Congenital Tick Borne Diseases: Is This An Alternative Route of Transmission of Tick-Borne Pathogens In Mammals?

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Abstract

Tick-borne diseases (TBDs) have become a popular topic in many medical journals. Besides the obvious participation of ticks in the transmission of pathogens that cause TBD, little is written about alternative methods of their spread. An important role is played in this process by mammals, which serve as reservoirs. Transplacental transfer also plays important role in the spread of some TBD etiological agents. Reservoir species take part in the spread of pathogens, a phenomenon that has extreme importance in synanthropic environments. Animals that accompany humans and animals migrating from wild lands to urban areas increase the probability of pathogen infections by ticks. This article provides an overview of TBDs, such as tick-borne encephalitis virus (TBEV), and TBDs caused by spirochetes, α-proteobacteria, γ-proteobacteria, and Apicomplexa, with particular attention to reports about their potential to cross the maternal placenta. For each disease, the method of propagation, symptoms of acute and chronic phase, and complications of their course in adults, children, and animals are described in detail. Additional information about transplacental transfer of these pathogens, effects of congenital diseases caused by them, and the possible effects of maternal infection to the fetus are also discussed. The problem of vertical transmission of pathogens presents a new challenge for medicine. Transfer of pathogens through the placenta may lead not only to propagation of diseases in the population, but also constitute a direct threat to health and fetal development. For this reason, the problem of vertical transmission requires more attention and an estimation of the impact of placental transfer for each of listed pathogens.

Key Words: Tick-borne diseases—Congenital diseases—Transplacental transmission.

Introduction

During the last 30 years, much attention has been paid to diseases transmitted by ticks—tick-borne diseases (TBDs). There is an extensive literature describing this issue, usually epidemiologically, and drawing attention to the methods of how the various pathogens are spread. Ticks function as vectors, but animals that are their reservoirs play an important role as well. Many publications describe the phenomenon of pathogen transfer between vectors—ticks—which can be done by co-feeding and vertically by germ cells. Relatively few publications describe cases of pregnant mother and newborn infections, pointing out another possibility of TBD pathogens spread by penetration through the placenta of infected animals and humans, in other words, the possibility of intergenerational infection. A properly developed placenta is supposed to be a selective barrier through which, theoretically, no pathogens should cross. However, this is not true. Clinical observations have provided information about etiological factors of congenital diseases that cross the placental barrier, thus confirming the transplacental transmission of such pathogens as viruses, bacteria, and protozoa (Robbins and Bakardjiev 2012).

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Vertical transmission of pathogens is a very important phenomenon from an epidemiological point of view, especially when it occurs in mammalian reservoirs. It can strengthen the effect of TBD pathogens spreading. This may occur when microbial virulence is low and does not reduce the number of individuals in a reservoir population. Infection in a variety of mammals caused by the same pathogen may have different effects. For this reason, it is important to determine not only the ability of pathogens to cross the placenta but also how this infection affects the mother and fetus. Medical and veterinary aspects of transplacental transmission of pathogens suggests that attention be paid to the mechanisms of this process and its effects. Therefore, this review concentrates on various cases of congenital infections and their symptoms.

**Tick-Borne Encephalitis Virus**

It is generally believed that tick-borne encephalitis virus (TBEV) is spread by ticks. This fact is, of course, indisputable. However, TBEV can also be transmitted through the oral route by food products, such as unpasteurized cheese, milk, and yogurt (Cisak et al. 2010). There have also been cases of infection through injury in a laboratory and by inhalation (Pancewicz et al. 2006).

Symptoms of TBE in most cases in humans are mild, sometimes even asymptomatic; however, there are cases of serious complications reported that can occur even several years after infection. Infections in animals may also have various effects. It has been observed, for example, that TBEV infection in dogs is usually asymptomatic (Pfeffer and Dobler 2011).

