Immunology of giardiasis

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Giardia, first recognized by Von Leeuwenhoek 300 years ago in his own stool, remains an enigma as yet. Its pathogenesis in causing disease is complex and unclear, though manifestation in human beings as asymptomatic cyst passers to frank malabsorption is well known.

This brevity of knowledge about the disease process hails from, lack of identification of true numbers of distinct giardia species, pathogenetic mechanism of the disease and host immunological response. The definition of antigenic differences among parasite species awaits isolation of these antigen. The absence of this immunological technology leaves the immunology of giardiasis at the state of gross phenomenological description. However, present knowledge of immunological aspects of giardia infection, throws some light to the disease caused by this parasite. Three aspects of giardia infection will be considered, viz: (i) Host immunity; (ii) immunopathogenesis; and (iii) immuno-diagnosis.

Host immunity

Observations both in human being and experimental setting indicate that different components of immune system get involved in giardia infection. These observations will be discussed as clinical observations and experimental observations.

Clinical observations: The variability of infection among infected persons is unexplained. The dominant question remains: what are the relative contributing roles of the infecting organism and host factors in the observed spectrum of host disease?

The absence of the clinical symptoms of malabsorption coupled with prolonged excretion of the organism raises the question of whether the vigorous immune response, which is resulting in elimination of infection, may also contribute to the intestinal alterations which result in clinical illness. With the acute explosive and frequently self limited phase of giardiasis on one hand and the prolonged asymptomatic cyst posser on the other, this hypothesis becomes attractive. However, the prolonged indolent illness associated with weight loss and chronic malabsorption in a subject, who is unable to terminate the infection, requires a more complex hypothesis to explain the role of immunity in both pathogenesis and elimination of infection.

One group of patients who may help to shed some light on this dilemma are immunologically deficient subjects in whom giardiasis is a frequent pathogen. A group of subjects, often children, originally described as ‘hypogamma-globulinemic sprue’, have been observed to be both immunodeficient and to have intestinal malabsorption and most of them have marked atrophic changes on jejunal biopsies. It was also shown that 80% of the immuno-deficient persons with intestinal malabsorption had documented giardiasis.
These observations of extensive intestinal alterations in the absence of clearance of infection indicate that immunopathogenesis in giardiasis may not involve humoral immune components alone. On the other hand humoral immunity may be specifically required for elimination of infection. Experimental studies discussed in later part of this chapter supports the later conclusion. It should be pointed out that while giardiasis is frequently found in association with certain humoral immune deficiency states, deficiency in circulating or secretory immunoglobulin is not found in otherwise healthy subjects with giardiasis.5-6

Epidemiological observations suggest that reinfection of humans with giardia may occur repeatedly in the same host. Whether this is because of infection by new strains to which protective immunity has not developed, on successive occasions or the result of incomplete protection following infection by the same strain, is unclear. It is apparent, however, that infection is more common in short term visitors than long term residents of an endemic area which suggests that some protective immunity may develop after primary infection.

In the only controlled prospective studies of giardiasis in prison volunteers, by using same strains of giardia, it was demonstrated that protective immunity rendered by a primary giardia infection is incomplete and reinfection by the same strain of the parasite is possible in few cases. However clearance of infection occurred in all subjects fed with the parasite and none had any clinical illness.

Few tentative conclusions from above discussions are evident: (a) clearance of infection occurs in majority of infected subjects; (b) while chronic infection and pronounced clinical illness are the rule in people with giardiasis already handicapped by humoral immune deficiency states, a minority of apparently healthy subjects will develop chronic infection as well; (c) protection against reinfection with giardia probably develops in an undefined proportion of subjects. as indicated by comparisons of endemic-population with visitors in area of high prevalence and by prospective studies on a small group of subjects.

Experimental status: Observations in human beings pointed towards a self limiting giardia infestation in which immunity plays a major role. This prompted scientists to look into various aspects of giardia infestation in experimental settings as well. Mouse was chosen as the model because it is easily studied in large numbers, inexpensive, and considerable immunological technology has been developed in various inbred strains.

Giardia infection in the mouse was found to be self limiting and within 6 to 8 weeks, mouse fed with giardia-cyst started clearing the cyst in their stool. As noted in human beings, mouse were also detected to be resistant to subsequent oral inoculation of giardia cyst after primary infection. Because infection was self limited and prior infection was protective, the assumption was made that some form of immunity was active.

Both cell mediated immunity and secretary immunoglobulins have been implicated in the host immunity as seen in mouse experiments.

Cell mediated immunity (CMI) was implicated by using nudes, trains of mice (athymic mice), in whom giardia inoculation revealed, either persistence
of infection for long period without causing any illness or severe wasting disease with high rate of cyst excretion leading to death. Thus CMI appears to be active in the clearance and resistance to subsequent infection in the mouse.

