EPIDEMIOLOGY OF *NEOSPORA CANINUM* INFECTION IN ANIMALS

Dịch tễ học của *Neospora caninum*

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Received date: 17.03.2011 Accepted date: 28.04.2011

TÓM TẮT

Neospora caninum **là một ký sinh trùng hình cầu sống ký sinh bắt buộc trong tế bào, có thể gây bệnh ở rất nhiều loài động vật. Trong vòng đời của mình, *N. caninum* cần một vật chủ trung gian và một vật chủ cuối cùng. Loài ký sinh trùng này tồn tại ở ba dạng và lưu truyền giữa các động vật thông qua hai con đường: lây truyền dọc từ mẹ sang con và lây truyền chéo giữa các cá thể. Tỷ lệ nhiễm *N. caninum* khác nhau ở các loài động vật và khu vực sinh sống. Ở động vật trưởng thành, bệnh do *N. caninum* gây ra có thể làm sẩy thai chủ yếu vào giữa thai kỳ và đó cũng là triệu chứng duy nhất được biết cho đến nay. Tỷ lệ sẩy thai ở bò có thể lên đến 44%. Những con non sinh ra từ mẹ bị nhiễm bệnh có thể không bị bệnh, hoặc bị bệnh nhưng không có triệu chứng hoặc thể hiện một số triệu chứng về thần kinh và gặp khó khăn khi vận động.**

Từ khóa: Dịch tễ học, *Neospora caninum.*

SUMMARY

Neospora caninum **is an obligate intracellular coccidian parasite, which can infect various animal species. The parasite has a two-host life cycle and exists in three stages. *N. caninum* can survive and disseminate among animals through horizontal and vertical transmissions. Prevalence of *N. caninum* infection in animals is different from species to species, from location to location. In adult animals, neosporosis causes abortion, which mostly occurs at mid-gestation and is the only known symptom so far. Pregnancy loss in positive cattle can be up to 44%. Offspring born to infected mothers may be free of disease, subclinically infected or clinically infected. Most clinical symptoms are related to neurological signs and difficulty in locomotion.**

Key words: Epidemiology, *Neospora caninum*.

1. INTRODUCTION

Neospora caninum is a parasite belonging to family Sarcocystidae in phylum Apicomplexa. This parasite was first detected in Norwegian dogs in 1984 and described in 1988 (Bjerkas et al., 1984; Dubey et al., 1988). The parasite can infect a variety of animals and is now recognized as one of the most important causes of bovine abortion worldwide. Considerable economic loss due to neosporosis has been demonstrated (Hasler et al., 2006), however, highly efficacious prevention and control has not been established. This review focuses on epidemiology of neosporosis in animals.

2. BIOLOGY AND LIFE CYCLE OF N. CANINUM

N. caninum has three stages of its life cycle which are tachyzoites, tissue cyst containing bradyzoites, and oocysts. Tachyzoites are lunate, ovoid or globular with size of 3-7 x 1-5µm depending on the stage of division. Dividing tachyzoites are 4 x 3 µm (Speer and Dubey, 1989). They are located within the parasitophorous vacuole or freely in the host cell cytoplasm (Dubey et al., 2002; Speer and Dubey, 1989).

Round or oval tissue cysts are primarily found in the neural tissues characterized by a thick-wall up to 4µm, and the diameter up to 107µm (Dubey et al., 1988; McGuire et al., 1997). Thin-walled (0.3-1µm) tissue cysts were reported in muscles of cattle and dogs naturally infected with N. caninum-like parasite (Peters et al., 2001a). Each neural tissue contains 50-200 bradyzoites measured from 7.3 x 1.5 to 8 x 2 µm with 6-12 rhoptries (Dubey et al., 2002; Speer and Dubey, 1989). Both tachyzoites and tissue cysts are found in several organs including brain, heart, kidney, liver, muscle, placenta, etc. (Dubey et al., 2006).

