were infected with *Candidatus* Neoehrlichia mikurensis, which may suggest a role of birds in the spreading of the pathogen to new areas (12).

In 2008 *Candidatus* Neoehrlichia mikurensis was identified in raccoons (*Procyon lotor*) in Georgia and the USA (13) and in bank vole (14).

In Europe, the disease was described in 12 patients (2, 3, 15, 16). Less than half of the patients in Europe remembered tick bite. Most patients had splenectomy, hematological disorders or have been subjected to

immunosuppressive therapy (15,16). Currently, it is suggested that in the case of symptomatic infection *Candidatus Neoehrlichia mikurensis* use the name "neoehrlichiosis" (15).

THE FIRST DESCRIBED CASE

The first described case of neoehrlichiosis was published in 2010 (16). A 77-year old male, has suffered from chronic lymphocytic leukaemia (B-cells) with autoimmune haemolytic anaemia treated with corticosteroids since 2007. In the second half of 2008 due to the persistence of anaemia he was also treated with cyclophosphamide. In June 2009, after splenectomy, platelet count normalized. On the 3rd of July 2009, after the kayak expedition, patient had diarrhoea, fever with chills, episode of loss of consciousness. He was admitted to hospital with a suspicion of sepsis (RR-85/60 mmHg, the temperature of 38.5 °C), accompanied by deep vein thrombosis of the lower limbs and the left pulmonary embolism. He was treated with ceftazidime and anti-thrombotic drugs. Etiologic agent of sepsis has not been established. In good general condition patient was discharged home. After a month the disease relapsed. The patient was hospitalized again. Developed a rash on the left leg, hypotension: RR-105/55 mmHg, fever up to 39.5 °C. Laboratory tests: HGB-8.5 g/dl, WBC-11 000/microlitr, CRP-54 mg/dL, Na⁺-134 mmol/dl. He was treated with cloxacillin, meropenem. Multiple cultures (3 blood cultures, 2 urine cultures and 1 swab from the throat) were negative. On the August 21st was discharged home with the recommendation of the use of loracarbef. On the 11th of September, despite antibiotic therapy symptoms occurred again: fever with chills, infection of the upper respiratory tract, erysipelas of the right lower limb. In the treatment clindamycin was implemented. On the 22nd of September patient symptoms reappeared. Fever rose up to 39 °C. Laboratory tests revealed anaemia, leucocytosis, increased CRP concentration and procalcitonine, hyponatremia. Piperacycline, tazobactam and meropenem were included to the treatment, obtaining an improvement of general condition. The fever subsided, but muscle weakness of left upper limb remained. Head CT scan was normal/showed no abnormalities; blood cultures (aerobic and anaerobic) remained negative. Amplification of DNA from blood showed 100% concordance with *Candidatus Neoehrlichia mikurensis* by GenBank BLAST program. Tests performed on the samples from the preceding hospitalization gave the same result. Treatment with doxycycline 2x100 mg was started. On the 5th of October the patient was discharged home with normalization of laboratory parameters. Samples taken in November for check-up by PCR, showed no bacterial DNA in the blood (16).

SYMPTOMS

Infection with *Candidatus Neoehrlichia mikurensis* runs mainly with fever, headache, nausea, arthralgia, thrombotic or haemorrhagic complications, aneurysms, subcutaneous haemorrhages, haemorrhagic rash and weight loss. The infection may take an acute or chronic course. One fatal case was described. The longest described duration of symptoms was chronic relapsing fever manifested itself for 8 months in addition to the symptoms of thrombotic disease, inflammatory changes in the lungs, swelling of limbs and aching joints (2, 3, 15,16,17).

IMMUNODEFICIENCY

Most patients described in Europe suffered from autoimmune disorders (SLE, psoriasis, primary sclerosing cholangitis, rheumatoid arthritis, chronic demyelinating polyneuropathy) or haematological diseases, among which the most frequently observed are B-cell chronic lymphocytic leukaemia, chronic lymphocytic leukaemia, lymphoma, large B-cell disorders, post-transplant lymphoproliferative and proliferation of T-cell large granular lymphocyte. Almost all patients received corticoids, cyclophosphamide, rituximab, or tacrolimus treatment. Majority (8 out of 11) of these patients underwent splenectomy (3,18,19).

All of the 7 patients of 622 surveyed in China because of fever after a tick bite were immunocompetent in whom *Candidatus Neoehrlichia mikurensis* was confirmed, no patient was suffering from haematological disorders or autoimmune diseases. All patients were farmers, at the average age of 41 years. None of them have been vaccinated against TBE, and the average time from the tick bite to the onset of symptoms was 8 days (2-35) (17). Similarly, described four cases of infection of healthy individuals concerned foresters without deviation in the immune system (20). The most common symptoms were nausea and vomiting (71% of patients), myalgia (57% of patients), arthralgia (28% of patients), stiff neck stiffness (57% of patients), cough (28% of patients), diarrhoea (14% of patients), erythema (14% of patients), confusion (14% of patients). In laboratory tests leukopenia (14% of patients), leucocytosis (14% of patients), thrombocytopenia (28% of patients) were observed. Aminotransferases activity remained normal (17).

DIAGNOSTICS

Analysis of symptoms and laboratory tests may indicate a significant difference between infection in Europe and China.

Differences in laboratory between patients infected with *Anaplasma phagocytophilum* and *Candidatus Neoehrlichia mikurensis* are shown in Table I.

Table I. Differences between the results of laboratory tests *Anaplasma phagocytophilum* infection and *Candidatus Neoehrlichia mikurensis*

| | <i>Anaplasma phagocytophilum</i> | <i>Candidatus Neoehrlichia mikurensis</i> |
|---|----------------------------------|---|
| Symptoms | Similar | |
| WBC (10 ³ /mm ³) | Leucopenia | Leucocytosis |
| PLT (10 ³ /mm ³) | Severe thrombocytopenia | Mild thrombocytopenia |
| CRP (mg/dL) | Increase 2-4 x | Increase 10-15 x |
| AspAT, AlAT (U/l) | Increase | Mild increase |
| IL-8 | Normal | Increase |

The PCR, multiplex TaqMan real-time PCR for the detection of the gene coding for 16S rRNA and other such *gro EL* (heat shock operon) and a blood smear are used for diagnostics. There is neither possibility of the culture, nor appropriate serological methods due to cross-reactions. Often, based on laboratory tests *Candidatus Neoehrlichia mikurensis* infection can be assumed. Laboratory abnormalities suggestive of infection *Candidatus Neoehrlichia mikurensis* after tick bite shows leucocytosis, increased CRP, procalcitonine, thrombocytopenia, anaemia, and hyponatremia (2,3,15 - 19).

TREATMENT

The drug of choice is doxycycline, also used in the infection with *Borrelia burgdorferi* and *Anaplasma phagocytophilum* (3,15).

SUMMARY

Due to the fact that the *Ixodes ricinus* ticks are common in Poland, there is a probability of infection with *Candidatus Neoehrlichia mikurensis* among patients bitten by ticks. *Welc-Faleciak* et al. showed the possibility of human infection with *Candidatus Neoehrlichia mikurensis* in the north-eastern Poland (20), confirming the necessity of research on a larger scale. Moreover, awareness of physicians about the possibility of infection in patients with non-specific symptoms after tick bite should be increased.

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