Secretary immunoglobulins also plays some role in protective immunity against giardia infection. When two groups of suckling mice, one suckling from immune group of mice (made immune by primary challenge of giardia cyst) and other suckling from a non immune group (no giardia inoculation was done), were challenged with giardia inoculation, than, infection was noted in all suckling mice of non immune group whereas none of the mice suckling from immune mothers showed giardia infection. The experiments showed that protection was transferred in the milk and not across the placenta. The milk of the immune mice were shown to contain specific antigiardia antibody of IgG & IgA type by using immune fluorescence test, where as these antibodies were shown to be lacking in the milk of non immune mice. It has been emphasized that gut associated lymphoid tissue (GALT) provides the precursor cells which travels to mammary gland and proliferate to become cells which secrete immunoglobulin components of the milk. During lactation, hormones like prolactin progesterone, estrogen are thought to induce diversion of GALT to mammary tissues.

Studies of murine giardiasis using scanning and transmission electron microscopic techniques have provided morphological data which suggests possible mechanisms of antigen processing which may initiate an immune response. Earlier studies in humans employing light microscopy have suggested that giardia may be found beyond the intestinal lumen between epithelial cells. Indeed, controversy prevails over the issue of whether active invasion of the epithelium by trophozoits ever occurs. Recent observation in murine models, revealed that lymphocytes could be found on occasion juxtaposed to intraluminal giardia trophozoites, and in between the epithelium. But most potential functional significance has been the demonstration of giardia trophozoites in various stages of degradation in subepithelial macrophages. These later observations provide the clearest demonstration to date of a mechanism where by antigen processing by hosts immune system might occur.

**Immuno patho-genesis**

Whether an immuno pathogenic response also occur in clinically significant giardiasis is nuclear and evidence of such a response is sparse.

The histological appearance of the small intestinal epithelium of the giardia infected bowel is one of increased numbers of inflammatory cells which include macrophages and lymphocytes while such an appearance suggests an immunologically mediated cellular response, it also may simply be the picture of a nonspecific inflammatory respose elicited by the presence of intraluminal infection. However preliminary data of Roberts Thomson and Mitchell showed that reconstitution of thymus, spleen, and mesenteric lymphnode cells from an immune donor to giardia infected nude mouse, resulted in jejunal epithelial alteration which strongly suggests a major role for the immune
system in the pathogenesis of the malabsorption in this infection.

**Immuno diagnosis**

Investigators seeking to demonstrate circulating humoral immune response to *Giardia* in humans have established that measurable circulating antibodies develop after infection.\(^{28-35}\) The biological role for these antibodies remains conjectural. However, their role in serodiagnosis of the disease is promising.

Immuno fluorescent antibody test (IFA) is by now well established for serodiagnosis of symptomatic *Giardia*.\(^{23-24}\) IFA have been found to be positive in dilution of more than 1:10 in about 90 per cent of patients\(^{23}\) of symptomatic *Giardia*, whereas in controls the titer is less than 1:4\(^{24}\) and the test is negative in patients of malabsorption due to other causes. These antibodies are of IgG type and persist for about 2 months.\(^{23-24}\)

Recently enzyme linked immunosorbent assay (ELISA) have been described as a sensitive as well specific method to detect the IgG type of circulating anti-*Giardia* antibody in infected symptomatic persons.\(^{25}\) It was shown that 81 percent of symptomatic *Giardia* patient in comparison to 14 percent control had the antibody which persisted from 2 weeks to 15 months after therapy.

Thus circulating antibody against *Giardia* seems to be promising in the evolution of the serodiagnosis of the disease.

The detailed mechanisms of the host response in giardiasis are far from completely defined but one may speculate with reasonable confidence that the following events probably occur (Table). The occasional trophozoite breaches the small intestinal epithelium by unknown devices. It is eventually engulfed and digested by a macrophage\(^{21}\) and antigen thereby gains access to the immune system. While CMI appears necessary for the protective immune response\(^{13-14}\) a secretory humoral response probably also makes a contribution. GALT is probably the provider of precursor cells of the immunoglobulin secreting cells. Circulating antibody\(^{23-25}\) also develops but its biological role is unclear. A combination of immunologic events ultimately clear the infection and memory develops in the majority of affected human hosts. How secretory antibody or cellular components react with *Giardia* is completely unknown. A relatively frequent failure of resistance to subsequent infection in apparently immunologically intact hosts is unexplained. Numerous possibilities present for conjecture: it may represent a genetically determined absence of immune response; it may reflect of lack access to the immune-system by trophozoite antigen, confined to the
intestinal lumen; and indeed, it may represent antigenic variability among multiple giardia strains. An immunopathogenic mechanism may be responsible for small intestinal structural alteration resulting in malabsorption, however, evidences in favour of this mechanism is sparse.

In looking to the future, the most important stepping stones to better understanding of the immunology of this infection will be purification and characterisation of biologically relevant antigens of giardia, which will clear many puzzles of this enigmatic parasite.

References

20. Owen RL, Newmanic PC, Stevens DP: Ultrastructural observations in giardiasis in a murine model, I. Intestinal distribution, attachment and relationship to the
immune system of giardia muris. 
*Gastroenterology* 76: 757, 1979


