Solitary Cysticercosis in Eye: Literature Review and A Hypothesis on Transmission of Infection

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Abstract: Ophthalmic cysticercosis due to larval *Taenia solium* infestation in eye is one of the common preventable causes of acquired blindness particularly in the tropics. Though haematogenously disseminated oncospheres of this parasite can lodge in any tissue or body parts in human, there is a known predilection for brain, skeletal muscle and eye where they develop into metacestode larvae or cysticerci. However a number of cases have been reported having solitary cysticercosis only in eye without affecting brain and/or skeletal muscles. It is not clear to understand the exact route of entry into eye, the timing and environmental circumstances that produce ocular invasion without affecting other tissues. In this article, we have highlighted on the possibility of an alternate non-haematogenous route of transmission of infection particularly affecting eye or its adnexa in *T. solium* endemic tropical developing countries with poor sanitation practice, and deficient environmental monitoring system. Experimental infection studies might be helpful to prove the hypothesis on direct inoculation with *T. solium* eggs causing larval infestation in eye.

Keywords: Solitary cysticercosis, *Taenia solium*, eye, larval infection, intra-ocular, extra-ocular, ocular cysticercosis, orbital cysticercosis.

1. INTRODUCTION

An increase in research and awareness of various systemic parasitic infections has placed a greater emphasis on the ophthalmologist's knowledge of ocular manifestations of these diseases [1]. One of such disseminated parasitic diseases affecting eye is ophthalmic cysticercosis (OC), which is caused by the larval form of the pork tapeworm, *Taenia solium*. Cysticercosis occurs due to haematogenous spreading of oncospheres, which are released from the parasite eggs in the intestine. While each oncosphere can develop to a metacestode or cysticercus larva in any human tissue, it has a predilection for the central nervous system (CNS), skeletal muscle, subcutaneous tissue, and eye [2]. Brain and eye cysts cause the most morbidity, with the brain being the most common location for cysts (60 to 90 percent) and the eye being the least common (1 to 3 percent) [3]. Depending upon the location of the parasite in the eye or its adnexa disseminated cysticercosis affecting eye may be called as intra-ocular (IOC) or extra-ocular cysticercosis (EOC) respectively [4].

A wide variety of clinical manifestations are seen in OC that depend on the location, size, relation to adjacent structures and stage of evolution of the cyst [1, 5, 6]. The most common and severe manifestations of ocular infection by this parasite often leading to blindness and atrophy of the eye is noteworthy [7]. The clinical picture of a living intra-vitreous or sub-retinal cysticercus is practically pathognomonic. Viable metacestode larva of the parasite induces a mild to moderate inflammatory response, whereas dying or dead parasite induces a more severe inflammatory reaction [8]. Thus symptoms usually manifest in a later stage of the infection and eye may be destroyed by inflammatory changes due to toxins and/or degenerated products from the parasite, which is usually accentuated on its death [1, 7, 9]. Intra-vitreous or sub-retinal cysts usually lead to blindness within three to five years unless the parasite is surgically removed from the eye [1]. Also medical treatment for IOC is known to cause severe intraocular complications, which may lead to blindness. Hence it is of paramount importance to diagnose the location of the parasite in the eye or its adnexa as EOC can be medically managed [10]. There is a scarcity in serodiagnostics to aid its laboratory diagnosis; thereby management still continues to pose a serious challenge [11].

Prevalence of *T. solium* taeniasis and CNS involvement of cysticercosis are well studied in most of the endemic tropical developing countries. Co-infection of ocular tissue with CNS infection is significant and often ophthalmologists come across these lesions in their clinical practice [12]. However OC is being recognized only recently because now it has been identified as one of the major preventable causes of acquired blindness in such endemic regions [13-14]. Moreover, an increase in tourism and transmigration of populations from and to *T. solium* endemic countries of

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the tropics is currently demanding a greater awareness of OC even in the developed as well as previously known non-endemic countries. The 2003 World Health Assembly declared that *T. solium* taeniasis/ cysticercosis is of worldwide public-health importance, and that it is an eradicable parasitic disease [15-17]. Hence, it is time to pay attention on this neglected tropical disease (NTD) in the context of its global elimination for which the first step is reporting of cases.

