Brief Report
Correlation Between the Clinico Radiological Heterogeneity and the Immune-Inflammatory Profiles in Pediatric Patients with Neurocysticercosis from a Tertiary Referral Centre

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Summary

Introduction: Neurocysticercosis (NCC) is the leading cause of epilepsy in developing world. Cysticercal lesions develop in brain depending upon a combination of host immune-inflammatory response, mainly mediated by cytokines produced by cysticercal antigens.

Aim and objectives: To correlate between MRI findings and levels of Th1/Th2 cytokines present in sera of children clinically suspected of NCC with generalized or partial seizure.

Material and methods: Fifty children presenting with history of seizures and/or mass effects and/or hydrocephalous, with a diagnosis of NCC based on the clinical and radiological profile were included. Antibody (IgM) for NCC and Th1/Th2 cytokine response (TNF-α/C11, IL-2/and IL-6) detection was done on sera from all the patients following manufacturer’s instructions.

Results: Out of 50 cases, 10 presented with acute symptoms of NCC with an immunological response of a predominance of pro-inflammatory cytokines (IL-2: 8, TNF-α/C11: 2). High IL-6 was found in 40 children indicating an active lesion with chronic granulomas suggestive of parasitic destruction and persisting presentation with seizures. However, the levels of IL-6 differed with values lower in patients with inactive (calcified lesions) forms of NCC. A significant proportion (43 of 50 cases) had negative serology, probably because of the waning of antibody response months or years after the parasites die.

Conclusion: Parasite maintains equilibrium with host immune response in early infection, a mild Th1 response is provoked; but later this equilibrium is disturbed toward Th2 response that leads to parasite destruction. Number or stage of the parasites along with immunogenetic aspects may explain the pleomorphic and unpredictable course of NCC.

Key words: neurocysticercosis, MRI, cytokines.

Introduction

Neurocysticercosis (NCC) is one of the most common neurological disorders, being even more frequent in developing countries where patients account for about three-quarters of all epileptic cases [1, 2]. It is difficult to exactly estimate the disease burden of NCC in a community study, because of the polymorphic presentation of the disease and the remarkably similar imaging and clinical features of various infective conditions, like tuberculoma, fungal granuloma, parasitic granuloma or cerebral metastasis.

Evidence from animal models and clinical studies shows that cysticerci remains clinically silent as a result of active immune tolerance and that symptomatic parenchymal disease occurs at the time of larval degeneration or death by cysticidal therapy, leading to leak of toxic content and incitation of a severe local inflammatory reaction [3]. Much of the pathology of NCC is thought to be due to the host immune response to the metacestode in the brain [4]. The immune response is thought to vary depending on the incubation period, the number and location of cysts in the brain and the stage of the cyst (alive or in any of various stages of disintegration) [5]. Recently, several reports on cysticercosis involving studies of the cellular infiltrate in humans and in animal models have indicated that a Th1 immune response predominates over a Th2 response [5], while studies of the cerebrospinal fluid have revealed a predominant Th2 response [6].
Cysticercosis has been recognized as a potentially eradicable disease as all the biological markers for transmission of *Taenia solium* taeniasis and cysticercosis exist in India. Parasitological examination of stool samples, imaging techniques and serological tests for identifying NCC have shown variable performances [7]. The objective of the present study was to evaluate the correlation between the levels of various cytokines present in the sera, clinical presentation and radio imaging findings among clinically suspected pediatric patients of NCC.

Materials and Methods
The present study was carried out in Departments of Microbiology and Pediatrics, UCMS and GTB Hospital, Delhi. A total of 50 clinically suspected cases of neurocysticercosis on the basis of presenting symptoms of generalized or partial seizure or radio imaging findings were included in the study. An additional 40 children composing of 20 healthy children attending the immunization clinic and 20 generalized epileptic children with no MRI findings suggestive of NCC, formed the control group.

Inclusion criteria included: presence of clinical history of seizures and/or mass effects and/or hydrocephalous. Exclusion criteria included: any history of intake of antiparasitic drugs within the past 2 months and presence of any other chronic or systemic illness. Informed consent was taken from the study group before collection of samples.

**Sample collection and processing**
Sera separated from the venous blood sample (3–4 ml) was transported to Microbiology Department and stored at −20°C for the following serological assays following manufacturer’s instructions.

(i) IgM antibody for neurocysticercosis (DRG<sup>R</sup> Cysticercosis EIA, DRG International, USA).
(ii) Th1/Th2 cytokine response (IL-2 and TNF-α/IL-6) (GenProbe Diaclone ELISA, France).
(iii) Presence of C reactive protein (CRP) was seen using latex agglutination assay.

**Results**
Majority of the cases were males (60%) with a male to female ratio of 3:2 and the maximum cases (~70%) presented in the age group of ≥8 years (Table 1).

In all, 35 out of the 50 (70%) cases presented with complex partial seizure with the rest (30%) showing generalized tonic clonic seizure. Only five cases had past family history of TB and/or antitubercular therapy (ATT), two had reactive Montoux test, two had past history of TB and ATT and only one had a past family history of epilepsy. Nine out of the total cases had normal CT/MRT findings, whereas majority of the cases (27) showed inflammatory granuloma with or without perilesional edema (Table 2).

