Original article:

Biochemical parameters in differentiating parenchymal solitary granular neurocysticercosis from intracranial tuberculoma—a pilot study.

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Abstract

Background: In India neurocysticercosis, caused by the larvae of the helminth, Taenia solium is considered to be the most common parasitic infestation of the central nervous system. A large majority of patients with this disease have single small enhancing CT lesions (SSECTL). This study was undertaken to evaluate the effectiveness of biochemical parameters in differentiating single small enhancing parenchymal CT lesion presumably of neurocysticercosis from tuberculoma.

Materials and methods: A total of forty patients between 10-50 years of age, comprising of twenty patients with a probable diagnosis of neurocysticercosis based on the revised criteria of Del Brutto et al, and 20 patients with a probable diagnosis of tuberculoma were selected from the inpatient wards of the departments of paediatrics and general medicine of Alluri Sitaramaraju Academy of Medical Sciences -Eluru. Cerebrospinal fluid analysis for glucose, protein and adenosine deaminase was done.

Results: There was a statistically significant difference in the mean cerebrospinal fluid adenosine deaminase levels in patients with neurocysticercosis, 1.56±0.62U/l versus tuberculoma 19.65±3.21U/l (p<0.0001), and also a significant difference in the mean cerebrospinal fluid protein concentrations between the two groups, the values being 36.45±15.47mg/dl and 82.8±13.15mg/dl respectively (p<0.0001).

Conclusion: Biochemical parameters like cerebrospinal fluid adenosine deaminase and proteins can be used to differentiate between the two conditions.

Key words: Neurocysticercosis, intracranial tuberculoma, adenosine deaminase

Introduction

Neurocysticercosis (NCC) is the most common parasitic infestation in India caused by the helminth, Taenia solium. NCC is caused by the larval form of Taenia solium. The encysted larval stage, ‘cysticercosis cellulosae’ is lodged in the central nervous system (CNS), with the brain parenchyma being the most common site. This is followed by the meninges, ventricles, eye and spinal cord. The parenchymal cysts remain dormant for many years. [1] The other clinical conditions include headache, hydrocephalus, chronic meningitis, focal neurological deficits, psychological disorders, dementia, ocular and spinal cysts.[2] Rajsekhar et al in 2006 found 28.4% of individuals had CT scan findings suggestive of NCC in a community survey of 50,617 in south India.[3] NCC is a chronic slowly progressive disease. NCC remains the most common cause of solitary small enhancing CT lesion (SSECTL).[4] Morphologically four stages of development and regression of the cysticercus in the CNS are recognised. They are (i) cystic or vesicular stage which is viable and is...
composed of well defined fluid filled membrane, that contains the scolex, (ii) degenerating colloid or granular stage that corresponds to parasite necrosis and associated inflammatory process. Oedema and/or necrosis of the surrounding neural tissue may be present in some cases, (iii) the nodular stage in which fibrosis develops with time and (iv) calcification of the fibrous nodule. Colloidal stage and nodular stage show inflammatory reactions, are symptomatic and show enhancing CT lesions.

The next common differential diagnosis of SSECTL after NCC is tuberculoma, which accounts for 5-10% of intracranial space occupying lesions in the developing world. In India tuberculous granulomas or tuberculomas account for 20-30% of intracranial tumours. Tuberculomas are thought to arise when tubercles in brain parenchyma enlarge without rupturing into the subarachnoid space. Usually they occur in the absence of tuberculous meningitis (TBM). They commonly occur as solitary lesions. They are a characteristic feature of tuberculosis. The objective of a tuberculoma is thought to be restriction of mycobacterial growth in the brain. These are tumour-like lesions and often manifest as intracranial space-occupying lesions. Seizures may be the presenting feature of patients with tuberculomas or tubercular abscess. Tuberculomas may present months to years after infection. Though serological tests like enzyme linked electro immuno transfer blot (EITB) done on serum and CSF have an overall sensitivity of 98% and specificity of 100% in detecting patients with NCC, its sensitivity in patients with single enhancing CT lesion is much lower.

The differentiation is usually done by starting a trial with anticysticercal drugs. One study observed that the occurrence of side-effects of albendazole therapy indicate that the intracranial lesion could be NCC. Rajasekhar et al have found that CT lesions which are irregular, solid >20mm, associated with severe perifocal oedema and focal neurological deficits are usually tuberculomas. They also observed that cysticerci on CT scan present as a round shape, 20mm or less in size with ring enhancement or visible scolex with usually no midline shift or focal neurological deficit. But these findings have not been corroborated by other authors. It was decided to use CSF ADA levels to differentiate between the two conditions as none of the diagnostic methods were specific to the disease. Cerebrospinal fluid adenosine deaminase (ADA) levels have been shown to be a promising diagnostic and prognostic marker in tuberculous meningitis and its role in the diagnosis of tuberculomas is being investigated.