The natural reservoirs for TBEV are small rodents (Bakhalova et al. 2006), and transplacental transmission of TBEV has been observed in these animals. Vertical transmission of TBEV between generations of *Myodes rutilus* Pallas has been demonstrated in naturally infected rodents and after experimental infection with various doses in strains belonging to the Siberian genetic subtype (Bakhalova et al. 2009). TBEV is spread unequally, because not all embryos in the litter are infected transplacentally. Because the virus can be spread through different methods, the prevalence of TBEV in reservoir species of mammals can be enormous.

**TBD Caused by Spirochetes**

Among TBD diseases, congenital Lyme disease is a highly controversial phenomenon. Due to the fact that *Borrelia burgdorferi* sensu lato (s.l.) is taxonomically related to *Treponema pallidum*, there are investigators who are looking for similarities in the effects of these organisms on offspring that were infected transplacentally (Hercogova and Vanvousova 2008). Considering the fact that an adverse effect of spirochetes on pregnancy and fetal development has been documented many times, such research is completely reasonable. Over the last two decades of the 20th century, a number of papers describing the effects of Lyme disease in pregnant women on child development have been published (Schlesinger et al. 1985, Markowitz et al. 1986, MacDonald 1989, Hercogova et al. 1993, Maraspin et al. 1999). The literature shows that effects of congenital Lyme disease may be different, including symptoms like spontaneous abortion, fetal death, cardiovascular defects, cryptorchidism, urologic abnormalities, hypoplastic enamel, delayed psychomotor development, cavernous hemangioma, and dysplasia coxae (Schlesinger et al. 1985, Helayne and Silver 1997).

Histological observations have confirmed the presence of *B. burgdorferi* in children with congenital Lyme disease. It is interesting that spirochetes may exist in the spleen, kidneys, bone marrow, and nervous system (Schlesinger et al. 1985, Weber et al. 1988, Helayne and Silver 1997). Tropism of spirochetes was focused on the nervous system, and these observations were confirmed by pediatric neurologists who observed children with transplacental neuroborreliosis living in endemic areas in the United States (Silver 1997, Shapiro and Gerber 2000).

Different symptoms of congenital Lyme disease in animals were presented by Elliott et al. (2001). The authors of this study suggest that the problem requires further study because observations have not given consistent results. Animal studies did not always confirm transplacental transmission, and epidemiological analyses of congenital human Lyme disease are not clear. Among authors presenting their findings in the 21st century, opinions are still heterogeneous. It was noted that complications of congenital Lyme disease that occur the most frequently are loss of the pregnancy and cavernous hemangioma; however, there is no specific pattern of teratogenicity, similar to the Hutchinson’ triad in syphilis (Lakos and Solymosi 2010).

It is possible that *B. burgdorferi* s.l. has a high ability to penetrate mammalian placenta due to its ability of active movement, antigenic and morphological variation, and many other features and causes diagnostic difficulties and problems. In cases of intratropical fetal infections among patients with Lyme disease, symptoms are not homogeneous. Thus, confirming that *B. burgdorferi* s.l. is transmitted transplacentally may play important role in the spreading of these pathogens.

Despite the fact that some authors consider that antibiotic therapy of a pregnant mother diagnosed with Lyme disease allows normal development of the child (Walsh et al. 2007, Leslein 2010), it must be kept in mind that the treatment of Lyme disease is sometimes long and difficult (Embers et al. 2012). The ability of long-term survival of *B. burgdorferi* s.l. in tissues and spreading of spirochetes in the body despite antibiotic treatment can contribute to intergenerational infection of Lyme disease. Weber et al. (1988) found *B. burgdorferi* in human neonatal brain and liver, although the mother had been treated with an orally administered penicillin for Lyme disease during early pregnancy.

Besides syphilis spirochetes (*Mascia* et al.1985, Wendel 1988), infection of offspring has been observed in the case of maternal infection with the etiological factor of leptospirosis (Lindsay and Luke 1949, Coghlan and Bain 1969) and *Borrelia recurrentis* (Steenbarger 1982, Yagupsky and Moses 1985). Relapsing fever is caused by *Borrelia* spp. that differ in surface antigens. Antigenic variation is responsible for repeated spirochetemias and stimulation of the immune system by new antigens, a situation resulting in a febrile response in patients (Dennis et al. 2005). These spirochetes are transmitted to humans by exposure to infected tick bites or contact with the hemolymph of an infected body louse (*Pediculus humanus*). *B. recurrentis* is the etiological agent of illness called louse-borne relapsing fever or epidemic relapsing fever (Southern and Sanford 1969).

