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THE IMMUNOLOGY OF TAENIASIS/CYSTICERCOSIS: IMPLICATIONS FOR PREVENTION AND TREATMENT

Carlton Evans [1] and the Cysticercosis Working Group in Peru [2]

INTRODUCTION

Cysticercosis is a parasitic disease that results from ingestion of *Taenia solium* tapeworm eggs. These microscopic eggs contaminate the environment in endemic areas and when pigs ingest them porcine cysticercosis develops. Porcine cysticercosis is the presence of pea sized *T. solium* larvae in pig tissues, making the pig the intermediate host for the parasite larvae. Pigs usually remain healthy despite this parasitosis, but their meat is greatly reduced in value. In the Andean region of Peru up to 50% of pigs have cysticercosis, contributing to economic hardship and malnutrition.[1]

When humans eat infected pork the *T. solium* larvae hatch out in the bowel where they may grow into adult tapeworms, growing up to 13 m in length. These tapeworms produce further eggs which are released into the environment in the faeces, completing the parasite life-cycle. Humans are therefore the natural definitive host to the adult tapeworm.

Infection of pig tissues with *T. solium* larvae and of the human bowel with adult tapeworms constitute the natural life-cycle which is essential for the continuing existence of the parasite in communities. This propagation depends upon evasion or modulation of host immunity: the larval and adult parasites must survive within their hosts without being destroyed by immune responses and without killing their hosts. The evolution of the parasite has selected parasites which most efficiently parasitize pigs and humans with minimal host disease.

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However, the principal significance of the *T. solium* parasite is its ability to infect humans as an 'accidental' intermediate host: when humans accidentally ingest microscopic *T. solium* eggs they develop cysticercosis. Cysticercosis is therefore caught from humans with tapeworms, not from pigs. The presence of *T. solium* larvae in human tissues is an important cause of neurological disability and mortality in many developing countries including 0.5 to 4% of people in Perú' and México.[3] This human cysticercosis is a 'dead end' for the parasite and there has therefore been no evolutionary pressure for the *T. solium* larvae to evade immune recognition in human tissues. The human host is not tolerant of the larval stage of the parasite and the resultant immune recognition and inflammation may contribute greatly to the pathogenesis of human cysticercosis.

IMMUNOLOGY OF ASYMPTOMATIC CYSTICERCOSIS

The pig is the usual intermediate host for the *T. solium* larvae and tolerates living cysticerci well. In some endemic regions examination of the pig's tongue for palpable living larvae has been routine practice before purchase since biblical times, because this reliably diagnoses cysticercosis.[1] The usual absence of apparent illness in infected pigs is remarkable considering that thousands of cysticerci are often found at autopsy, scattered throughout neurological and other tissues.

In humans, autopsies of victims of warfare and road traffic accidents have revealed that a large proportion (typically 80%) of neurocysticercosis infections are asymptomatic, discovered incidentally at necropsy.[4] Living cysticerci may occasionally cause disease through local pressure effects or by obstructing the flow of cerebro-spinal fluid, despite the absence of a host inflammatory response. Asymptomatic human cysticercosis may be diagnosed serologically or by biopsying subcutaneous lesions. Although circulating anticysticercus antibodies have access to the surface of cysticerci, as illustrated by imaging studies with radio-labelled antibodies,[5] hundreds of eight mm cysticerci may live within human tissues, evading immune destruction and symptomatic inflammation.

The immune response to cysticerci has been studied mainly because of the need for a diagnostic blood test. Although the literature is confused by numerous serologic tests evaluated with varying degrees of scientific rigor, it is clear that virtually all cases of symptomatic cysticercosis are associated with a detectable humoral immune response, the exception being a minority of

single-cyst infections. Furthermore, sero-epidemiological studies in endemic regions have revealed a similar rate of antibody positivity in healthy people to the prevalence of asymptomatic cysticercosis in autopsy series.[2]

How do *T. solium* larvae survive within pig and human tissues without causing symptomatic inflammation in the majority of cases, despite the presence of circulating antibodies and evidence of cell mediated immunity? Our understanding of the complex mechanisms employed by helminths to prevent immune-mediated destruction is increasing rapidly[6] and several of the mechanisms employed by cysticerci have been elucidated.[7]

MECHANISMS OF IMMUNE MODULATION BY CYSTICERCI

Sequestration. After a brief period of migration, *T. solium* larvae lodge in host tissues and form cysticerci. The site at which they settle and the nature of their relationship to the encapsulating host may contribute to sequestration of the parasites from immune attack. The unequal distribution of cysticerci throughout body tissues does not mirror regional blood flow but may result from selective invasion by the parasite or differential survival and encystment of larvae in different tissues.