Biochemical analysis of CSF for glucose, protein and ADA is cost effective when compared to EITB or ELISA which are out of the reach of most patients in rural India.

The present work was planned to differentiate between a single small enhancing CT lesion of probable cysticercus aetiology with a similar picture of tuberculoma using biochemical parameters like CSF glucose, protein and ADA.

Material and methods: After obtaining informed consent from the parents of the subjects (in case of children) and the subjects (in case of adults) and ethical committee clearance from the head of the institute, twenty patients with a probable diagnosis of NCC according to Del Brutto’s criteria (based on one major and 2 minor criteria) and 20 patients with suspected tuberculoma in the age groups of 10 to 50 years were selected. The probable diagnosis of NCC was done by the clinician based on the presence of solitary small enhancing CT lesion- a major criterion of Del Brutto, presence of seizures and aggravation.
of existing symptoms or appearance of new symptoms following anti cysticercal drugs- both being minor criteria. In this manner 20 patients were selected. A detailed history was taken and clinical examination was done by the clinician in patients suspected to be suffering from tuberculoma and they were selected if the CT scan lesion revealed a solitary small enhancing lesion (SSECTL). History of contact with a tuberculous patient was also elicited. The selected patients were from the inpatient ward of paediatrics and general medicine department of Alluri Sitaramaraju Academy of Medical Sciences - Eluru. The study was undertaken between 2011 January to 2012 December. The inclusion criteria were a SSECTL of either a suspected tuberculous aetiology or NCC. The exclusion criteria were subjects suffering from AIDS or other immune compromised conditions, pregnant women and patients with other causes of intracranial space occupying lesions like fungal granuloma, gliomas, metastasis or pyogenic abscess, all of which were excluded after clinical examination and the requisite investigations. Two ml of CSF was analysed for glucose, protein, and adenosine deaminase. Analysis was done on a semi automated clinical chemistry analyser (Microlab 200 – Merck.) using standard kits (Erba) and after running the quality control specimens. All the laboratory parameters were estimated immediately. Healthy controls could not be taken because of ethical considerations. Descriptive statistics was used to calculate the mean and standard deviation and ‘t’ test was used on the results obtained and a ‘p’ value of <0.05 was considered significant.

**Results:** There were more females in the tuberculoma samples when compared to NCC (12 vs.8). The number of children was more in NCC samples when compared to adults (13 vs.7) and in tuberculoma subjects it was (11 vs. 9) The biochemical parameters are given in table 1. The mean CSF glucose levels were 42.95±8.12mg/dl, proteins 36.45±15.47mg/dl, and ADA levels were1.56±0.62U/l in patients with suspected NCC. In patients with suspected tuberculomas the respective values were 46.9±7.53mg/dl, 82.8±1.15mg/dl and 19.65±3.21U/l.
**FIG. 2. MEAN CSF PROTEIN AND GLUCOSE VALUES IN NEUROCYSTICERCOSIS AND TUBERCULOMA.**

![Mean CSF protein and glucose values.](image)

**TABLE 1: MEAN AND STANDARD DEVIATION AND PROBABILITY VALUE OF THE THREE BIOCHEMICAL PARAMETERS IN CSF.**

<table>
<thead>
<tr>
<th>Groups</th>
<th>CSF ADA U/l</th>
<th>CSF proteins mg/dl</th>
<th>CSF glucose mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculoma</td>
<td>19.65 + 3.21</td>
<td>42.3 + 7.53</td>
<td>82.8+13.15</td>
</tr>
<tr>
<td>Mean + SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td>1.56+0.62</td>
<td>45.95+8.12</td>
<td>36.45+15.47</td>
</tr>
<tr>
<td>Mean + SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-stat</td>
<td>24.68</td>
<td>-0.9</td>
<td>10.2</td>
</tr>
<tr>
<td>‘p’ value</td>
<td>&lt;0.0001</td>
<td>0.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inference</td>
<td>Highly significant</td>
<td>Not significant</td>
<td>Highly Significant</td>
</tr>
</tbody>
</table>

