Cyclospora Cayetanensis

Subjects: Microbiology | Others | Others
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Cyclospora cayetanensis is a coccidian protozoan that causes cyclosporiasis, a severe gastroenteric disease, especially for immunocompromised patients, children, and the elderly. The parasite is considered as an emerging organism and a major contributor of gastroenteritis worldwide. Although the global prevalence of cyclosporiasis morbidity and mortality has not been assessed, global concern has arisen since diarrheal illness and gastroenteritis significantly affect both developing and industrialized countries. In the last two decades, an increasing number of foodborne outbreaks have been associated with the consumption of fresh produce that is difficult to clean thoroughly and is consumed without processing. Investigations of these outbreaks have revealed the necessity to increase the awareness in clinicians of this infection, since this protozoan is often ignored by surveillance systems, and to establish control measures to reduce contamination of fresh produce.

Keywords: Cyclospora cayetanensis ; Enteric ; coccidian ; cyclosporiasis ; gastroenteritis ; protozoan

1. Introduction

Diarrhea is one of the leading causes of mortality worldwide. In 2016, it was responsible for the death of more than 1.6 million people, with 90% of the deaths being reported in South Asia and sub-Saharan Africa [1]. It is also estimated that diarrhea is the second cause of death in children under five, killing nearly 525,000 every year [2]. Enteric protozoan parasites are among the leading causes of human diarrhea disease [3]. *C. cayetanensis* is one of these protozoan parasites that is considered as an emerging organism able to cause cyclosporiasis, a severe gastro-enteric disease especially for immunocompromised patients, children, and elderly.

Cyclospora is an apicomplexan, cyst-forming coccidian protozoan that belongs to subphylum Apicomplexa, subclass Coccidiasina, and family Eimeriidae [4]. Currently, nineteen *Cyclospora* species have been reported to be causative agents of disease in various animal species [5] and only one species, *C. cayetanensis*, is known to be associated with syndromes of acute and chronic diarrhea in humans. It is endemic in tropical and subtropical areas, but it has been identified as the causative agent of several outbreaks worldwide in the last two decades and it is also considered as a significant contributor to global gastroenteritis spread [6]. Most of the cyclosporiasis cases reported in non-endemic areas have been linked either with travelers returning from endemic areas or with imported foods from developing countries. It is however noteworthy that there is a significant number of reported cases in non-endemic areas, as the risk of exposure to uncommon diseases has been increased. This increase has mainly occurred because of the augmentation of international travel, the globalization of food supply and change in consumers' dietary habits [4]. *Cyclospora* is highly resistant to disinfectants used in the food industry [4], while globalization of food supply disseminates pathogenic organisms over wide geographical areas introducing important hazards. Besides, thanks to the increasing popularity of fresh fruits and vegetables—due to consumers' tendency to eat healthier—produce have become important vehicles in food-borne illness statistics [7].

2. Historic Taxonomy and Molecular Characteristics

The genus *Cyclospora* was first described in Old World moles (Talpinae) and subsequently in reptiles, birds, and myriapods [8][9]. The first documented human cases were diagnosed in 1977 and 1978 and reported by Ashford in 1979 [10], who isolated the organism from the stools of three patients in Papua New Guinea and correctly concluded that the organism was a coccidian parasite. However, because of its morphology and his uncertainty about the number of the sporozoites in the sporocysts, he wrongly presumed that the organism was a species of *Isospora* [10].

In 1986 Soave et al. [11] reported a new enteric pathogen that was the causative agent of a flu-like illness in four travelers to Haiti and Mexico, while in 1989 Naranjo et al. [12] described a '*Cryptosporidium muris*-like object' reporting that it was probably an unidentified flagellate. In following reports, the organism was described as a cyanobacterium-like body, coccidian-like body (CLB), blue-green algae, or large *Cryptosporidium* [13][14][15][16]. Eventually, in 1993 Ortega et al.

[17] classified this new organism in the genus *Cyclospora* and in 1994 they proposed the name *C. cayetanensis* for the new human parasite (derived from their university —Universidad Peruana Cayetano Heredia) [18]. Since then, many studies have been performed to identify the biological and epidemiological characteristics of this organism.