In humans, cysticerci occur commonly within the brain, spinal cord and eye, all of which may be considered to be 'immunologically privileged sites'. The central nervous system differs from other tissues in: the presence of the blood brain barrier which prevents conventional lymphocyte recirculation; the inducible rather than constitutive expression of major histocompatibility class I and II molecules; and the presence of specialized cells that execute immunological effector functions. These features may explain the unique interaction between the central nervous and immune systems[8] and the resistance of the brain parenchyma to leukocyte diapedesis.[9] Recent evidence also suggests that inflammatory cell apoptosis is up-regulated in these sites.[10] However, we are not aware of systematic study of the number of cysticerci in human brain compared with non-neurological tissues and the apparent predilection for the brain may simply reflect the severe symptoms which result from lesions in this organ.

The firm, fibrous encapsulation which surrounds some cysticerci, particularly in non-neurological tissues, is unlikely to form a physical barrier to immunity since humoral factors do gain access to the internal fluids of cysticerci[11] and chemotherapeutic challenge or death of cysticerci is followed by immediate intense inflammatory cell infiltration.[12]

Antigenic shifts. In concomitant immunity, hosts are protected against newly invading larvae whilst tolerating an established worm infection. This may result from changes or 'shifts' in the antigens expressed by parasites as they develop through different stages of their life-cycle. Alternatively, or additionally, adult larvae may be able to counteract those immune effector mechanisms that kill immature forms. Concomitant immunity has been demonstrated for *T. saginata* and *T. hydatigena* where vaccine derived living cysticerci exist in animals which are resistant to egg challenge, but not in *T. solium* cysticercosis. It may explain the lack of overwhelming cysticercosis in hyperendemic regions since animals may only be able to acquire cysticercosis for one or two weeks after primary exposure to the parasite. Thereafter, the animal may be resistant to re-infection despite the survival of viable cysticerci resulting from the primary infection.[2]

Molecular mimicry by parasites is the evasion of immune recognition by the synthesis of host-like antigenic determinants. Willms *et al*[13] detected immunoglobulin G (IgG) on the surface of *T. solium* cysticerci by immuno-electronmicroscopy, but after purification this IgG showed no specificity for antigens on the cysticercus. The possibility that it was synthesised by the parasite was tested *in vitro* by translation of parasite-derived messenger-RNA. One of the protein products was precipitable with rabbit anti-pig IgG, providing evidence that the cysticercus itself synthesized host-mimicking antigens. The occurrence of homologous genome sequences in host and parasite may explain the selectivity of cestodes for particular hosts, for example *T. solium* for pigs and humans.

Masking of cysticereal antigens by host immunoglobulins. The presence of host antibodies has been studied in fresh cysticerci obtained from human surgery compared with the patient's serum and CSF. Although circulating human IgG was present with the same frequency as IgG on the surface of the parasite, IgM, IgA and IgE were present only on the surface of the parasite and could not be detected in the serum or CSF. Furthermore, *T. solium* cysticerci have recently been shown to express an Fc receptor for IgG. These results, reviewed by Flisser,[7] may suggest that cysticerci mask themselves with host immunoglobulins, although the importance of this possible mechanism of immune evasion has not been established.

