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Review Article

A Literature Review of *Neospora caninum* Infection in Humans

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Abstract

Background: Neosporosis is a parasitic disease caused by *Neospora caninum*. This parasite is an obligate intracellular coccidia similar to *Toxoplasma gondii* with a global distribution. With regard to the experimental studies, vertical transmission of the parasite in the monkey (non-human primates) has increased the concern about the zoonotic potential of this disease. The principal aim of the current research was to perform a mini-review on investigations regarding the *Neospora* infection in humans on a global scale for the first time.

Methods: All peer-reviewed articles (published until April 2021) on the *Neospora* infection in humans were searched in English databases such as Google Scholar, ScienceDirect, Scopus, PubMed, and ProQuest.

Results: Based on data in the available articles, the presence of antibodies against the *Neospora* infection was between 0 and 37.7% in people from different countries. The seroprevalence rate of this infection in HIV-positive individuals was higher (26.6% and 37.7%) compared to other cases. Finally, the genomic DNA of *Neospora* was detected up to 1% using molecular biology techniques.

Conclusions: Overall, the detection of anti-*Neospora* antibodies in humans indicated that people have been exposed to the parasite. Comprehensive research studies are essential for clarifying the risk factors associated with the *Neospora* infection in humans. This report provides the baseline information for future researchers. Molecular investigations and genotypic works on *N. caninum* isolates are highly recommended as well.

Keywords: Epidemiology, *Neospora caninum*, Human, Zoonosis

Background

Neosporosis caused by *Neospora caninum*, a *Toxoplasma*-like parasite belonging to obligate intracellular coccidian from the Toxoplasmatidae family, is a common parasitic disease in animals around the world (1). The *Neospora* infection was first distinguished in six Norwegian Boxer puppies in 1984. Neuromuscular problems such as encephalitis and myositis were the predominant clinical findings in all sick dogs (2). This parasite was misdiagnosed by *Toxoplasma gondii* before its introduction (3).

Meanwhile, a wide range of animals and birds are definitive and intermediate hosts for *N. caninum*. Domestic dogs and dairy cattle are commonly definitive and intermediate hosts in the life cycle of this parasite, respectively (3). Interestingly, dogs may simultaneously play a role in both final and intermediate hosts (4). The infection has been accounted for various species of warm-blooded vertebrates, some of which may serve as intermediate hosts in domestic and sylvatic cycles (3,4).

Neosporosis is a serious disease in animals. The significant role of the disease in abortion and other reproductive failures in cattle is clear (4,5). The annual economic losses related to the *Neospora* infection have been estimated at more than US$1.3 billion on a global scale (6). The detection of this infection is possible by different laboratory methods such as serology and molecular biology in animals and humans (1,4).

Currently, there is no report on clinical neosporosis in humans (7). Regarding the close phylogenetic relationship between *N. caninum* and *T. gondii*, as well as a wide range of intermediate hosts, the possibility of the *Neospora* infection in humans is undeniable (8), and the pathology, immunology, and epidemiology aspects of the infection in humans must be further studied accordingly (9). *N. caninum* is an important cause of fatal infections through experimentally transferring to pregnant cases with the lesions closely resembling those caused by congenital toxoplasmosis (10). A different level of antibodies to the *Neospora* infection have been detected in humans' sera (3,4). *N. caninum* was successfully cultured in various cell lines of humans. Furthermore, Rhesus monkeys (*Macaca mulatta*) were experimentally infected with *N. caninum* (11,12). Barr et al (11) demonstrated the vertical transmission of this parasite in monkeys, reinforcing the concern about the zoonotic potential of the disease. In this regard, the present study mainly aimed to first review the

global investigations on the *Neospora* infection in humans.

Methods

All published peer-reviewed articles (from January to April 2021) were searched in some English databases (e.g., Google Scholar, ScienceDirect, Scopus, PubMed, and ProQuest) using different keywords including "*Neospora*", "*Neospora caninum*", "neosporosis", "epidemiology", "prevalence", "anti-*Neospora* antibodies", and "human". All articles by reputable journals (ISI and/or Scopus) were included in this study.

Results

All data on the *Neospora* infection in humans are tabulated in Table 1 (8-10,12-21). Based on the results, 13 articles were found on the *Neospora* infection in humans. Antibodies to the *Neospora* infection were between 0 and 37.7%. It was relatively high in HIV-positive individuals (26.6% and 37.7%) versus other cases. There were two studies on this subject based on molecular biology techniques (0-1%).