Unsporulated oocysts whose walls are colorless are reproduced from the sexual activity of the parasite and excreted with feces by the definitive hosts. Measurements of oocyts are 10.6-12.4 x 10.6 x 12 µm with the length-width ratio of 1.04 (Lindsay et al., 1999). One oocyst encompasses two sporocysts which are 8.4 x 6.1 µm consisting of four sporozoites measured about 6.5 x 2µm in each. After being shed, oocysts sporulate within 3 days and become infective to its hosts (McAllister et al., 1998b).

N. caninum has a two-host life cycle in which both sexual and un-sexual replication of the parasite take place in final hosts and un-sexual reproduction occurs in intermediate hosts (Dubey et al., 2002). As current findings, the parasite has three proven definitive hosts, i.e. dogs, coyotes and Australian dingoes (Gondim et al., 2004b; King et al., 2010; McAllister et al., 1998a).

The most important intermediate host of N. caninum seems to be cattle since it causes a substantial economic loss in cattle farming. Isolations of N. caninum from aborted fetuses, calves and cows have been reported (Canada et al., 2004; Okeoma et al., 2004; Rojo-Montejo et al., 2009). Buffaloes were also a vulnerable intermediate host of the parasite since N. caninum was demonstrated from six infected buffaloes by using bioassay and cell culture (Rodrigues et al., 2004). Furthermore, sheep, white tailed dear, red foxes, chicken and pigeons are also illustrated their role as the intermediate hosts of N. caninum (Almeria et al., 2002; Costa et al., 2008; Pena et al., 2007; Rojo-Montejo et al., 2009; Vianna et al., 2005). Rhesus monkeys have been successfully experimentally infected with N. caninum and induced transplacental transmission and fetal infection (Barr et al., 1994). This discovery shows possibility of being zoonotic potential of the parasite. In addition, antibodies to N. caninum in human have been demonstrated (Lobato et al., 2006). Fortunately, no DNA or parasite have been found in the human tissues. However, the question that whether human behaves as a host of parasite is still unanswered. Presence of antibodies to N. caninum in many other species suggests that this parasite may have a wider range of intermediate hosts rather than known ones (Dubey et al., 2007a).

3. TRANSMISSION

Transmission of N. caninum between hosts is classified as postnatal or horizontal transmission and transplacental or vertical transmission. Horizontal transmission occurs when animals ingest tissue cysts, tachyzoites and oocysts while vertical transmission is induced when the parasites from the dams transmit to their offspring through placentas.

Vertical transmission in dog is not effective. Only 4 out of 118 pups born to 17 positive bitches are positive (Barber and Trees, 1998). Low rate of vertical transmission suggests that there should be an effective horizontal transmission of neosporosis in dogs. However, feeding dogs with infected fetus does not always successfully induce the infection of N. caninum (Cedillo et al., 2008). In other studies, feeding dogs with infected buffalo brains, mouse brains and calf tissues could successfully predisposed the excretion of oocysts (Gondim et al., 2002; Lindsay et al., 2001; Rodrigues et al., 2004). Higher amount of oocysts is shed by pups and dogs fed with infected calf tissues than adult dogs and dogs fed with infected murine tissues, respectively. That dogs defecating oocysts is of apparentness but whether ingesting of oocysts can induce neosporosis in dog is still questionable. Vertical transmission in cattle seems to be much more effective than that reported in dogs. Studies have shown that the frequency of transplacental transmission is very high in cattle from 58% to 95.2% (Chanlun et al., 2007; Davison et al., 1999). Horizontal transmission in cattle is usually less than 5% per year (Chanlun et al., 2007; Davison et al., 1999; Hietala and Thurmond, 1999). However, in some cases, this rate can be up to 47% within 6 months (Dijkstra et al., 2002; More et al., 2009).