Studies of tick-borne relapsing fever have shown a high influence on pregnancy and offspring. Tick-borne relapsing fever caused by *B. hermsii* is a dangerous illness, and its vertical transmission may be a cause of spontaneous abortion, preterm delivery, or perinatal mortality (Barclay and Coulter 1990, Jones et al. 2015). Complications during pregnancy (miscarriages and neonatal death) are also caused by *B. duttonii* (Jongen et al. 1997, Rustenhoven-Spaan et al. 2013). Larsson et al. (2006) established a murine model of gestational relapsing fever infection for pathological studies of complications. These authors confirmed that *B. duttonii* can transmigrate through the placental barrier, causing congenital infection. Relapsing fever in pregnancy caused by *B. duttonii* results in intrauterine growth retardation, placental damage and inflammation, impaired fetal and placental circulation, and decreased maternal hemoglobin levels.

The possibility of an alternative way of spirochetes spreading by vertical transmission in mammals seems to be more likely in the case of *B. burgdorferi* s.l. than of spirochetes causing tick-borne relapsing fever. Compared with Lyme disease, tick-borne relapsing fever is characterized by acute symptoms and very often is a cause of miscarriages. These results are from clinical observations and experiments on animals.

### TBD Caused by *α*-Proteobacteria

#### Rickettsiosis

Etiological factors of rickettsiosis transmitted by ticks are *Rickettsia aeshlimannii*, *R. africae*, *R. australis*, *R. conorii*, *R. heliogiangensis*, *R. helvetica*, *R. honei*, *R. japonica*, *R. marmionii*, *R. massiliae*, *R. parkeri*, *R. raoultii*, *R. rickettsii*, *R. sibirica*, *R. sibirica mongolotimonae*, *R. slovaca*, and others (Fournier and Raoult 2009). Although the possibility of transplacental transmission models of this group of bacteria, for example, *R. prowazekii* transmitted by *P. humanus* in guinea pigs, has been demonstrated (Kurganova and Klimchuk 1996), this form of transmission through the placenta of mammals other than *Rickettsia* spp. has not been demonstrated. For example, it has been demonstrated that rickettsiosis during pregnancy caused by *R. rickettsii* and *R. conorii* presented no risk of vertical transfer of these pathogens to offspring (Stallings 2001). The small amount of information about congenital rickettsiosis is not evidence that this problem does not exist. The problem should be analyzed in different mammals, which can serve as reservoir species.

Another obligatory intracellular bacterium that can be transmitted transplacentally to progeny that is common is *Anaplasma phagocytophilum*, which causes human granulocytic anaplasmosis (HGA) with many nonspecific flu-like symptoms (Dhand et al. 2007) or tick-borne fever (TBF) in cattle and sheep (Walker and Dumler 1996, Henniger et al. 2013). What is interesting and unexplained is the problem of the *A. phagocytophilum* transmission mechanism through different types of placentas, i.e., the hemochorial placenta of human and the epitheliochorial placenta of ruminants. The mild immunosuppression during pregnancy is a particular physiological state during which potential relief of the infection’s symptoms favors infecting embryos through the placenta. This immunosuppression may cause fetal infection with various TBD pathogens.

There are scientific reports describing transplacental transmission at the same time of *A. phagocytophilum* and *B. burgdorferi* s.l. in humans (Brzostek 2004). Co-infections with pathogens causing TBD occur in animals and humans, but are rarely diagnosed, which does not mean that they occur rarely.