Discussion

Zoonotic diseases are a developing concern because of their novel and erratic nature, as well as their fast circulation and ability to emerge anywhere. To design the Lunch Control Programs of zoonosis, it is essential to obtain knowledge on the risk factors and epidemiology of diseases in animals (22). Most clinical manifestations of neosporosis in animals are similar to those of toxoplasmosis (1). The tachyzoite form of the parasite may be disseminated in various tissues (i.e. blood, placenta, and amniotic fluid). Although no convincing evidence exists indicating that *N. caninum* effectively infects humans, there is still a concern and ambiguity for transmitting the infection (23). Serologic findings confirmed humans' exposure to this parasite, especially in immunodeficiency people (Table 1) although complementary works are essential to determine the extent and significance of humans' exposure (15). Neosporosis is yet an uncertain issue in medical infectious diseases (4,7). Regarding the high frequency of the *Neospora* infection in the transplacental transmission mode of cows (up to 90%), and the close similarity with the *T. gondii* infection, the possibility of *Neospora* posing a risk for pregnant women should receive special attention (24).

In an experimental work by Carvalho et al (25), the transplacental transmission and teratogenic lesions of the *N. caninum* infection were found in non-human primates parallel to histopathological lesions caused by *T. gondii*. Additionally, humans' cervical cells and trophoblasts were successfully infected by the tachyzoite form of *N. caninum in vitro*. The differences in susceptibility to the infection, cytokine production (type and rate), and cell viability were calculated in this evaluation (25). Some studies also focused on humans' neosporosis in the world. There is a limit of knowledge on epidemiology, pathology and the zoonotic aspect of Neospora-infection. The overall prevalence of the *Neospora* infection was estimated 17.14% (95% CI: 15.25-19.10%), 20% (95% CI: 18-21%), and 48.4% (95% CI: 47.5-49.3%) in dogs, cattle, and buffaloes, respectively, and 13.46% (95% CI: 10.26-17.42%) in horses and donkeys in different countries (26-29).

Nam et al (13) first reported the *Neospora* infection in humans from Korea. In this work, the seroprevalence rate was 4.6% (13/282) in blood donors. In Brazil, antibodies to the *Neospora* infection were detected between 26.6% and 37.7% in HIV-positive people, as well as 18%, 10.5%, and 5% in patients with neurological signs, farmworkers, and newborn children, respectively (10,16,17). Moreover, no antibodies to the *Neospora* infection were found in women with a history of abortion and genitally failures in serological studies by Petersen et al (8) and Trees and Williams (18). On the other hand, the genomic DNA of *Neospora* was not detected in cases (n = 600) with clinical manifestations in favor of toxoplasmosis and negative for the *T. gondii* infection in molecular evaluations. According to their opinions, there was an unlikely opportunistic zoonotic agent (21).

The seroprevalence rate of infection to *N. caninum* and *T. gondii* in pregnant women was 24.3% and 26.8% using the immunofluorescence antibody test (IFAT), respectively (9). Two samples of the cord blood from *Neospora*-seropositive humans were positive using the molecular biology assay. Direct sequencing showed 98-99% homology compared to the reported strains from other countries. Based on the findings, tissue cysts and/or inflammatory infiltrate lesions related to the *Neospora* infection were not observed in histopathology examinations. There was a statistically significant association between seropositivity to the *Neospora* infection and the presence of domestic animals ($P = 0.039$), as well as dogs ($P = 0.038$) in the studied regions. This research acquired significant findings in terms of the *Neospora* infection in humans based on both serology and molecular biology tests (9).

With regard to the close biologic similarity between *N. caninum* and *T. gondii*, along with the possible presence of the parasite in immunocompromised individuals, it has been speculated that the *Neospora* infection can be transmitted to humans (8,10). According to Graham et al (14), the presence of *N. caninum* in the cotyledonary villi of the bovine placenta can be a risk option and a possible source for humans' infection, especially in farmers and veterinarians. The infected dogs easily contaminate the environment life of humans by excreting the parasite oocytes through their feces (5). Due to the close contact of humans with dogs (pet dogs and sheepdogs are common in urban and rural regions, respectively), the chance of humans' exposure to the *Neospora* infection is extremely high (15). The assessment of tissue liquids in individuals with immune deficiencies and fetuses suspected with toxoplasmosis during pregnancy could confirm that a subpopulation of the patients were infected with *N. caninum* (15). A significant association was detected between the seroprevalence of *N. caninum* and *T. gondii* infections in HIV-positive people and those with