Phylogenetic analysis of the *C. cayetanensis* small subunit rRNA (SSU rRNA) gene sequences and mitochondrial genome have demonstrated that this organism is closely related to the *Eimeria* genus [19][20], while phylogenetic analysis based on the 18S rDNA sequences has indicated that this relation can even be compared to that existing within *Eimeria* species [21]. At the same time, cluster analysis of apicoplast (non-photosynthetic plastids) genomes originating from different Apicomplexan parasites have revealed a strong relation among *C. cayetanensis, Eimeria*, and *Toxoplasma,* and a common evolutionary history [22]

Lack of geographic segregation and existence of genetically homogeneous *C. cayetanensis* parasites has also been demonstrated [23][24]. In 2013, Sulaiman et al. reported a lack of genetic polymorphism at the regions of 70kDa heat shock protein (HSP70) locus, while a year later a study revealed minimal genetic diversity among 17 human *C. cayetanensis* isolates based on their 18S ribosomal RNA gene [24]. In 2016, Cinar et al. [22] performed comparative analysis of 11 *C. cayetanensis* apicoplast genomes originating from different geographical areas and reported high conservation with only a few polymorphisms. Nevertheless, it has not been indicated yet whether all human *Cyclospora* isolates belong to the same species, or that species that are disease agents in low primates cannot also infect humans [6].Studies have reported that *C. cayetanensis* was not detected in primates, suggesting that some primates are unlikely to be reservoirs for the human pathogen [21][25][26]. Moreover, the strong relationship that characterizes *Cyclospora* and *Eimeria* suggests that *Cyclospora* is probably a host-specific pathogen [27]. However, the pathogen genome's further characterization is necessary to improve knowledge of this organism regarding its taxonomic position, as well as to understand its transmission dynamics and pathogenic potential.

3. Control and Prevention

Cyclosporiasis is an infection that occurs after the consumption of contaminated foods or water, while person-to person transmission is unlikely. Therefore, avoiding food and water from contaminated sources is the optimum way to prevent *Cyclospora* infection, especially when water sanitation programs are less attentive (e.g., in developing countries). Good agricultural practices, such as rigorously sanitized irrigation water, can be conducive to decreased parasite contamination in the field and in the produce packing plants. Furthermore, good personal hygiene, appropriate food washing, and sanitary conditions can reduce the pathogen transmission, especially in endemic areas. However, it has been indicated that, even if these practices are strictly followed, the risk of exposure in this parasite may be reduced but not eliminated [4][28].

Hence, several studies have been performed to validate the efficiency of different hurdle methods in the reduction and inactivation of the parasite oocysts (viability indicator). According to Sathyanarayanan and Ortega [29], parasite's oocyst exposure in extremely low or high temperatures (−70 °C, 70 °C and 100 °C) resulted in sporulation inactivation in basil samples, whereas room and refrigeration temperatures, did not affect the sporulation in various food samples. Treatment with chemical disinfectants has also been examined, with significant reductions in sporulation and protozoan population being reported. Magnesium oxide (MgO) nanoparticles showed antimicrobial activity against *C. cayetanensis* sporulated and unsporulated oocysts [30], while the population levels of the parasite decreased when fruits and vegetables were dipped in sodium dichloro-isocyanurate (NaDCC) solution (1 g/L) [31]. Despite this, chemical disinfection cannot guarantee product safety, since its efficacy depends on various factors, such as the initial population level of the microbe, the food matrix, and the environmental conditions [32]. In addition, irradiation (gamma and ultraviolet) and high-pressure technologies have also been evaluated utilizing surrogate parasites (e.g., *Eimeria acervulina*), revealing effective anti-parasite activities [33][34]. Nevertheless, the data are limited, and further research is necessary for the development of reliable control methods for this pathogenic parasite.

4. Conclusions

C. cayetanensis was indicated as a foodborne pathogen in the mid-1990s. Since then, efforts have been made to identify the variability of the parasite and develop methods for its detection. However, the increase of foodborne outbreaks, especially related to produce consumption, continuously underlines the necessity for a better global understanding of the pathogen and the establishment of drastic control measures.

The low infectious dose and the long sporulation period complicate the performance of active surveillance. However, the outbreaks that occur highlight the necessity to overcome these difficulties and control the presence of the pathogen in water and fresh produce, especially in endemic countries. This will be achieved by cooperation between developed and developing countries. Developed countries ought to conduct further research on epidemiological aspects of this infection and coordinate with endemic countries to set up measures that will decrease the risk of producing and distributing unsafe food items.

At the same time, cyclosporiasis outbreaks that have occurred in developed countries have revealed the necessity to raise physicians' awareness of this infection. Clinicians should be well informed about the infection's typical symptoms and should request specific diagnostic tests for *Cyclospora* detection, especially in patients with prolonged diarrhea and travel history. Patients' travel history should be recorded to provide important information for doctors and investigators and to assist investigators in determining the source of contamination. Moreover, clinical laboratories should be aware of the existing testing methods, and new techniques such as genome sequencing should be developed to investigate and detect the source of outbreaks.

Finally, it is noteworthy that the control procedures that currently exist in the fresh produce chain mainly examine the presence and levels of pathogenic and spoilage bacteria, without addressing the impact of these procedures on parasites' survival. Hence, investigations on current methods and their effect on parasites, including *C. cayetanensis*, should be performed and addressed. In addition, novel methods that will ensure parasites' control should be determined and included in the existing procedures that concern fresh produce safety.

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