Modulation of host immunity. Some evidence suggests that *T. solium* cysticerci may not only 'hide from' the host immune system, but may also actively suppress host immunity. A secretion product of living cysticerci, antigen B, has been shown to bind to and inhibit C1q, the first component of the complement cascade.[14] As yet unidentified secretory products of cysticerci also have a suppressive effect on cultured human lymphocytes stimulated with phytohemaglutinin.[15] Similarly, viable cysticerci implanted into the peritoneal cavity of mice release factors which depress rather than enhance lymphocyte reactivity.[15]

IMMUNOPATHOLOGY OF SYMPTOMATIC CYSTICERCOSIS

Although *T. solium* larvae commonly live within humans as accidental intermediate hosts for many years without causing symptoms or significant inflammation, the principal importance of the parasite is the failure of this immune tolerance which may cause symptomatic disease. Human cysticercosis occurs most importantly within the brain and is usually associated with inflammation around at least one degenerating cysticercus, as revealed by excision biopsies from patients with epilepsy and by autopsy examinations of neurological patients. Further evidence that it is the death rather than the presence of cysticerci which causes disease is provided by the effects of cestocidal therapy, discussed below, and the time-course of human infection.

A study of 450 British soldiers who acquired cysticercosis whilst stationed in India[16] provided an opportunity to study the time course of disease. Few soldiers returned from India with epilepsy, the majority developed seizures two to eight years after infection. The longest interval between infection with cysticercosis and appearance of symptoms was 30 years. This is remarkable because studies in pigs and humans have shown that cysticerci take only 60-70 days to reach maturity after infection.[17]

To explain this, MacArthur suggested in 1935 that a biologic objective of cysticerci while in the tissues of the intermediate host is to remain quiescent, with obvious evolutionary advantage, and that the death of the parasite may liberate toxins, causing irritation.[16] Alternatively, the death of cysticerci may end active immune evasion by the parasite allowing immunologically mediated inflammation to develop and cause symptoms. The fact that pigs are usually slaughtered in their first year of life may contribute to the absence of apparent porcine disease, pigs usually dying before any cysticerci degenerate and cause inflammation. Alternatively, *T. solium* larvae may be better able to evade immune recognition in pig than human tissues because of the evolutionary pressures discussed in the introduction.

THE IMMUNE RESPONSE TO TREATMENT OF CYSTICERCOSIS

A single low dose of the cestocidal drug praziquantel given to treat intestinal parasitosis may cause sufficient damage to latent asymptomatic cysticerci that inflammation and epilepsy results, providing evidence for active immune evasion or suppression by living cysticerci.[19] Rarely, full dose cestocidal therapy administered for the empiric therapy of human neurocysticercosis has also precipitated overwhelming, fatal cerebral inflammation[20] when the human brain has contained many cysticerci. We have observed a similar phenomenon of epilepsy and even death following cestocidal therapy for porcine cysticercosis.

Studies of the experimental treatment of 'asymptomatic' cysticercotic pigs showed that while parasites had little macroscopic or histopathological evidence of damage prior to treatment, praziquantel lead to accumulation of eosinophils around cysticerci followed by lymphocytes and macrophages which appeared to phagocytose cysticercal material and cell debris. The macroscopic (and radio-imaging) disappearance of killed cysticerci took two months.[7] We have observed similar results with albendazole[21] and other cestocidal drugs.

THE IMMUNE RESPONSE IN SYMPTOMATIC CYSTICERCOSIS

The cause of degeneration of untreated cysticerci in human tissues is not known but it has been proposed that death of the parasite may simply occur at the end of its natural life-expectancy. Cumulative damage from chronic host inflammation is an alternative possibility. The human tissue response to a degenerating cysticercus is granulomatous, consisting of plasma cells, lymphocytes, eosinophils and macrophages enclosed in a network of connective tissue. In later stages host cells penetrate into the remnants of the parasite. After one or two months a glial or connective tissue scar remains, which may then calcify.[4]

This relatively benign natural history is often reported from Southern India where, in some hospitals, patients with epilepsy resulting from degeneration of a solitary parenchymal cysticercus are treated symptomatically until inflammation and resultant symptoms resolve. In contrast, one or more degenerating cysticerci may cause chronic, progressive granulomatous inflammation which may prove fatal despite steroid and or surgical therapy, a clinical syndrome which appears to be more common in

South America. There have been reports of chronic neurocysticercosis dependant upon chronic steroid therapy to suppress inflammation, which at autopsy have revealed only the remnants of degenerated cysticerci surrounded by granulomatous inflammation. It is not clear whether variations in the parasite or the host response explain these variable clinical syndromes.

