

# Immunopathogenesis of Neurocysticercosis: Role of Cytokines

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## Abstract

Neurocysticercosis (NCC) is caused by the larva of *Taenia solium*, when it is lodged in the central nervous system (CNS). NCC is identified as the major cause of community acquired epilepsy, especially in the developing countries. It is also increasingly being reported in the developed world due to human migration from the disease endemic countries. However, some individuals with similar NCC lesions may remain asymptomatic and the reason for this asymptomatic status largely remains unknown. However, studies from our center suggest that cytokines play important role in disease pathogenesis. In the present review, we have discussed the role of different cytokines in the pathogenesis of NCC in human.

**Keywords:** Neurocysticercosis; Immune response; Immuno-endocrine response; Cytokines

## Introduction

Neurocysticercosis (NCC) is most common helminthic parasitic infection of the central nervous system (CNS), caused by *Taenia solium* larvae/metacestodes (cysticerci). It is a major public health problem and the single most common cause of epilepsy in the developing countries [1,2]. *T. solium* cysticerci may infect different internal organs (cysticercosis) including brain (NCC) both in human and swine (intermediate hosts) through ingestion of eggs excreted in faeces by human *T. solium* carrier. Humans also act as the definitive host by eating undercooked meat from cysticercotic pigs. Cysticercosis can be found in communities where pigs roam freely, the people eat undercooked pork and the basic sanitary facilities are lacking [3].

This review deals with the pathogenesis of NCC associated with the inflammatory process. We focus on role of pro-inflammatory and anti-inflammatory cytokines in individuals with NCC having symptomatic and asymptomatic disease.

## The Clinical Features of Human NCC

In human, the clinical features of NCC vary with number, stage and the distribution of *T. solium* cysticerci (cysts) in different organs. When cysticerci lodge in the brain, they cause the most severe form of infection in human like active epilepsy (seizure disorder). Brain parenchyma is the commonest site of CNS for cysts infection followed by meninges, ventricles, eye and spinal cord [4]. The outcomes of NCC are heterogeneous; it may be symptomatic or asymptomatic for indefinite period. When metacestodes infect the brain without any apparent symptoms, this form is called as asymptomatic NCC and it depends on number and stage of cysticerci [5]. Viable cysts may cause an asymptomatic infection through active evasion and suppression of immune response in the host [6]. The clinical manifestations include seizures, headache, chronic meningitis, hydrocephalus, focal neurological deficits, psychological disorders and cognitive disorders [7,8]. A systemic review showed, epilepsy as the most common

manifestation (78.8%) followed by headaches, focal deficits and signs of increased intracranial pressure [9].

## Immune Response in NCC

When pathogen infects the host, an innate immune response is initiated. This immune response may be two ways process i.e. benefits and costs to the host. The immune response may kill the invading oncospheres and cysticerci, and thus protect the host. But it can also promote an injury to surrounding tissues and cause inflammatory reactions in the brain with significant clinical consequences [8]. Viable cysticerci may cause an asymptomatic NCC through active evasion and suppression of immunity. Histological studies have demonstrated that viable cysticerci have little or no surrounding inflammation in humans and pigs [7,10]. In contrast, degenerating or dead cysticerci are often associated with inflammatory response. When the parasite begins to degenerate, either naturally or due to anti-helminthic treatment, a granulomatous inflammatory response develops around cysts in human and swine. Granuloma includes macrophages, lymphocytes, eosinophils and plasma cells. These infiltrating immune cells produce cytokines and other immune mediators that are involved in the development of symptoms in NCC patients [10,11].

When a pathogen enters into an organ, a non-specific innate and a specific adaptive immune response is initiated to destroy the pathogen. Innate immune response produces non-specific inflammatory response locally in the surroundings of the pathogen whereas adaptive immune response initiates the proliferation and differentiation of T-helper cells into Th1 and Th2 cells that subsequently produce different cytokines or help in the production of specific antibodies through plasma cells.

## CNS immune response and cytokines

Dying cysticerci initiate a pro-inflammatory response that leads to the disruption of blood-brain barrier (BBB), followed by infiltration of immune cells at the site of infection. Immuno-histochemical studies of granuloma surrounding dying cyst have shown the infiltration of macrophages, B and T lymphocytes, plasma cells, and mast cells. These cells produce different immune mediators including cytokines. The

brain tissue surrounding dying cyst having granuloma, produce higher level of Th1 cytokines (IFN- $\gamma$ , IL-18 and TGF- $\beta$ ) and low amount Th2 cytokines (IL-44, IL-13 and IL-10) in human NCC [11]. Another histological and immune-histochemical study on human brain specimen with NCC has shown the presence of inflammatory cytokines (IFN- $\gamma$  and IL-18) and immunomodulatory cytokines (TGF- $\beta$  and IL10) in granulomatous lesions [12]. Similarly, a study on swine NCC has shown the expression of regulatory cytokine (IL-10), Th1 cytokines (IFN-  $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , IL-2, IL-6 and IL-8) and a mixed Th1/Th2 cytokines (IL-4, IL-10, TNF- $\alpha$  and IL-6) in the brain tissue surrounding the viable, degenerating and calcified cysts, respectively [13]. The data available for local immune response from human and swine demonstrate that a mixed cytokine response (Th1/Th2) with multiple immune cells exists at the chronic stage of NCC. However, an anti-inflammatory immune response is associated with acute NCC. The cytokine response displayed by brain tissues to chronic NCC lesions appears to contribute to the local tissue damage, and hence, may be responsible for the pathology of NCC.