Other species of the genus *Anaplasma* can also be transmitted vertically between mammalian generations. *A. marginale* is a pathogen of cattle and other animals that is transmitted by ticks and causes a number of acute or chronic symptoms associated with the destruction of erythrocytes. Bovine anaplasmosis caused by *A. marginale* can be transmitted to the offspring through the placenta, especially when the disease is in a chronic state or if infection of the female takes place in the second or third trimester of pregnancy (Potgieter and van Rensburg 1987, Grau et al. 2013). Epidemiological surveys of transplacental transmission of *A. marginale* in chronically infected cows suggest the importance of this route of transmission in areas of enzootic instability.

#### Bartonellosis

*Bartonella* spp. are Gram-negative bacilli or coccobacilli that occur intracellularly in the mammalian host. Among the *Bartonella* spp. transmitted by ticks are *B. vinsonii berkhoffii*, *B. vinsonii arupensis*, and *B. tamiae* (Breitschwerdt et al. 2012). Bartonellosis can cause a variety of symptoms, such as fatigue, restlessness, myalgia, malaise, liver, and/or spleen involvement, abdominal pain, infectious mononucleosis-like syndrome, and granulomatous hepatitis. Bartonellosis may have the character of a chronic disease that causes a variety of complications, such as encephalopathy, endocarditis, and cardiomegaly.

Isolation of *Bartonella* spp. from embryos of naturally infected rodents suggests the possibility of transplacental transmission. Besides rodents, congenital bartonellosis has also been described in cattle and horses. *B. birtlesii*, *B. bovis*, and *B. henselae* may be transferred from females to offspring (Lakes 2012). In the case of infection by *B. henselae*, the possibility of such a phenomenon in cats has not been described (Breitschwerdt and Kordick 2000).

Vertical transmission of bacteria in humans from the genus *Bartonella* is not clearly confirmed. Breitschwerdt et al. (2010) assumed the possibility of infections in utero by *B. vinsonii* subspp. *berkhoffii* and *B. henselae* and documented a case of fetal infection, although it could not be excluded that the infection occurred during cesarean section. Perhaps the differences in placentation or placental structure of various species of mammals are responsible for predisposition to diverse methods of the vertical transmission of pathogens. This problem needs further investigation.
Brucellosis

Coccobacilli of the genus *Brucella* spp. are obligatory intracellular bacteria. Ticks transmit *Brucella* spp. occasionally, and brucellosis is mentioned among the TBDs. Among the few known species pathogenic to humans are *B. abortus*, *B. suis*, *B. canis*, and the most common in the world *B. melitensis* (Galińska and Zagórski 2013). Brucellosis is primarily a disease of animals and a zoonotic disease of humans. The main reservoirs of *Brucella* spp. are goats, sheep, pigs, and cattle.

Deliveries and abortions in infected animals also play an important role in the dissemination of *Brucella* spp. in the herd. Contamination of pastures by infected blood, genital secretions, and fetal death can be the methods by which brucellosis is transmitted (Memish and Balkhy 2004). This phenomenon is important from an epidemiological point of view.

Brucellosis occurs in various forms. It is a multisystem disease with a broad spectrum of clinical signs. Among the most common are nonspecific symptoms—fever, malaise, sweats, arthralgias, lower back pain, and headache. Andriopoulos et al. (2007) presented multiple organ dysfunction effects, such as splenomegaly, osteoarticular involvement, cervical lymphadenitis, hepaticomegaly, genitourinary involvement, cholecystitis, breast abscess, and acute abdomen. Mental and physical exhaustion occurs in chronic brucellosis, as well as apathy, sleep problems, loss of consciousness, changes in the central nervous system, mental disorders, convulsions, and temporary paralysis.

Human congenital brucellosis is a rarely described phenomenon (Imani et al. 2007, Glocwicz et al. 2010). There are very few cases of proven congenital brucellosis in liveborn infants (Giannacopoulos 2002, Poulou 2006). However, premature delivery of infected newborns with disseminated brucellar disease and nonspecific signs of septicemia has been documented (Shamo’on and Izzat 1999, Koklu et al. 2006). Mesner et al. (2007) described a case of a physician who assisted during the resuscitation of a newborn with congenital brucellosis. *B. melitensis* was in the blood of this infant, and serological diagnostics demonstrated presence of antibodies against *Brucella* spp.