IMPLICATIONS FOR THERAPY OF CYSTICERCOSIS

If it is not simply the presence of living *T. solium* larvae but rather their death that causes inflammation and symptoms in the majority of cases of human neurocysticercosis, then what is the role of cestocidal treatment? Since the discovery of the drug praziquantel, and more recently albendazole, both effective at killing *T. solium* larvae, they have been widely used for treating human neurocysticercosis. Although they have been shown to cause radiological resolution of cerebral cysticerci, this is associated with some morbidity and rarely mortality. Since community epidemiological research has shown that the natural history of asymptomatic neurocysticercosis is most commonly benign and hospital based studies suggest that symptomatic inflammation often signifies the start of cysticercal degeneration and resolution, there is reason to question the value of cestocidal therapy for human neurocysticercosis.

The management of human neurocysticercosis is constdered in detail elsewhere in this volume, but our understanding of the immunopathogenesis of neurocysticercosis makes it unsurprising that recent randomized, placebo controlled trials have shown no clinical benefit from cestocidal therapy over steroid therapy alone[22,23] and have focused attention on the methodology of earlier studies.[24]

PREVENTION AND CONTROL OF CYSTICERCOSIS

Cysticercosis is a disease of poverty and social under-development. Human cysticercosis may be prevented by provision of sanitation and treatment of tapeworm carriers. The parasite life-cycle may be broken by enforcing meat inspection, freezing/adequately cooking pork or by large scale commercial pig rearing which denies pigs access to human faeces. Such improvements in public health and animal husbandry have led to the virtual eradication of human and porcine cysticercosis in wealthy countries but these measures are currently of limited relevance in less developed rural areas.[4]

PROTECTIVE VACCINATION TO PREVENT CYSTICERCOSIS

Human vaccination to prevent cysticercosis has not been widely considered as an appropriate intervention in endemic regions because little is known about the immunology of human cysticercosis and symptomatic cysticercosis is greatly under-diagnosed.[2] It has been suggested that cysticercosis occurs with greater than expected frequency in immunologically deficient children[1] but this uncontrolled observation may reflect a chance association or diagnostic bias rather than an effect of immunodeficiency on susceptibility. Cysticercosis has not been noted to be common in immunosuppressed or immunodeficient adults.[25]

In common with most other human cestodes, protective immunity against the adult tapeworm does not appear to occur and adult tapeworm carriage does not appear to protect against cysticercosis. However, there is evidence in experimental animal models that a definitive host can reject a tapeworm or cause it to destrobilate and that antibody may be present.[4]

Vaccination of pigs to prevent porcine cysticercosis has been proposed to improve animal health, meat yield and to break the parasite life-cycle, potentially preventing human disease. Molinari *et al*[26] showed that vaccination of healthy pigs with cysticercal antigen caused partial protection against the subsequent development of porcine cysticercosis. Likewise, immunization of pigs with excretory-secretory products of *T. solium* oncospheres caused a decrease in the number of cysticerci which developed from subsequent challenge infection.[27] Similar protective vaccination has been developed for other *Taenia* species.[28,29] Oral vaccination against *T. solium* has not been attempted. Prophylactic vaccination may not be practicable in areas where cysticercosis is common, where pigs are typically free-roaming and are reared by individual families on a subsistence basis.[4]

IMMUNOTHERAPY FOR PORCINE CYSTICERCOSIS

In contrast to preventative measures which are difficult to apply in endemic regions, an inexpensive treatment for porcine cysticercosis may be of practical value in the poorer areas where the disease is most common. Such a treatment may be sought after and used by owners of infected pigs if it improved animal health, meat yield and especially if it caused the degeneration of cysticerci that are easily visible in infected 'measly' pork, halving its value.[1] Such a treatment for porcine cysticercosis may, therefore, be a cost-effective

way of breaking the life cycle of the parasite, preventing human as well as animal disease. Our group are investigating treatments for porcine cysticercosis with drug therapy[4] and immunotherapy.[30] Immunotherapy may have the advantage of increasing protection against re-infection.

