Emerging parasitic infections

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1. Introduction

It should come as no surprise that parasitic disease is on the rise. Many parasitic diseases currently appearing or reappearing in industrialized nations have a long history as public health problems in developing countries of the tropics, and several diseases previously thought to be under control in developing countries are increasing in incidence. The factors that influence emergence or re-emergence of protozoal and helminthic diseases are the same as those that affect other infectious diseases: a change in the parasite or the host that favors increased human infection or disease expression; any environmental or demographic change that favors increased human contact with the parasite; or increased recognition of a previously existing problem that had escaped detection or had been underestimated. In the case of parasitic infections, changes that affect the invertebrate vector can also be very important.

2. Cryptosporidia and cyclospora

Two parasitic infections that have recently come to widespread public attention in the United States are Cryptosporidium parvum and Cyclospora cayetanensis. These protozoans, causes of enteritis with persistent diarrhea, are usually acquired by ingestion of contaminated water or food. Parasites of the genus Cryptosporidium were first recognized as animal parasites around the turn of the century, and Cryptosporidium parvum has a surprisingly wide host range. It is estimated that over 90% of the dairy cattle herds in the United States are infected with this parasite, which may play a role in its transmission [1].

It was not until 1976 that the first human case was diagnosed, followed in 1981 by the first case in an AIDS patient. It is estimated that 10–15 percent of the chronic diarrhea and wasting observed in AIDS patients in the United States is due to infection with Cryptosporidium parvum; this estimate increases to 30–50 percent for AIDS patients in developing countries [1].

Since 1983, when the first outbreak in a child-care center was observed, there have been numerous widely distributed outbreaks in the United States, many of them associated with surface water. Recent water-sampling surveys indicate that over 50 percent of rivers and lakes in the United States may be contaminated with this parasite [1]. But cryptosporidiosis came to general public attention in the U.S. in 1993 as a result of the very large outbreak that occurred in Milwaukee, WI, that affected some 403,000

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people – approximately a quarter of the population of that city [2].

The ‘emergence’ of this parasite resulted from several influences, not the least of which has been enhanced recognition as a result of increased efforts to detect parasites in stool specimens. The AIDS epidemic was a major factor in improvement of the overall detection of cryptosporidiosis. Both infection levels and disease expression are markedly increased in those who are immunosuppressed. Thus, recognition of the association of this parasite with intense gastroenteritis in AIDS patients has contributed to a more widespread appreciation of its pathogenic potential in humans generally. Cryptosporidiosis also causes severe disease in both the very young and the elderly, whose immune defenses may be weakened by immaturity or advanced age. In fact, globally, in terms of actual numbers of people infected, cryptosporidiosis probably presents more of a problem in immunocompetent people than in AIDS patients. It has been documented to be an important cause of persistent diarrhea in children living in developing countries [3].

Various environmental and technological aspects have also contributed to the emergence of human cryptosporidiosis. Major surface water outbreaks in the U.S. have almost always been associated with heavy rain or snowfall, as appeared to be the case in the Milwaukee outbreak, where water draining from surrounding cattle farms due to melting of an unusually heavy snowfall caused contamination of the city’s major water supply [1]. It is important to note that ordinary water purification techniques do not completely remove or inactivate this parasite. Human transmission in the United States has also been enhanced by the increasing popularity of recreational water parks that accept young children.

Unfortunately, there is still no adequate treatment for cryptosporidiosis, and in immunocompetent individuals the infection is usually allowed to self-resolve with only supportive care. But in the case of the very severe diarrhea that occurs in immunosuppressed individuals the drug Paromomycin has been applied, with reports of increased intestinal function and decreased infection intensity at least in a portion of these patients [3]. Relapses of illness, however, remain common after treatment.

_Cyclospora cayatensis_, another protozoan parasite, was also identified around the turn of the century in animals, but it wasn’t until 1979 that it was first diagnosed in human cases in Papua, New Guinea. In that report it was described as a ‘previously undescribed coccidian’. In subsequent reports, the parasite was variously misidentified as a ‘blue-green algae’ or a ‘cyanobacterium-like organism’, or as _Cryptosporidium muris_, as was the case in the report of a limited outbreak that occurred in a Chicago hospital in 1990 which was traced to a contaminated water supply [4]. Not until 1993 was this parasite actually characterized and named in the course of ongoing studies in Peru [5]. Little attention was paid to subsequent sporadic reports of _Cyclospora cayatensis_ infection, but widespread public attention was aroused again in the summer of 1996 following reports of over 1500 cases from 14 states and Canada [6].

Globally, cyclospora infection probably affects approximately equivalent numbers of immunocompetent and immunosuppressed individuals. Fortunately, unlike the case with cryptosporidiosis, cyclospora infection is readily susceptible to treatment with trimethoprim-sulfamethoxazole [3].