ADA: adenosine deaminase

**Discussion:** Females were more in number in the tuberculoma group (12 females vs. 8 males). This finding is similar to a study by Anuradha et al, where intracranial tuberculomas were found more frequently in females. These findings have been explained on the basis of several experimental studies that demonstrated that female sex hormones are responsible for greater immune reactivity. The incidence of tuberculomas is slightly higher in children. Up to 41% of intracranial space occupying lesions have been found to be tuberculous in nature. A similar finding was seen in the present study where 11 children showed evidence of tuberculoma when compared to only 9 adults who had intracranial tuberculomas. Solitary granulomas due to NCC were more common in children than adults (13 children vs.7 adults). This finding is corroborated by a study by Gadgil and Udani who reviewed cases of paediatric epilepsy and found that 60-70% of patients had single parenchymal granulomas. Calcified lesions were fewer when compared to adults (15% vs. 55%). Figure 1 shows the mean difference between the CSF ADA levels of the two conditions is very significant p<0.0001. Similarly
CSF protein also showed a significant variation between the two conditions with the ‘p’ value being <0.0001, figure 2. Very few studies are available in the literature where CSF ADA levels were estimated in tuberculoma or NCC. A recent case report by Rakesh Lalla et al shows elevated levels of CSF ADA levels in a 15 year old girl who had clinical features of a space occupying lesion and multiple ring enhancing lesions in both cerebral hemispheres, cerebellum, and left half of medulla and pons on magnetic resonance imaging (MRI). CSF ADA level was 20U/l, proteins 120mg/dl and glucose 50mg/dl. In the present study also there was significant elevation in the CSF ADA levels in tuberculoma patients when compared to the NCC group. Another case report of a tuberculoma in AIDS patient was reported by Chandra et al. In this study the CSF ADA levels were 40U/l, proteins were 120mg% and glucose was 33mg%. Magnetic resonance (MR) spectroscopy which is a confirmatory investigation for diagnosing the aetiology of SSECTL, showed a large heterogeneous enhancing ill-defined lesion in the left parieto-occipital lobe with a lipid lactate peak suggestive of an infective aetiology. There are several studies showing the predictive value of CSF ADA levels in tuberculous meningitis. CSF ADA is thought to be released by T lymphocytes during cell mediated immune response to tuberculous infection. Levels of ADA in CSF are known to differentiate patients of tuberculous meningitis (TBM) from aseptic meningitis and controls, but its role in predicting CNS tuberculomas has not been studied. Cerebrospinal fluid proteins are elevated in tuberculoma, and this elevation is more when compared to NCC. This is in consonance with another study by Anuradha et al, where the CSF of patients with tuberculomas showed elevated protein levels, suggesting an enhanced immunological reaction. A case report by Ahn et al showed a negative culture of CSF for Mycobacterium tuberculosis in a patient with intracranial tuberculoma.

The CSF ADA and proteins in NCC patients were not as elevated as in tuberculoma patients. A study by Machado et al found that CSF ADA and protein are elevated mainly in the reactive forms of NCC when compared to the weakly reactive or non reactive forms. The reactive forms are the cystic and colloidal forms of NCC. The nodular form is weakly reactive and the calcified form is non reactive. The nodular forms of NCC also show ring enhancement on CT scan. Our study could have had more of the weakly reactive forms, which explains the low CSF ADA and protein levels in the NCC group. There was also no significant difference in the CSF glucose values between the two groups in the present study, figure 2. Unless there is TB meningitis, CSF glucose is usually within the normal range in tuberculoma patients, as very rarely Mycobacteria have been cultured from CSF in a tuberculoma patient. Machado et al also have not found any significant fall in CSF glucose levels in NCC. In the present study preference was given for a biochemical CSF profile in these two conditions rather than a MR spectroscopy as the cost of this investigation is prohibitive and many patients belonging to a low socio-economic background can’t afford it. CSF analysis for the antibodies to cysticercus cellulosae using ELISA is not specific. CSF ELISA using antigens was found to be 87% sensitive and 95% specific. It is a useful supportive tool for diagnosing NCC but its sensitivity in detecting solitary granuloma of NCC was low. The
latest EITB serological assay was found to be specific for human cysticercosis, though the sensitivity was related to the number of cysticerci in the brain. There was 98% sensitivity with 3 or more cysticerci but only 65% sensitivity with 1 or 2 cysticerci. This assay is more likely to be positive in serum than CSF samples. \[1,21\] The access to EITB in India is limited.

This is a pilot study undertaken in a rural population at ASRAM medical college-Eluru. It is always a diagnostic dilemma when there is an SSECTL as it is very difficult to differentiate a solitary granuloma of NCC from a solitary intracranial tuberculoma by CT scan findings alone. In this study patients with solitary intracranial tuberculomas had high levels of CSF ADA and protein when compared to patients with solitary granulomas of NCC. Therefore CSF ADA and protein can be used as a marker to differentiate between these two conditions.

**Conclusion:** As the cost of other investigations like EITB and MR spectroscopy is prohibitive to a patient from a third world country like India, and ELISA is nonspecific biochemical analysis is an economical alternative. Further studies using a larger sample size need to be done to study the effectiveness of using CSF ADA and protein levels in diagnosing solitary intracranial tuberculoma and excluding a diagnosis of solitary granuloma of NCC. Further CSF ADA and protein levels in the different stages of parenchymal NCC can also be studied.

**References:**


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