Cysticerci may be destroyed by immunological processes. Herbert and Oberg[31] infected nine pigs with cysticercosis at the age of two months and re-infected four of these pigs two months later. Paradoxically, autopsy revealed significantly fewer cysticerci in the pigs that had been infected twice, suggesting that re-infection accelerated cysticercus degeneration and absorption. Similarly, re-infection of cows infected with *T. saginata* and of sheep infected with *T. hydatigena* caused degeneration of established cysticerci.[32,33]

Most significantly, Molinari, Meza and Tato[34] reported that immunotherapy caused the resolution of porcine cysticercosis. Inoculation of naturally parasitized pigs with cysticercal antigen caused eosinophilia and autopsies at four and eight weeks revealed increasing macroscopic degeneration of cysticerci. There was an intense inflammatory reaction around cysticerci with eosinophilic infiltration and more than 90% were 'degenerating'. However, only 12 cysticerci were examined from each of two inoculated and one control pig and no assessment was made of the viability of cysticerci for causing human infection. This immunotherapy was also evaluated in a field trial.[30] Although the prevalence of cysticercosis fell significantly in two villages where 447 pigs were vaccinated repeatedly with 1,076 doses of immunotherapy, there was no control group and cysticercosis was diagnosed by tongue palpation only, limiting interpretation of these results. Seven cysticercotic pigs given immunotherapy were studied in more detail and 73% of cysts excised from them failed to evaginate versus 5% in seven untreated cysticercotic pigs.

These encouraging results led us to further investigate the effect of immunotherapy on porcine cysticercosis in a prospective, randomized, controlled and blinded study, described in full elsewhere in this volume. This study confirmed that when pigs naturally infected with *T. solium* cysticercosis were inoculated with cysticercal antigen the viability of cysticerci was significantly reduced. The percentage of cysticerci that showed no evidence of viability was more than doubled in the group of pigs given crude antigen and most of these animals developed new EITB bands suggesting an antibody response to the immunotherapy. However, all of the pigs remained

macroscopically heavily infected and most of the cysticerci in the majority of the treated animals appeared viable for causing human disease.

The statistically significant effect of immunotherapy on parasite viability illustrates the active nature of the host-parasite interaction and the potential for manipulating this relationship in the prevention and treatment of this infection.

CONCLUSIONS

T. solium has evolved to survive within pig tissues and the human bowel without causing morbidity sufficient to impair host reproduction but there has been no such evolutionary pressure to limit pathology when the larval stage of the parasite accidentally infects human tissues. Little is known about the immunology of adult tapeworm infections in the human bowel but some of the mechanisms by which tapeworm larvae survive within human tissues have been established. Manipulation of this host-parasite relationship may provide an opportunity for controlling the parasite.

Symptomatic human neurocysticercosis most commonly results from breakdown of host tolerance, often because the parasite dies. The resultant inflammation may be asymptomatic, transiently symptomatic, chronic or overwhelming. Neurocysticercosis may be managed with anticonvulsants and anti-inflammatory drugs with or without cestocidal therapy to kill the parasites. The additional of cestocidal therapy is unlikely to affect the course of the disease once cysticerci are degenerating or destroyed and research is in progress to clarify the value and safety of using cestocidal drugs to kill cysticerci in patients with asymptomatic cysticerci or those with epilepsy. This is likely to be influenced by the number and location of the cysticerci.

SUMMARY

Taenia solium cysticercosis is an important cause of human neurological disease in many developing countries. Porcine cysticercosis contributes to economic hardship and completes the parasite life-cycle. In humans and pigs cysticerci usually live within host tissues without causing inflammation or disease. The mechanisms of immune evasion by living cysticerci may include sequestration within immunologically privileged sites; antigenic shifts; molecular mimicry of host-like antigenic determinants; masking of cysticercal antigens by host immunoglobulins; and modulation of host immune responses.