Venereal transmission is an aroused concern since DNA of N. caninum is found in the semen of naturally infected bulls (Ferre et al., 2005). However, the presence of parasite is low, i.e. 1-10 parasite/ml and intermittent, and live tachyzoites in the semen have not been specified (Ferre et al., 2005). Moreover, in a study of intrauterine N.

caninum inoculation of heifers and cows using contaminated semen, the minimum number of tachyzoites used to induce neosporosis was 50,000 (Serrano-Martinez et al., 2007). Recently, experimentally infected bulls have failed to induce seroconversion in dams through natural breeding (Osoro et al., 2009). Presence of DNA of N. caninum is also demonstrated in colostrum threatening the possibility of lactogenic transmission of the disease. However, live tachyzoites have not been demonstrated from milk (Moskwa et al., 2007).

Transmission of N. caninum has also been reported in several other animals. Vertical transmission is indicated in sheep and goat since DNA of N. caninum is found in aborted fetuses (Eleni et al., 2004; O'Handley et al., 2003). Mice and cats are also suffered from neosporosis which results in vertical transmission (Dubey and Lindsay, 1989; Haldorson et al., 2005; Miller et al., 2005). In a research in buffaloes in Brazil, the vertical transmission rate was demonstrated as high as 74% (Rodrigues et al., 2005). Moreover, two rhesus monkeys are experimentally infected by N. caninum tachyzoites and predisposed transplacental transmission (Barr et al., 1994).

4. PREVALENCE

N. caninum infection has been reported in several countries over the world. A considerably large number of kinds of animals from domesticated to zoo and wild, carnivorous as well as herbivorous animals have been investigated.

Dogs are an interesting subject of neosporosis studies because of its role as the definitive host of the parasite. The seroprevalence of N. caninum in dogs was different from continent to continent and from country to country. In Europe, it was reported that up to 46.4% tested dogs are seropositive to the parasite (Ferroglio et al., 2007; Lasri et al., 2004; Wouda et al., 1999b). The proportion of positive dogs in Asia was also demonstrated from 1.2 % in Thailand to 46% in Iran (Kyaw et al., 2004; Malmasi et al., 2007). In South America, prevalence also varies from 0% to 58.9% (Figueredo et al., 2008).

Among all of animals, cattle are most studied subject in neosporosis. The individual prevalence of N. caninum in cattle varies widely ranging from as low as 0% to as high as 87 % (Akca et al., 2005; Stenlund et al., 2003). Reports frequently show a prevalence of less than 30% (Dubey et al., 2007a). Dairy cattle seem to have higher prevalence of N. caninum comparing with beef cattle (Dubey et al., 2007a). Almost all studies state an individual seropositive status of less than 30% in beef cattle except one which found 79% aborted beef positive in America (McAllister et al., 2000). Herd level prevalence was also reported variably between 16% and 94% (Bartels et al., 2006; Woodbine et al., 2008).

In the buffaloes, the prevalence of N. caninum ranges from 0% up to 70.9% (Gennari et al., 2005; Yu et al., 2007). Interestingly, the prevalence in river buffaloes (34.6% to 70.9%) seems to be higher than that in swamp buffaloes (0%-3.5%). In sheep and goat the proportions of seropositive experimented subjects have been found up to 26.3% (Konnai et al., 2008). Prevalence of N. caninum has been also studied in a wide range of wild carnivorous, herbivorous, zoo and marine animals (Dubey et al., 2007a).

The possible zoonotic aspect of N. caninum has been a concern due to the demonstration of antibodies against this parasite in human. N. caninum seropositive people were reported in Brazil (Lobato et al., 2006). In that study, 38% and 18% people who had acquired immuno-deficiency syndrome and neurological disorders were respectively positive to N. caninum. Testing 1,029, 247 and 172 blood donors in the United States, Northern Ireland and Korea, results showed that 6.7%, 5.3% and 6.7% samples were positive, respectively (Graham et al., 1999; Nam et al., 1998; Tranas et al., 1999).