There are solitary cases of cysticercosis reported only in eye without affecting brain, skeletal muscles, or elsewhere in the body. Table **1** summarizes representative studies reporting solitary cysticercosis cases in eye [18-28]. So far understanding of the exact route of entry into human eye, the timing and environmental circumstances that produce only ocular invasion are not clear. Hence it may be wise to consider alternate transmission pathways contributing to acquire *T. solium* larval infection other than the established accidental oral ingestion of eggs by consuming food and water contaminated with eggs [29].

2. CHANGING TREND IN LOCALIZATION AND EMERGENCE OF OC

New advances in the diagnosis and treatment, as well as studies of the pathogenesis and histological features of OC are continually being reported in last decade with a majority of studies being originated from India [13, 30-39]. Though less frequent, however, cases of OC are also documented from many other countries that include but not limited to Korea [40], Mexico [41], Thailand [42], Zimbabwe [43], Canada [44], Madagascar [5], Nigeria [45], and Indonesia [21].

IOC is predominant in the Western countries, whereas EOC is more common in the Indian population and several authors have attributed geographic and environmental factors responsible for this variation [46]. However none of these geographic or environmental factors are elaborated in literature. Recent molecular studies of *T. solium* worldwide have revealed that there are two Asian vs Afro/American geographic genotypes [47-50]. There is a hypothesis that Asian NCC cases are often found with subcutaneous cysticercosis, whereas Afro/American NCC cases are without subcutaneous cysticercosis. Therefore, there is a wave to fix the two genotypes and the pathological differences. However, there is no real direct evidence to support it [16]. Anyway, we may consider the host susceptibility and the parasite's organo-tropism as well as living environment, for example, with or without dry season.

In a recent review on 118 surgically excised cases, a changing trend in localization of OC has been reported from India [51]. This report reveals that the frequency of surgically excised cases of OC has remained constant over last two decades with an

Table 1: Representative of Studies Reporting Cases of Solitary Cysticercosis in Eye

Description of Case(s)	Country	No. of Cases	Reference
Extra ocular orbital cysticercosis involving the inferior rectus muscle	Karimnagar. India	1	[10]
Six cases of cysticercosis of single extra ocular muscles in which there was no evidence of CNS or subcutaneous involvement.	Bombay, India	6	[18]
Isolated orbital cysticercosis is rare	New Delhi, India	1	[19]
Intraocular cysticercosis affecting unilaterally diagnosed in 21 young patients. The cyst located in either the vitreous cavity or the sub-retinal space.	Arvind Eye Hospital, India	21	[20]
An ocular cysticercosis case of a nine-year-old Balinese girl who presented with redness and pain in the left eye and showed a cysticercus in the anterior chamber.	Bali, Indonesia	1	[21]
Cysticerci (live and degenerated) were found in the vitreous chamber of 5 out of 8 patients, whereas 3 out of 8 possessed sub-retinal infection with no CNS involvement.	Kunming, China	8	[22]
A case of intraocular cysticercosis in a 5-year-old child presenting with leucocoria, and simulating retinoblastoma.	Hyderabad, India	1	[23]
Isolated unilateral ptosis due to orbital cysticercosis is exceedingly rare	Aligarh, India	1	[24]
Orbital cysticercosis is well-documented but isolated involvement of extra-ocular muscles is uncommon	New Delhi, India	--	[25]
Solitary cases of cysticercosis in eye (n=5) without affecting brain or other body parts.	Pondicherry, India	5	[26]
Solitary intraocular cysticercosis with retinal detachment	Amritsar, India	1	[27]
Solitary cysticercosis in eye	Patiala, India	16	[28]

increasing manifestation of intra-vitreal cysticercosis in the recent years. This could imply either improved diagnostic modalities, available expertise in vitreoretinal surgery or ineffective medical treatment for intraocular parasitic infection. The relative decrease in EOC is probably due to the increased preference and success with medical management. However it is hard to extrapolate this observation to the wider scale or global scale occurrences of OC.

3. TRANSMISSION CONSIDERATIONS

The usual life cycle of *T. solium* involves human as the definitive host where the adult worm grows in the intestine and continues releasing gravid segments filled with eggs contaminating the environment; pig serves as the natural intermediate host, the ingested eggs release the oncosphere which in turn penetrate into the circulatory system and invade all tissues of the pig developing into metacestode larvae (cysticerci). The life cycle completes when human become infected by ingesting undercooked pork containing viable cysticerci, which mature in the human intestine into the adult worm causing taeniasis. However, cysticercosis in human occurs when a person accidentally becomes an intermediate host by consuming food and water contaminated by the eggs of the parasite or by endogenous auto infection due to reverse peristalsis in individuals carrying the adult worm in the intestine. The larval cysts can develop in any human tissue but common sites in the decreasing order of frequency are the CNS, subcutaneous tissue and striated muscle, eye and, rarely, other tissues [2, 52]. EOC in the orbit is very uncommon, despite the frequency of ocular and brain involvement [44].