Brucellosis seems to be a serious public health problem, and the level of morbidity persists at a high level. However, knowledge about this disease among physicians is low. In a substantial fraction of patients, brucellosis was diagnosed after the causative symptoms. Bacteria were detected in cultures of blood or exudate (Mesner et al. 2007). Congenital brucellosis also plays an important role in the dissemination of pathogens, and this phenomenon is important from the epidemiological point of view.

**TBD caused by γ-Proteobacteria**

*Tularemia*

*Coxiella burnetii* is the etiological agent of Q fever. Because this bacterium is resistant to various environmental factors, ticks rarely transmit *C. burnetii* (Bielawska-Drózd et al 2013). Naturally infected animals are sheep, goats, and cattle. Animals infected with *C. burnetii* usually do not show symptoms of the diseases. In the acute phase, the presence of the *C. burnetii* bacterium during its intense proliferation can be demonstrated in the blood, lung, spleen, and liver; nevertheless, the symptoms may be not noticed, even in the form of fever. In this condition, the bacteria are excreted with feces and urine. High concentrations of pathogens in different organs among females have been observed, for example, in the uterus, mammary glands, and placenta. This promotes the spread of *C. burnetii*. The only pathological manifestations that have been associated with chronic *C. burnetii* infection in animals are miscarriages, mainly in sheep and goats, and lower birth weight and infertility in cattle (Maurin and Raoult 1999).

This dangerous pathogen causes miscarriages in pregnant women, premature births, and lower neonatal weight (Maurin and Raoult 1999). Observations of pregnant women infected with Q fever have not clearly confirmed increased risk of birth defects in children due to infection (Poucault et al. 2004, Carcopino et al. 2007, Anderson et al. 2013). It is believed that changes within the urinary tract and the cardiovascular system observed in neonates could be a result of pharmacotherapy received by pregnant women. Results of tests used to confirm the danger of these drugs to the fetus are not clear (Carcopino et al. 2007). *C. burnetii* is activated during pregnancy and therefore is responsible for the higher rates of miscarriage, premature birth, and birth weight reduction. Transplacental transmission of *C. burnetii* is not an alternative route of its spread. Although intrauterine transmission of *C. burnetii* has been rarely documented, consequences of congenital Q fever remain to be determined (Honarmand 2012).
TBD caused by Apicomplexa

Babesiosis

Babesiosis is a disease recorded in animals and humans (Casapulla et al. 1998, Vannier and Krause 2012). Most often, the etiological agents of human babesiosis are Babesia divergens and B. microti (Homer et al. 2000). This disease shows diverse symptoms, including anemia, elevated temperature, splenomegaly, hepatomegaly, jaundice, and hyperbilirubinemia. People with these symptoms, who confirm contact with ticks, especially I. ricinus in Europe and I. scapularis in America, help direct doctors to perform TBD-differentiating tests. However, in cases when a patient’s contact with a tick is not recorded or the disease affects a newborn, it is very difficult to direct the physician to diagnose babesiosis. In this case, babesiosis, as well as other diseases from the group of TBD can be very dangerous.

Congenital babesiosis in humans has been described very rarely. Most cases of reported babesiosis in neonates were a result of transfusion by infected blood. In 2009, only three documented incidents of infants infected through the placenta were recorded (Esernio-Jenssen et al. 1987, New et al. 1997, Sethi et al. 2009). Aderinboye and Syed (2010) and Joseph et al. (2012) described a number of other cases of such infection. The sparse literature would suggest that the phenomenon of vertical babesiosis is marginal, but this should not be underestimated for several reasons: The amount of literature is not a measure of the scale of female babesiosis carriers who are potential mothers; babesiosis in clinical practice is a problem that is often difficult to observe; and a series of epidemiological studies should be performed in different populations.