5. CLINICAL SIGNS

Neosporosis have been reported in dogs at different ages with the most found clinical signs of locomotor ataxia, paresis or paralysis of either hindlimbs or forelimbs, or both (Basso et al., 2005; Crookshanks et al., 2007; Dubey et al., 2007b). The hindlimbs are usually more severely affected than the forelimbs (Dubey et al., 2007b). Other dysfunctions may include rigidity of the legs (Reichel et al., 1998), muscle atrophy, stiff jaws and dysphagia (Basso et al., 2005), rigid hyperextension (Barber and Trees, 1996) and Horner’s syndrome (Mayhew et al., 2002). Multifocal nodular dermatitis, ulcerative and pyogranulomatous dermatitis were also found in dogs infected with N. caninum (Boyd et al., 2005;

La Perle et al., 2001; Perl et al., 1998). How dogs develop neuromuscular symptoms is not clear but it is most likely that they are affected by the damage in the central nerve system such as cerebella atrophy, multifocal non-suppurative encephalitis (Dubey, 2005; Lorenzo et al., 2002), multifocal non-suppurative meningoencephalomyelitis (Patitucci et al., 1997), myeloencephalitis (Pumarola et al., 1996) and myositis (Crookshanks et al., 2007).

In the adult cattle infected with N. caninum, abortion is the only demonstrated clinical sign. Infection of N. caninum at the early stage of gestation may result in fetal death, resorption or mummification (Ghanem et al., 2009; Williams et al., 2000) while exposure to the parasite at later stage may result in either calving with congenital infected calves or abortion (McCann et al., 2007; Rosbottom et al., 2008). Abortion due to neosporosis was documented to occur through the period of gestation but the majority is between 5th and 7th month of pregnancy (Huang et al., 2004; Wouda et al., 1997). N. caninum-positive cattle have from 12.2 to 23.6 times higher risks of being aborted than their neosporosis negative counterparts (Lopez-Gatius et al., 2004a; Weston et al., 2005). In several herds, up to 44% pregnancies of positive animals could be aborted (Lopez-Gatius et al., 2004a).

Although most of calves born to positive dams are congenitally infected, majority of them are clinically healthy and some express abnormal clinical signs (Pare et al., 1996). Infected calves may be born underweight, unable to rise and with the neurological signs. Either hindlimbs and/or forelimbs could be flexed or hyperextended. Neurological examination reveals ataxia, decreased patellar reflexes and loss of conscious proprioception (Barr et al., 1993; Parish et al., 1987). Clinical signs in infected calves may be due to the pathological damage including lesions in brain characterized with non-supportive necrosis foci, focal necrotizing encephalitis, non suppurative encephalomyelitis, non suppurative myositis, myocarditis (De Meerschman et al., 2002; Pescador et al., 2007; Razmi et al., 2007; Zhang et al., 2007).

Abortion caused by N. caninum was also found in buffaloes, sheep, goats and pigs with a variety of systematic disorders in fetuses including myocarditis, myositis, pneumonitis, nephritis, hepatitis and encephalitis (Buxton et al., 1998; Buxton et al., 2001; Dubey et al., 1996; Guarino et al., 2000; Jensen et al., 1998; McAllister et al., 1996). In addition, meningoencephalomyelitis and myeloencephalitis were found in deer and horses, respectively (Marsh et al., 1996; Soldati et al., 2004). Moreover, rhinoceros and antelopes are infected with N. caninum with symptoms such as myocarditis and stillbirth, respectively (Peters et al., 2001b; Williams et al., 2002). Recently, experiments to infect chicken and embryonated eggs with N. caninum have induced arthritis in feet joints of chicken and death of embryonated eggs (Furuta et al., 2007; Mansourian et al., 2009).

6. PATHOGENESIS OF ABORTION IN ANIMALS

In cattle, abortion is defined as the termination of pregnancy between day 42nd and 260th of gestation (Lopez-Gatius et al., 2004b). It is still unclear how the parasite causes abortions but there are several possible explanations for this phenomenon including direct effects of fetal tissue damage affected by the multiplication of the parasite, and the response of maternal and fetal immunities to the parasite which results in death of placental tissue and subsequent insufficiency of oxygen and/or nutrition (Dubey et al., 2006).