In *T. solium* endemic tropical developing countries with poor sanitation practice and deficient environmental monitoring system, there may be the possibility of an alternate route of transmission of infection affecting the eye or its adnexa in contrast to the hematogenous dissemination of the oncosphere following its release in the intestine.

The dispersion patterns of the parasite eggs in the environment as well as the climatic condition might be playing a major role in transmission of *T. solium* larval infection in endemic countries of the tropics. The eggs of the parasite present in the environment can contaminate the food and water consumed by the community living in those affected areas. Heavy contamination in the soil can also spread to vicinity through wind flow as in case of other soil transmitted helminthes [53]. It has been speculated that in villages located in a dry, windy and dusty region, in addition to well-established transmission mechanisms, the villagers may be exposed, perhaps through contamination of uncovered drinking-water wells and inhalation, to wind-borne *Ascaris* eggs [53]. However there is no clue to find out whether infective stage of any parasite can cause infestation due to direct inoculation into the eye transmitted through dust.

Till date there is no evidence available from any laboratory animal study to support the hypothesis on possible direct inoculation with *T. solium* eggs into eye causing larval growth that is independent of the haematogenous dissemination of the parasite as in natural process of infection following ingestion and release of oncospheres in the intestine. However direct inoculation into eye has been found successful in survival and development of other parasites as studied in case of toxoplasmosis [54,55], and toxocarosis [56].

However, there is one report stressing the usefulness of ante-mortem diagnosis of cysticercosis in pigs by checking the eyelid in Papua [57]. Six heavily infected pigs were confirmed ante-mortem to have cysticercosis by checking in the eyelids for detection of cysts (4/6), or by muscle examination (1/6), and also by use of traditional “arrows” to biopsy muscles (1/6). So far, we prefer to examine the eyelids of pigs for ante-mortem detection of cysts in Papua. It is great contrast to human cysticercosis in Papua [58], since they did not describe any OC. All pigs infected with cysticerci were suspected by serology using glyco-proteins (GPs) purified iso-electro-focusing method [59]. The quality of diagnostic GPs by iso-electro-focusing appears to be better than by lentil-lectin affinity chromatography [60] reviewed by Ito [61]. Pigs in endemic areas could be easily detected serolo-gically using GPs prepared by iso-electrophoresis [49, 57-59] or cation exchange chromatography [62].

There is a concept that the bile salt is the essential prerequisite for activation of hatched oncospheres in the small intestine. However, non-activated but just hatched oncospheres of any Taeniid species can infect through subcutaneous injection of oncospheres [61, 63-70], function of the bile salt is exclusively essential in the intestine. Therefore, if oncospheres could escape from the embryophores in the eye side, they may grow into cysticerci. Furthermore, intraocular cysticerci showed minimal growth and some were eliminated. This model was never used in subsequent time. There is no experiment done so far to drop egg suspension into the eye of pigs. It is the most important and highly suggestive for our hypothesis. In an experimental

ocular toxocarosis study in BALB/c mice, the arrival of larvae to the eye was observed to be an independent event, unrelated to the kind of administered dose. High levels of specific antibodies were observed but they did not prevent the arrival of the larvae to the brain and the eye [56].

4. POSSIBLE EXPLANATIONS FOR SOLITARY CYSTICERCOSIS CASES IN EYE

There are many cases of solitary cysticercosis of eye only where no evidence of CNS and/or subcutaneous involvement has been noticed (Table **1**). The extra-ocular muscle (EOM) form is the most common type of orbital cysticercosis. However isolated involvement of EOM by cysticercus is uncommon [25]. But Ureskar *et al.* [18] have reported six cases of cysticercosis of single EOM in which there was no evidence of CNS or subcutaneous involvement. The inferior rectus and the medial rectus are the most common EOM involved [46]. Usually intraocular infection occurs when the larva enters the choroidal circulation [71]. In the ocular form, the most favored sites are the vitreous and the sub-retinal space. Within the ocular tissues the cysts may be located in descending order of frequency, sub-retinal (35%), vitreous (22%), conjunctiva (22%), anterior segment (5%) and orbit (1%) [46]. A solitary cysticercus may develop in the eye especially in the vitreous and in the sub-retinal space where it can cause blindness [72].