Like cryptosporidiosis, our understanding of the emergence of cyclospora infection has been influenced by the AIDS epidemic and resultant improvements in diagnosis. Environmental influences contribute to the contamination of water and fresh produce with the parasite, but advances in technology allowing increased long distance shipment of produce are facilitating wider public exposure to contaminated food.

3. Microsporidia

The microsporidia, a huge phylum of organisms that includes over 700 species which infect every kind of insect and animal studied, are another important cause of parasitic infections that have been emerging in the context of the AIDS epidemic. Included among the four recognized as human pathogens are _Enterocytozoon bieneusi_ and _Septata intestinalis_, both of which are intestinal parasites that cause chronic diarrhea in AIDS patients. Two encephalitozoon species also are capable of producing
disseminated disease. The microsporidia appear to be a bigger problem in AIDS patients than in non-immunocompromised individuals, as there have been only occasional sporadic reports of infection in immunocompetent individuals. Again, therapy is inadequate. It appears that *Septata intestinalis* is susceptible to albendazole treatment, but there is no effective therapy for many of the other types of microsporidia [3].

4. Other emerging parasites

Cryptosporidia, cyclospora, and the microsporidia are not the only parasites that have been increasingly recognized in the context of the HIV-AIDS epidemic. *Isospora belli* is another protozoan parasite that causes diarrhea, and *Toxoplasma gondii* is a well-known protozoal parasite with a global distribution that is acquired by ingestion of either undercooked meat or food contaminated with feces from infected cats. Usually the latter infection is handled well in immunocompetent people, but in the presence of immunosuppression, latent infections can become reactivated, with severe neurological consequences.

Other recently recognized parasites have not yet come to such widespread public attention as those mentioned above. For example, *Acanthamoeba* species represent another newly emerging parasitic infection, which can cause conditions ranging from chronic ulceration of the cornea to progressive disseminated disease. These free-living amoeba are usually acquired through contact with contaminated water or soil. Balamuthia species, identified in 1986, are also capable of producing a chronic progressive neurological disease known as granulomatous amoebic encephalitis (GAE) [7]. In the United States by late 1995, there were 26 cases of GAE resulting from balamuthia infection, along with 60 or more cases of acanthamoeba-related GAE. In addition, over 500 cases of chronic ulcerative disease of the cornea [8] had been reported to CDC (D.G. Colley, personal communication).

Interesting new zoonotic infections are also gaining recognition. We have known for some time that tick-borne *Babesia microti* is a source of human infection in areas of the northeastern United States, but recent reports out of Wisconsin suggest that this species may be spreading. Moreover, observations from the western United States suggest that a previously unrecognized type of babesia can cause disease in splenectomized patients. This particular form appears to be more closely related to canine babesia than to *Babesia microti* [9].

While most emerging parasitic infections seem to be caused by protozoa, there are some cases where the human pathogenic potential of helmith parasites is only becoming fully appreciated. The raccoon round worm, *Baylisascaris procyonis*, has recently been recognized as a human pathogen due to several reports of serious, sometimes fatal, neurological disease following inadvertent ingestion of parasite eggs [10]. In addition, of course, there are periodic reports of outbreaks of acute illness due to anisakiasis or other intestinal helmith infections acquired by consumption of raw fish, which has gained increasing popularity in the U.S.

In addition to those parasitic infections that appear to be newly emerging, either in terms of actual incidence or recognition, there are several others which were previously thought to be controlled but are recently ‘re-emerging’ for various reasons. The tropical disease, leishmania, deserves more a detailed discussion in this context. Leishmania parasites are obligate intracellular protozoan parasites of macrophages. To a large extent the clinical manifestations – cutaneous, mucocutaneous or visceral disease – vary according to the species of infecting parasite. It is estimated that from three hundred million to three hundred fifty million people live in areas where they are at risk for this parasite. It is not thought to be endemic in the United States, although a cutaneous form, *Leishmania mexicana*, has been detected in rodent populations in south Texas and there have been reports of locally acquired human cases in that region [11].

Leishmaniasis represents a classic example of parasite re-emergence in response to virtually every type of influence imaginable. Like some of the above-mentioned parasitoses, leishmaniasis has been affected by AIDS-related immunosuppression. An interesting experimental observation suggests that leishmania, and toxoplasma as well, may interact with HIV in a way that promotes the progression of both parasitic and viral diseases [12,13]. These parasites cause the macrophage to produce increased
levels of the cytokine, tumor necrosis factor alpha, which then stimulates the binding capability of the nuclear regulatory factor, NF kappa B, resulting in increased expression of HIV. Further, one might postulate that increased viral progression would in turn decrease the function of CD4+T lymphocytes and impair cell-mediated immunity, the protective arm of the immune response in the case of both of these protozoal infections, thus exacerbating subsequent parasite burden.