The immune response is also characterized in CSF to understand the pathogenesis of NCC. When cysticerci infect the brain parenchyma, the inflammatory response is limited to the area surrounding the cysticerci and CSF usually remains normal, and the infection may remain benign or lead to seizure disorder. But when cysticerci are lodged in the ventricles or in the basal subarachnoid space, they promote an increased CSF cellularity and worsened inflammatory process, which may result in hydrocephalus or vasculitis [14]. Severe NCC is accompanied with increased eosinophilic infiltration in CSF and production of mixed Th1/Th2 cytokines (IL-5, IL-6 and IL-10). Disease severity increases with the number of cysticerci as patients having multiple cysts show higher expression of IL-5 and IL-6 than patients having single cyst [15-17]. Increased expressions of IgG, IgM, IgE, IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were observed in the patients having cysts in the subarachnoid spaces. A higher expression of IL10 in CSF was also observed; perhaps it participates in regulation of the inflammatory response in NCC [18,19].

Both human and swine show the variable expression of different cytokines in brain tissues as well as in CSF. These alterations also exist with different stage, number and location of the cysts. The expression of both anti- and pro- inflammatory cytokines at the chronic NCC at necropsy and in CSF may be responsible for the heterogeneity in disease outcome [15,17].

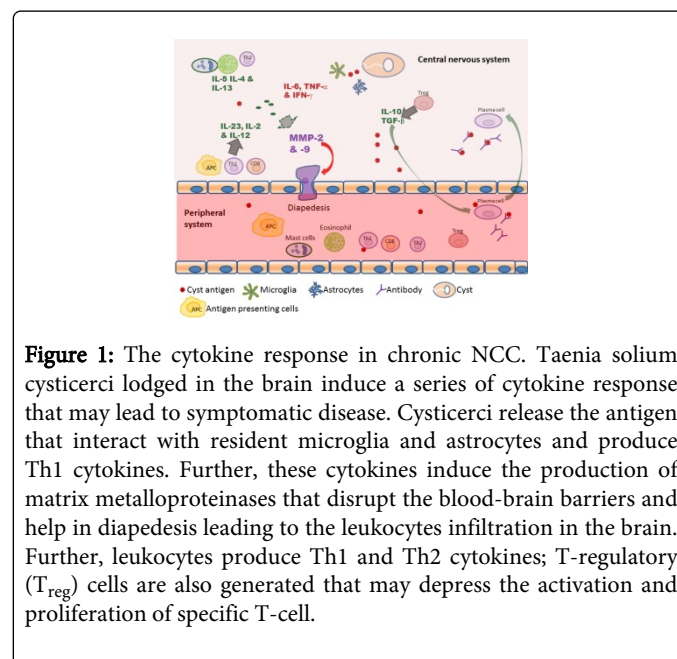
### Peripheral immune response and cytokines

When cysticerci are lodged in CNS, a local immune response is induced by the host to secreted antigens [20]. These antigens may also reach to the peripheral blood from brain due to damage of BBB and as a result, a systemic immune response is initiated. It may modulate the local immune response in the brain. Thus, both local and systemic immune responses to the parasite may be responsible for variable disease outcome. However, studies associated with systemic immune response with different clinical outcomes in NCC are lacking. Different studies have shown the variability in their results that may indicate towards the heterogeneity of disease presentations. PBMCs stimulated with *T. solium* antigen showed Th2 (IL-4, IL-5 and IL-13) and Th1 (IL-12) response and low plasma levels of all specific IgG subclasses in asymptomatic patients, whereas symptomatic patients showed a depressed specific cellular immune response and increased levels of all specific IgG subclasses [21]. Another study had shown Th1 (IL-12, TNF- $\alpha$ , ICAM-1 and VCAM-1) response with depressed cell

proliferation (PBMCs) in symptomatic NCC while asymptomatic patients showed a mixed Th1/Th2 (IL-6, IL-10, IL-12 and TNF- $\alpha$ ) response [22]. There are some studies which showed the contradictory results i.e. PBMCs from NCC cases showed increased cell proliferation with higher levels of IFN  $\gamma$  and IL2 [23]. Similarly, cyst fluid antigens from *T. solium* metacestode induced significantly greater PBMCs proliferation in NCC patients than control. When PBMCs were stimulated with different fractions of cyst fluid antigens (F1, <10 kDa; F2, 10.0-15.1 kDa, F3, 15.1-16.7 kDa and F4, 16.7-25.8 kDa), all of them induced Th1 (IL-1b, TNF-a, IL-2) response except fraction F2 that induced Th2 (IL-4 and IL-10) cytokines [24].