Congenital transmission of babesiosis in animals, which are natural intermediate hosts for Babesia spp., has already been proven (Stodki and Jasik 2012, Stodki et al. 2013). Despite various symptoms of the diseases, the chronic phase is very extended and is scarce in symptoms. It should be taken into epidemiological consideration that Babesia spp. can be spread by vertical transmission in mammals.

Theileriosis

Species of the genus Theileria are a large group relative to Babesia and are classified as Apicomplexa: Piroplasmda (Bishop et al. 2004, Lack et al. 2012, Sivakumar et al. 2014). These parasitic organisms, as with the Babesia spp., are characterized by their complex development cycle (Shaw 2003). The intermediate hosts may be mammals, specific for Babesia spp., whereas the definitive hosts are several hard ticks. Geographical coverage of Theileria spp. is diverse. Theileriosis is primarily a disease of cattle and small ruminants and is a serious veterinary, and thus economic, problem. In animals, significant swelling of the lymph nodes, loss of appetite, diarrhea, and deep respiratory failure characterize the acute phase.

Transplacental transmission of pathogens has been described in cases of infection with T. sergenti, T. annulata, and T. equi (Allsopp 2007, Heim et al. 2007, Gül and Issi 2009). Theileriosis can also have a chronic course, which increases the carrier effect and may cause a vertical spread of the pathogen.

Summary

TBDs are a broad group of diseases caused by various etiological factors. Many pathogens show specificity for the host, the reservoir, and the vector. Therefore, it can be assumed that the relationship with the host organism is subject to evolutionary fit. Invasion of pathogens, exclusively or conditionally transmitted by ticks, is associated with a variety of adaptations that are responsible for ability of the host to be infected. As with each parasitic system, the higher the expansiveness of an microorganism, the lower is its virulence and the weaker its symptoms. Minor symptoms of chronic diseases and a weakening immune response of the host organism create the possibility of long-term survival of the pathogen in a population and thus better spread.

Mechanisms for pathogens crossing the placental barrier have been discussed in many studies, but there is often much ambiguity. The method of crossing the placental barrier probably depends on the species of infected organism and hence its placental type. In humans and nonhuman primates, who produce hemochorial placentas, despite many safeguards against fetal infection, the number of barriers between the blood of the mother and fetus are relatively small. This also applies to rodents and rabbits, i.e., animals that serve as a reservoir for many pathogenic bacteria and protozoal TBDs.

Apart from placental architecture, the specificity of the immune system of the pregnant female is a very important issue. Semiallogeneic organisms are connected through the placenta during pregnancy and therefore immunomodulation occurs in the maternal body (Mor and Cardenas 2010).

For some pathogens it is assumed that an important factor for transplacental transmission is the ability to exist intracellularly. Syncytiotrophoblasts play an important role in this process. There are suggestions that some pathogens may invade fetuses through damage to the syncytiotrophoblast (Crocker et al. 2004, Robbins and Bakardjiev 2012). On the other hand, there are pathogens that can move from the maternal blood circulation to the fetal blood circulation without damage to the placental cells. It seems important that the tropism of pathogens to epithelial cells, leukocytes, or phagocytes may be involved in pathogen migration from maternal to fetal blood circulation (Robbins and Bakardjiev 2012, Doran et al. 2013). Model studies of these mechanisms take into account that pathogens are transferred by macrophages from the maternal blood through syncytiotrophoblasts, syncytiotrophoblast damage, penetration directly through cytrophoblasts, interactions of the bacterial virulence determinant internalin A with E-cadherin, and a number of other methods (Robbins et al. 2010, Robbins and Bakardjiev 2012).

Many pathogens attack the placenta, but not much is known about their active penetration through the placental barrier (Doran et al. 2013). Placental infection can lead to miscarriage, premature birth, and infection of the fetus or newborn. The effect of transmission depends on the stage of pregnancy and the species of pathogen. Tick-borne pathogen transmigration through the placenta to the fetus and the impact on fetal development and fetal survival are factors that determine whether transplacental transmission has potential epidemiological importance. For this reason, the problem of vertical transmission requires more attention, as does the estimation of the impact of placental transfer for each of pathogens listed in this review.
Author Disclosure Statement

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