Cattle embryos within 7 days of gestation do not expose to parasite in positive dams (Moskwa et al., 2008). From day 34th to 90th of pregnancy, there is no association between abortion and seropositivity to N. caninum (Lopez-Gatius et al., 2004b). However, there is evidence that neosporosis increases the number of services per conception in cattle (Hall et al., 2005). In later period of gestation, infection of N. caninum might result in fetal death or congenitally infected progenies. Time of infection seems crucial to outcome of disease when challenging pregnant cows with N. caninum tachyzoites at day 70th of gestation results in fetal death while infection at day 210th confers transplacentally infected calves (Rosbottom et al., 2008; Williams et al., 2000). In cows infected at day 70th, widespread necrosis and inflammation in placentas are found while those pathological symptoms are absent in the group of cows infected at day 210th (Rosbottom et al., 2008). Before about day 100th of gestation, fetus could not recognize and respond to pathogens (Osburn et al., 1982) then the parasite could easily invade and multiplicate. The parasite may reinvade placentas from fetuses and causes more severe necrosis in placentas (Gibney et al., 2008). As the result, fetuses might be dead due directly to the destruction of the parasite or the cytotoxic effects of the necrosis process that damages the trophoblast cells. Furthermore, there is a speculation that the infection of bovine neosporosis in the first trimester may induce the T helper cell-1 cytokines response and lead to the generation of IL-12, IFN-γ and TNF-α and subsequent production of free oxygen radicals such as nitric oxide, all of which may be lethal to parasite but may also kill fetuses (Quinn et al., 2002). That is why the infection of N. caninum in the first trimester usually results in severe pathogenesis in the placenta and death of fetus.

After day 100th of gestation, immune system of fetus is competent to recognize and respond to antigens (Osburn et al., 1982). However, abortions due to neosporosis peaked during month 5th -7th of gestation (Gonzalez et al., 1999; Moen et al., 1998). Challenging of pregnant cows with N. caninum oocyst at different stages of gestation results in abortions at group infected at day 120th of pregnancy while there are no abortions in groups infected at day 70th and 210th (Gondim et al., 2004a; McCann et al., 2007). This may be explained by the pattern of progesterone in the gestation of the cattle which increases steadily from early to mid-gestation then significantly declined few weeks before parturition (Pope et al., 1969). Supplementation of progesterone at mid-gestation increased the risk of abortion in Neospora-infected dairy cows and high antibody titer was reported (Bech-Sabat et al., 2007). In addition, the peak response of cell mediated immunity (CMI) to parasite occurs at the early and late gestation when the level of progesterone is low (Innes et al., 2001). In other words, CMI responds to parasite less effectively at mid-gestation than at first and third trimesters. When immune response of mother changed to facilitate pregnancies, it might also favour the multiplication of parasite. As a result, modulation of CMI might influence the recrudescence of a previous persistent infection causing bradyzoites to excyst resulting in parasitaemia (Innes et al., 2001). Another suggestion is that as pregnancies progress to mid-gestation, parasite will have sufficient time for further implication (Lopez-Gatius et al., 2004b). Those hypotheses may explain why abortion peaks between month 5th and 7th of gestation.

In the third trimester, infection of N. caninum usually predisposes persistently infected progeny, otherwise healthy calves (McCann et al., 2007; Rosbottom et al., 2008). Immuno-competence is very important to survival of fetus. In an experiment, inoculating tachyzoites to 2 groups of pregnant cows at 10th and 30th weeks of pregnancy, an increase in response of Th1 to presence of parasites was observed in both groups (Williams et al., 2000). Despite this fact, fetal death occurred only in the former group, in the latter group calves were born congenitally infected. There is a suggestion that the response of Th1 might be too late to affect an existing, well-established Th2 response at maternal-fetal interface. T helper 1 cytokines facilitate pro-inflammatory cytokines which effectively kill infected cells and parasites while T helper 2 cytokines work less effectively than the former (Quinn et al., 2002). Throughout the gestation, the ratio of Th2:Th1 increases because of the production of Th2 from the fetal tissue (Wegmann et al., 1993). The modulation of response of Th2 may result in less necrosis and inflammation in the placenta and fetus but favour survival of parasite and its invasion to fetuses and subsequently congenitally infected offspring (Williams et al., 2000).