Additionally, Verma et al found, the elevated levels of IL-10 and IL-4 in asymptomatic NCC cases, whereas the levels of IFN- $\gamma$ , TNF- $\alpha$ , IL-17, IL-23 and sICAM-1 were significantly higher in symptomatic NCC patients compared to asymptomatic NCC individuals. The authors also reported a higher TLR4 fluorescence intensity in PBMCs isolated from symptomatic patients that correlated with production of pro-inflammatory cytokines [25].

Different studies have variable outcomes regarding the immune response associated with symptomatic NCC. It indicates towards the differences in inclusion criteria of NCC cases, genetic factors associated with different ethnic population, geographical locations such as whether NCC cases belong to endemic or non- endemic area. Studies have shown that male and female NCC subjects have variable immune response. The cytokine response associated with chronic NCC is summarized in Figure 1.



**Figure 1:** The cytokine response in chronic NCC. *Taenia solium* cysticerci lodged in the brain induce a series of cytokine response that may lead to symptomatic disease. Cysticerci release the antigen that interact with resident microglia and astrocytes and produce Th1 cytokines. Further, these cytokines induce the production of matrix metalloproteinases that disrupt the blood-brain barriers and help in diapedesis leading to the leukocytes infiltration in the brain. Further, leukocytes produce Th1 and Th2 cytokines; T-regulatory ( $T_{reg}$ ) cells are also generated that may depress the activation and proliferation of specific T-cell.

Recent studies have shown that TLR-4 and ICAM-1 gene polymorphisms are found to be associated with symptomatic NCC [26,27]. Additionally, MMP-9 polymorphism was associated with symptoms in NCC patients having calcified cysts [28].

Human subjects from endemic and non-endemic areas may have variable immune response. A study from Mexico had shown that asymptomatic NCC was associated with a Th2 response (IgG4, IL-4, IL-5, and IL-13). Non-NCC subjects from endemic area had higher levels of specific antibodies (IgG1, IgG2, IgG4, IgE) and specific cell

proliferation than subjects from non-endemic area [29]. This suggests that non-NCC subjects from endemic area are exposed to *T. solium* that may interfere with the parasite establishment.

### Immuno-endocrine response and cytokines

Recent evidence suggests that helminthes not only evade the immune response, but also use the hormonal micro-environment of the host for their establishment, growth and reproduction [30]. Several studies on murine model had shown the role of hormones in regulation of immune response [31,32]. The first study by Chavarría A et al. on human NCC showed gender specific immunological differences. They showed higher expressions of IL-6 and IL-5 in women [15]. Another study on NCC patients showed decrease of estradiol and increase of luteinizing hormone (LH) in males, and reduction of adrenal hormone dehydro-epiandrosterone (DHEA) in both male and female. In clinically severe female patients, low levels of progesterone and androstenedione were found, while in clinically severe male patients, high level of follicle stimulating hormone (FSH) and low level of testosterone were found. Authors also found a significant correlation between estradiol and IL-10 in male patients whereas female patients showed correlation between DHEA and IL-1 $\beta$ , and androstenedione and IL-17 [33].

Results in this review show that when cysticerci infect the human brain, a race between development of protective immune response by the host and immune evasion mechanisms by the cysticerci develop during the initial phase of infection [6]. Then, an equilibrated host and parasite relationship develops that last for longer time. In this phase, a regulatory response (IL-10) and Th2 response is elicited around viable stage of cysts [13]. Death of the parasite ends this balance resulting a granulomatous inflammatory response. Studies have shown that, early granulomas are predominantly associated with Th1 response, whereas later granulomas have a mixture of Th1 and Th2 response [11]. It has been also reported in murine NCC that initially a Th1 type (characterized by high level of IL2, IFN- $\gamma$  and IgG2a) immune response predominates against parasite, which shifts to a late permissive Th2 type response (characterized by high levels of IL4, IL6, IL10, IgG2b, and IgG1) [34]. Thus, Th1 response appears to play an important role both in the pathogenesis of disease as well as in the clearing of the parasites, with Th2 involved in the down regulation of the initial Th1 response.

### Conclusion

NCC is a “complex disease” with variable clinical outcomes. These heterogeneous responses may depend on several factors viz. number, stage and location of cysts in the CNS, and host’s genetic and hormonal response. Host immune response, especially cytokine response, may play important role in disease pathogenesis. Different studies have shown the variable cytokine response such as Th1, Th2 or mixed response in NCC. These cytokine responses may destroy the parasite lodged in the brain or may cause tissue injury that leads to seizure disorder. Since the cytokine responses are variable in symptomatic and asymptomatic NCC individuals, the exact role of cytokines in disease pathogenesis and as therapeutic tools needs to be further investigated.

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