The degeneration of one or more cysticerci is associated with granulomatous inflammation which in humans may result in transient or progressive symptoms. Although treatment of human neurocysticercosis with cestocidal drugs has been widely adopted and accelerates radiological improvement, treatment can precipitate harmful inflammatory reactions and randomized, placebo controlled trials have not shown clinical benefit of cestocidal treatment over the administration of anti-inflammatory drugs alone.

Cysticercosis is a disease of poverty. Public health and animal husbandry measures have virtually eradicated the disease from developed countries but are difficult to apply in endemic regions where pigs are usually reared on a subsistence basis. Prophylactic vaccination against porcine cysticercosis causes partial protection and immunotherapy with cysticercal antigens may cause degeneration of cysticerci, but this immunological reaction has not been shown to be great enough to be of value in preventing human disease.

RESUMEN

La cisticercosis por *Taenia solium* es causa importante de patología neurológica en países en desarrollo. La cisticercosis porcina causa pérdidas económicas y completa el ciclo vital del parásito. En humanos y cerdos, el cisticerco usualmente reside en los tejidos del hospedero sin causar inflamación o enfermedad. Los mecanismos de evasión inmune utilizados por los cisticercos vivos incluyen: secuestración en sitios inmunológicamente privilegiados, variaciones antigénicas, mimetismo por simulación de los determinantes antigénicos del hospedero, enmascaramiento de sus antigenos con inmunoglobulinas del hospedero, y modulación de las respuestas inmunes del hospedero. La muerte y degeneración de uno o más cisticercos se asocia a inflamación granulomatosa que en el humano puede resultar en sintomatología progresiva o pasajera. Aunque el tratamiento de la cisticercosis humana con drogas cisticidas ha sido ampliamente adoptado y acelera la mejoría radiológica, este tratamiento puede precipitar reacciones inmunológicas peligrosas, y estudios randomizados, controlados con placebo no han mostrado beneficio clínico del tratamiento cisticida sobre la administración de solamente drogas antiinflamatorias.

La cisticercosis es una enfermedad de la pobreza. Medidas de saneamiento y control de la crianza de animales la han virtualmente erradicado de los países desarrollados, pero son difíciles de aplicar en regiones endémicas donde la crianza doméstica del cerdo es usual. La vacunación profiláctica

contra la cisticercosis porcina ocasiona protección parcial, y la inmunoterapia con antígenos de cisticerco puede causar degeneración de cisticercos establecidos, pero esta reacción inmunológica no ha mostrado ser de grado suficiente para su uso en la prevención de enfermedad humana.

ACKNOWLEDGEMENTS

Dr. Carlton Evans gratefully acknowledges financial support from Trinity College, TEMCO, Rhone-Poulenc PLC, and the British Medical Research Council

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APPROACHES TOWARDS A VACCINE FOR HUMAN, PORCINE AND BOVINE CYSTICERCOSIS

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INTRODUCTION

The two economically and medically important taeniid parasites of man, *Taenia saginata* and *Taenia solium*, typically pass their metacestode developmental stages in the bovine and porcine, respectively. The *T. solium* metacestode may also develop in man and is therefore also responsible for human cysticercosis, with neurocysticercosis being a frequent, and sometimes fatal, complication. In spite of this major biological difference, the two species are highly antigenically cross reacting, so that diagnostic and therapeutic tools developed for one species are applicable to the other.[1,2] *T. saginata* and *T. solium* are responsible for public health problems, in addition to creating financial losses to pig and cattle producers in endemic areas. While control of the parasite can be achieved to some extent through improvements in public health, sanitation and animal management or husbandry practices, the development of a vaccine would greatly assist control. It is possible to work on both species since they are so closely related that they contain many cross-reactive determinants and can be regarded as reciprocal models. In view of the hazards in working with *T. solium* oncospheres, our strategy is therefore to develop reagents and clone genes directly relevant to *T. saginata* and then confirm the expected applicability to *T. solium*.

The most rational molecular targets for a protective vaccine against *T. saginata* are components of the surface, and functional proteins essential for

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[*] *The nucleotide sequence reported in this article was deposited in the GenBank™ EMBL databank, under accession number [illegible].*

Teniasis/Cisticercosis por T. solium

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Editorial Universo S.A.
Lima, Perú
1996