Also there was a case of solitary cystic nodular swelling inside the lower lip of a 40 years old man in India later histopathologically confirmed to be a case of solitary cysticercosis [73]. This case was one more addition to this series of rare manifestation of cysticercosis. In spite of the abundance of muscular tissue in the oral and maxillofacial region, this is not a frequent site of occurrence for cysticercosis. The patient in the above case had no occurrence of cysticercosis at any other site or any other symptoms. Hence it is important to consider the diagnosis of cysticercosis in oral solitary cystic nodular lesion presenting in patients living in an endemic area.

In the previous section it was clear that eye is the known least common site of cysticercus infestation following CNS, subcutaneous tissue, and striated muscle. Hence solitary cyst growing in eye or any other sites without affecting the more common sites appears to be a matter of discussion which enforces to think of any alternative route of entry of this pathogen with restricted localization of infestation. It may be hypothesized here that like other soil transmitted helminthes *T. solium* eggs can also spread through dust thereby contaminating uncovered water and food materials for everyday consumption. Also this infective stage of the parasite can cause OC through direct contact with eye. In such condition, the oncosphere embryo gets released from the egg upon local proteolytic digestion of the eggshell just like it happens in intestine. Therefore the parasite may not need a long migration disseminating through haematogenous route rather it causes infestation at a local convenient position. The lachrymal secretions might be aiding in destruction of the egg shell delivering the oncosphere embryos locally. This may be the possible explanation for occurrences of solitary cases of cysticercosis in eye only without affecting other tissue or body parts in the affected individual.

In the recent time zoonotic cause of human parasitic diseases are being recognized worldwide because they can cause a major threat to the socio-economic development, mainly in developing countries. A number of different helminthes that affect human eyes may cause blindness with severe socio-economic consequences to human communities. Basic parasitological research in this field is often fragmentary due to the fact that experimental human infections are rarely done, and the retrieval of helminthes from the patients' eyes may be an infrequent occurrence during the ophthalmologic examination [74].

Tear fluid and the corneal epithelium combine to make a formidable defense against bacterial infection that involves the expression of proteases, antimicrobials, and immunomodulators [75]. The basal lamina represents the final barrier to bacterial penetration [76]. But in *Pseudomonas aeruginosa* eye infection various factors can help overcoming above defenses (i.e., bacterial adaptation, expression of the type III secretion system, proteases, and biofilm formation). In addition there may be IgA-dependent and independent protective factors that provide protection as reported to inhibit *Acanthamoeba*-induced cytopathic effect [77]. So lachrymal secretions supposed to be protective to the host against pathogens invading into the eye. However, it is not clear how helminthes can survive this host protective barrier and eventually can establish the infection as seen in experimental toxocariasis and *T. crassiceps* cysticercosis too [7, 56, 78].

5. CONCLUSION AND RECOMMENDATIONS

Solitary cases cysticercosis in eye only without affecting brain and/or skeletal muscles is of a concern. A detailed epidemiological study in endemic tropical country might provide a clearer insight on the

associated socio-demographic factors responsible for occurrences of these solitary cases. Moreover experimental cysticercosis studies employing animal models might be helpful in order to prove the hypothesis of direct inoculation with *T. solium* eggs causing larval infestation in eye, which is independent of the haematogenous spread from intestine to the eye. There is a speculation that some of OC might be caused due to direct contact with dusts or hands contaminated with the parasite eggs. Then the question arises on how to proof this hypothesis? So, an experimental infection applying egg suspension drops onto the eyelid in a suitable animal model is warranted. Of course, as mentioned above, many OC cases are solitary. It suggests the hatching rate is very low. Another recommendation is to do *in vitro* hatching and activation experiment using artificial or natural components of tears.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Conceived and designed the hypothesis: PSS, AI. Contributed to the writing of the manuscript: PSS, AI. All authors read and approved the final version.

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LIST OF ABBREVIATIONS

CNS: Central nervous system

EOC: Extra-ocular cysticercosis

EOM: Extra-ocular muscle

GPs: Glycoproteins

IOC: Intra-ocular cysticercosis

NCC: Neurocysticercosis

NTD: Neglected tropical disease

OC: Ophthalmic cysticercosis

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