An interesting, but preliminary, observation of altered leishmania infection in immunosuppressed individuals concerns a relatively obscure species of this parasite, *Leishmania infantum*, which is known to produce cutaneous disease in Mediterranean countries. There have been recent reports that normally dermatropic strains of this parasite tend to visceralize in immunosuppressed people. Moreover, new viceraling strains not normally found in immunocompetent individuals have been observed. Thus, it appears that the parasite may be significantly changing its behavior in immunosuppressed individuals [14].

Among the other factors influencing the re-emergence of leishmaniasis are ecological changes related to development projects. Water-management projects and changes in land use associated with the opening of the rain forest to commercial enterprises have led to an increased interaction between humans and the sand-fly vector of this disease. In addition, changes in migration having to do with the movement of populations from non-endemic areas into endemic areas, and from rural endemic areas into previously non-endemic urban areas, are also significantly increasing the potential for transmission of this parasite to humans. Breakdown in public health infrastructure, either as a result of civil wars in endemic countries or as a result of lapses in national vector control programs, also has been shown to result in increased incidence of leishmania infection. And finally, there is evidence that this parasite is developing resistance in many parts of the world to antimonial drugs, long the treatment of choice.

Although emphasis has been placed here on parasitic diseases that are currently either emerging or re-emerging, it is important to remember that other parasitic infections are likely candidates for re-emergence in the future. For the purpose of this discussion, three in particular come to mind. One of these is the tape-worm parasite, *Echinococcus multilocularis*, which causes a zoonotic disease normally maintained in foxes and other wild canines. In people it can cause extensive damage to the liver and other organs. Unlike the many parasitic infections which are thought of as tropical, this particular parasite appears to be restricted to the northern hemisphere. The reason this tape worm is thought to have the potential for re-emergence as a human infection has to do with the observation of its increased prevalence in foxes, both in the United States and in Europe, and the spread of these foxes to regions that were not previously known to be endemic for the parasite. For example, in the continental U.S. it is thought that this parasite was introduced into southern Canada sometime prior to the 1960s in a region around the border between Canada and North Dakota. It has since spread into the midwestern states as far down as central Illinois, and there have been recent reports of the translocation of infected foxes from these areas to the southeastern United States for hunting purposes [15]. A more rapid southerly spread of the disease in wild animals might therefore be expected in the near future.

The protozoan parasite, *Trypanosoma cruzi*, is the causative agent of Chagas disease or South American trypanosomiasis. It is prevalent throughout Latin America, where in its chronic form it causes cardiomyopathy and conditions known as megaesophagus and megacolon. In these endemic regions there has been an increased observation of the parasite in association with HIV infection and other immunosuppressive conditions. A very limited, unpublished, survey conducted a few years ago found seropositivity for this parasite of approximately one out of eighty-five hundred blood donors in the Los Angeles and Miami areas, providing evidence for the potential emergence of this parasite in areas where infection is not currently endemic.

The pork tape worm, *Taenia solium*, is also highly prevalent in Latin America and focally distributed in several other parts of the world where it has been shown to be a very significant factor in the occurrence of seizure disorders. Certainly this parasitic infection, like the others, has the potential to be spread as a result of increased travel and migration.
In order to show that this is a real threat, we have only to look at the fact that there have been several locally acquired cases documented in the United States in people who have never traveled to endemic areas [16].

5. Conclusion

In conclusion, it is clear from the data presented in this paper and in others included in this conference that protozoan and helminthic parasites, like other microbial pathogens, are emerging and re-emerging throughout the world. The association of certain parasitic infections with immunosuppression has led to improved diagnosis, and thus renewed our recognition of the potential health importance of parasitic diseases endemic within developed countries. Moreover, given the dramatic changes that are occurring in human demographics, travel, and technology, it is unwise for residents of industrialized countries to ignore the global public health threat posed by 'exotic' pathogens that are so common in developing countries.

Unfortunately, there is a lack of solid epidemiological data on which to base accurate assessment of the current and potential impact of any of these emerging parasites, either in the United States or in the world. There are many extremely important epidemiological, basic and applied research questions that remain to be answered, especially those regarding mechanisms of transmission and pathogenicity. These questions concern: the role of asymptomatic infection, potential reservoir hosts, and other environmental sources of contamination; the role of strain variability in epidemic situations; and the nature of immunity to infection. The global nature of these diseases emphasizes the need for increased international collaboration to derive answers to these questions and to develop improved methods for detection and intervention.

References