7. RISK FACTORS OF NEOSPOROSIS

7.1. Risks of infection

There are certain factors that play as risks of infection in neosporosis. Studies of canine neosporosis showed that seroprevalence of N. caninum is higher in dogs in rural areas than that in dogs living in urban areas (Ferroglio et al., 2007; Hornok et al., 2006a; Sharma et al., 2008). Farm dogs are more likely to be positive than urban dogs, house dogs and rescue dogs (Cruz-Vazquez et al., 2008; Hornok et al., 2006a; Paradies et al., 2007). Due to postnatal transmission, age has a positive correlation with the N. caninum sero-status in dogs (Malmasi et al., 2007). Climate condition might influence the development of N. caninum oocysts then affect seroprevalence of animals living in that region. In Spain, carnivores living in high humid areas have higher prevalence of antibodies to the parasite (Sobrino et al., 2008).

Presence of dogs in farms increases risks of being positive to N. caninum of cattle (Bartels et al., 2007). Rabbits and ducks are also a putative risk factor of seropositivity in cattle (Ould-Amrouche et al., 1999). Risk of being positive increases with age and parity of cattle (Dyer et al., 2000; Sanderson et al., 2000). Seroprevalence of N. caninum is also different from breeds to breeds as Limousin is reported to have lower sero-status comparing with other breeds (Armengol et al., 2007). In the same breeding condition, dairy cattle seem to be more vulnerable to N. caninum than beef cattle (Moore et al., 2009). Infection of Infectious Bovine Rhinotracheitis is reported to predispose seropositivity of N. caninum in cattle since the former disease harmfully affects the immune system of cattle and creates opportunity for the latter pathogen to infect animals (Rinaldi et al., 2007). It is likely to be true that cattle with higher antibody titer would have more chances to transmit infection to their calves than cattle with lower antibodies titer (More et al., 2009). In water buffaloes, age and sex were reported to have influence on seroprevalence of animals since older and female buffaloes have higher risk of being positive than younger and male buffaloes, respectively (Campero et al., 2007; Guarino et al., 2000; Mohamad et al., 2007).

7.2. Risks of abortion

Seropositive cows are more likely to abort than their negative counterparts (Gonzalez-Warleta et al., 2008; Moore et al., 2009). The abortion risk increases with increasing levels of N. caninum antibodies in individual animals (Kashiwazaki et al., 2004; Waldner, 2005). Herds with high prevalence of N. caninum antibodies are associated with increased risk of abortion (Hobson et al., 2005; Schares et al., 2004). Age and parity of cattle are found to be protective factors of abortion (Hernandez et al., 2002; Stahl et al., 2006). Presence of other animals in the farm contributed as either risk or protective factors to abortion of cattle. Farms with presence of dogs and horses are reported to have higher rate of pregnancy termination whereas presence of cats in farms could decrease abortion rate of dairy cattle (Hobson et al., 2005). Perhaps, cats had interrupted transmission of parasite from intermediate hosts like rats to dogs by eating them or replaced presence of dogs in farms then decreased the dissemination of parasites and abortion of cattle. The risk of abortion is 15.6 times higher in cows that did not produce IFN-γ than sero-negative cows whereas neosporosis had no effects on seropositive cows that produce IFN-γ (Lopez-Gatius et al., 2007). High levels of prolactin have protective effect on abortion rate caused by neosporosis while supplementation of progesterone in mid-gestation of high antibody titer cattle increases abortion rate (Bech-Sabat et al., 2007; Garcia-Ispierto et al., 2009). High humidity climate was also a risk of abortion. The suggestion is that humid environment favored oocysts to sporulate and to infect and cause abortion in cattle (Wouda et al., 1999a).

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