Ten cases (20%) presented with acute symptoms of NCC with an immunological response of a predominance of pro-inflammatory cytokines (IL-2: 8, TNF-α: 2) and 40 (80%) children had high IL-6 levels indicating an active lesion with chronic granulomas suggestive of parasitic destruction and persisting presentation with seizures. However, the levels of IL-6 differed with values lower in patients with inactive (calcified lesions) forms of NCC (Table 3). A significant proportion (43 of 50 cases i.e. 86%) had negative serology probably because of the waning of antibody response months or years after the parasites die (Table 4).

**Discussion**
Though NCC has been less well studied in children, clinical experience suggests that the clinical and inflammatory response may differ from that of adults. One can verify the disease’s manifestation in both genders with a greater frequency in older children [8, 9]. Excretion of *Taenia* eggs being intermittent, direct parasitologic examination of stools is not sensitive [10]. In addition to high cost, routine CT scan for children presenting with a first partial seizure in an area with a high prevalence of NCC failed to identify findings other than neurocysticercosis that meaningfully altered clinical management [11]. Also failure to identify cases by antibody or antigen serology as possible, NCC is compatible with the reported decline in detectable levels of antibody to *T. solium* over time [12].

Cysticercal lesions develop in the central nervous system (CNS) due to a combination of host immune-inflammatory response, mainly mediated by cytokines produced by resident and infiltrating cells activated by cysticercal antigens [13]. Immune response predominantly consisting of Th1 lymphocytes [5] and the later development of a mixed Th1 and Th2 response associated with parasite destruction [14]. Calcified infraparenchymal cysts may serve as a focus for remote symptomatic seizures as

**TABLE 1**
**Demographic profile of the study group**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Male number</th>
<th>Female number</th>
<th>Total (% out of 50 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2–5</td>
<td>2</td>
<td>1</td>
<td>3 (6)</td>
</tr>
<tr>
<td>5–8</td>
<td>7</td>
<td>4</td>
<td>11 (22)</td>
</tr>
<tr>
<td>≥8</td>
<td>21</td>
<td>15</td>
<td>36 (72)</td>
</tr>
<tr>
<td>Total (% out of 50 cases)</td>
<td>30 (60)</td>
<td>20 (40)</td>
<td>50 cases</td>
</tr>
</tbody>
</table>
late sequelae of NCC [4]. Most helminthic infections
become chronic because of weak innate immunity
and the ability of the parasite to evade elimination
by adaptive immune response. A predominance of
TH2 (IL-6) response in our study allows prolonged
survival of the parasite as well as exacerbations of
lesions occur due to suppressive actions of IL-6.

Immunological response showing a predominance
of pro-inflammatory cytokine like IL-2 and TNF-α,
when induced by cysticerci in meninges, can contrib-
ute to an active lesion with a local tissue damage but
it may vary and may not be observed in detectable
levels in the serum in the early stages of the disease.
However, the release of IL-6 demonstrable in the
serum indicate the systemic microenvironment favor-
able for an active helminthic infection subsequently
leading to massive destruction of the parasite, unlike
the microenvironment of CNS which favors a TH1
response. Such an increased response of IL-6 there-
fore can behave as an indicator toward the chronicity
of the lesion and reduced chances of relapses or seiz-
ures in future.

Multiple courses of cysticidal treatments have
been advocated without clear evidence for overall
benefit in humans (e.g. cysticercotic encephalitis,
granulomas and calcification) [15]. In addition to
the number or stage of the parasites, intrinsic

<table>
<thead>
<tr>
<th>Localization of the lesion</th>
<th>CT/MRI findings</th>
<th>CRP Positivity</th>
<th>IgM Positivity</th>
<th>TH1 cytokine profile IL-2</th>
<th>TNF-α</th>
<th>TH2 cytokine profile IL-6</th>
<th>Total</th>
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<tbody>
<tr>
<td>Inflammatory granuloma with/without peri focal edema</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Inflammatory degeneration with peri focal edema</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td></td>
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<tr>
<td>Ring enhancing lesion with peri lesional edema</td>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>26</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Calcified lesion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>4</td>
<td></td>
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<tr>
<td>Total</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>2</td>
<td>40</td>
<td>41^a</td>
<td></td>
</tr>
<tr>
<td>Healthy control</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
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^aNine had normal CT/MRI.

<table>
<thead>
<tr>
<th>CT/MRI finding</th>
<th>Mean IL-6 levels (pictograms/ml)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Inflammatory lesions</td>
<td>13.3</td>
<td>&lt;0.05</td>
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<tr>
<td>Granulomatous lesions</td>
<td>36.5</td>
<td></td>
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<tr>
<td>Calcified lesions</td>
<td>26.8</td>
<td></td>
</tr>
<tr>
<td>Healthy controls</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>
characteristics of the parasites as well as immunege-
etic aspects may play important role in the pleo-
morphic and unpredictable course of epilepsy due
to NCC.

References