Table 1. The Prevalence of the *Neospora caninum* Infection in Humans From Different Countries

Country	Year	Source of Samples		No. of Cases	No. of Positive	Diagnostic Method	Reference
Korea	1998	Blood donors	*Toxoplasma*-positive sera	172	12 (6.7%)	IFAT-ELISA-IB	(13)
			Toxoplasma-negative sera	110	1 (0.9%)		
Ireland	1999	Blood donors	General population	199	11 (5.5%)	IFAT	(14)
			Farm workers	48	2 (4.2%)		
Denmark	1999	Repeated abortion		76	0	IFAT-ELISA-IB	(8)
United States	1999	Blood donors		1029	69 (6.7%)	IFAT	(15)
Brazil	2006	HIV-positive		61	23 (37.7%)	IFAT-ELISA-IB	(10)
		Neurological problem		50	9 (18%)		
		Newborn children		91	5 (5.5%)		
		General population (control group)		54	3 (5.6%)		
	2009	Healthy farmers		67	7 (10.5%)	IFAT	(16)
	2015	HIV-positive		342	91 (26.6%)	IFAT	(17)
	2020	Pregnant women (cord serum and whole blood)		201	IgG: 49 (24.3%) IgM: 0	IFAT	(9)
					2 (1%)	PCR	
United Kingdom	2000	Farm workers and women with abortion history		400	0	IFAT	(18)
	2008	Cases referred to medical laboratories	General population	3232	0	IFAT-ELISA	(12)
			Farm workers	518	0		
Egypt	2009	Pregnant women		101	8 (7.9%)	ELISA	(19)
France	2009	HIV-positive		400	4 (1%)	IFAT	(20)
		Healthy women		500	0		
Spain	2019	Patients with toxoplasmosis signs and negative-PCR for *Toxoplasma*		600	0	PCR	(21)

Note. No. Number; IFAT: Immunofluorescence antibody test; ELISA: Enzyme-linked immunosorbent assay; IB: Immunoblotting, PCR: Polymerase chain reaction.

neurological problems (10). In a report by Graham et al (14), the *Neospora*-seropositive sera samples were negative for the *T. gondii* infection, which was not responsible for cross-reactivity. No cross-reactivity was found between *N. caninum* and *T. gondii* infections in serology examinations with IFAT (4). However, using laboratory methods with high sensitivity and specificity is suggested for avoiding false-positive and false-negative reactions.

Different options such as the main purpose for designing the research, sampling and sample size, and laboratory diagnostic methods, as well as climatic and environmental factors of the studied location are crucial in the reported results in Table 1 (24). The sporulation (time and rate) and the survival of the oocysts in the environment with different temperature and air humidity rates are of various types (3).

A wide range of serological diagnostic methods with different sensitivity and specificity rates have been used in previous studies (8,10,12,13). An investigation is recently conducted based on the molecular biology technique (21). The sensitivity of enzyme-linked immunosorbent assay and specificity of IFAT are higher compared to other serologic methods (3,4). *Toxoplasma* and *Neospora* were classified in the same family (Toxoplasmatidae). Thus, the rate of infections and clinical manifestations should be high in immunosuppressed individuals. For this reason, the seroprevalence rate of the *Neospora* infection was high (26.6% and 37.7%) in HIV-positive humans in Brazil (10,17).

Conclusions

This literature review is the first one to focus on the *Neospora* infection in humans. It was found that the presence of antibodies to *N. caninum* is due to humans' exposure to the parasite. A comprehensive and systematic research study is essential for identifying the risk options related to the *Neospora* infection in humans. In addition, the figure of the *Neospora* infection and its complications must be properly identified during pregnancy. The findings may contribute to the implementation of diagnostic tests in routine prenatal screening, especially in people with impaired immune systems. The results of this research can be used as the baseline information for designing and expanding future studies. Therefore, further research using molecular biology tools should be conducted to detect the genomic DNA of *Neospora*, as well as the genotypic diversity of the isolates.

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Ethical Approval

Not applicable.

Conflict of Interests

The authors declare that they have no competing interests.

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