Original Article

Cognitive Dysfunction and its Determinants in Patients with Neurocysticercosis

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ABSTRACT

Introduction: Neurocysticercosis (NCC) is the most common parasitic infection of man. In addition to a headache, seizures, and focal deficits, this is associated with significant cognitive dysfunction. Many studies revealed that the number and location of lesions are not always responsible for cognitive dysfunction. Cholinesterase and pseudocholinesterase are found in the walls of the cysticercus which could contribute to cholinergic depletion and thus cognitive dysfunction. **Patients and Methods:** A total of 43 patients who presented with NCC were evaluated for cognitive deficits, as well as cholinesterase levels in cerebrospinal fluid (CSF) with control CSF from patients undergoing spinal anesthesia. Blood levels of interleukin-10 and tumor necrosis factor alpha were also estimated and correlated with cognitive deficits. **Results:** There is a mild increase in the acetylcholinesterase in CSF of patients compared to controls, but it did not correlate with cognitive deficits. There is an increase in interleukins to a significant level which correlates with vesicular stage of the organism and cognitive impairment. The number of lesions also correlated with cognitive impairment even though the location did not. The domains of cognitive deficits seen are sustained attention, category fluency, verbal working memory, planning, set shifting, verbal learning, visual memory, and construction. **Discussion and Conclusion:** NCC is associated with multi-domain cognitive impairment correlates with vescicular stage, proinflammatory cytokines and number of lesions but not location, vesicular stage, and proinflammatory cytokines.

Key words: *Cholinesterase levels, cognitive dysfunction, neurocysticercosis*

INTRODUCTION

Taenia solium Linnaeus is otherwise called pork tapeworm or armed tapeworm of man.[1] The adult worm resides in the jejunum of man and larval stage is in the intermediary host which is pig. Eggs excreted in human feces are swallowed by the animal. In the intestine of the pig, the oncospheres are liberated which enters the portal vessels and mesenteric lymphatics and reach the general circulation. Then reaches the liver, right-sided chambers of the heart, lungs, and then to muscles of

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the tongue, neck, shoulders, and ham. On reaching this destination, the oncospheres lose their hooks and forms a vescicle with scolex in a weeks' time called cysticercus. This process takes about 60-70 days. Thus infested pork is called as measly pork. The scolex exvaginates in the gut of man who eats the measly pork. It matures to adult in 3 months which can be as long as 2-3 m. Humans can become an intermediate host by the eggs producing autoinfection by retrograde peristalsis from the primary host himself or by consuming vegetables or food materials with fecal contamination. The mature cyst in the muscle of the intermediate host, the pig or accidental host man is 5 mm in width and 10 mm in length. It has a dense white scolex with hooks and suckers. It can live for several months in that stage. They can infest the skin, eyes, and brain apart from muscles [Figures 1-3]. In India, cysticercosis is underreported, but the incidence is less in Kerala and Jammu Kashmir which can be related to general hygiene and food habits. Neurocysticercosis (NCC) is considered to be the most common parasitic infestation of the central nervous system and the single most common cause of epilepsy in the developing countries. The other features are headache, hydrocephalous, chronic meningitis, focal neurological deficits, psychiatric dysfunction, and spinal cyst.[2-4] Patients also show impairment in executive functions, verbal and nonverbal memory, praxis, and verbal fluency.[5] Dementia is more common with older age, lower education level and probably number and location of the cyst.[6] However, the exact pathogenesis of cognitive dysfunction is controversial. The vesicular membrane of the scolex is found to have cholinesterase and pseudocholinesterase.[7] The bladder wall has more of this enzyme activity. Hence, it is likely that there is enhanced breakdown of acetylcholine as well as neurogenic inflammation which might contribute to the cognitive dysfunction in patients. There is an increase in the levels of interleukin-10 (IL-10), IL-5 reported in the blood of patients with NCC.[8] Hence in this study, we decided to analyze the role of cholinesterases and cytokines IL-10 and tumor necrosis factor alpha (TNF-α) in our patients as it might suggest a role for anticholinesterases and anti-inflammatory agents in patients with NCC associated dementia in addition to number of lesions, stage, and location of lesions in magnetic resonance imaging (MRI) of brain.

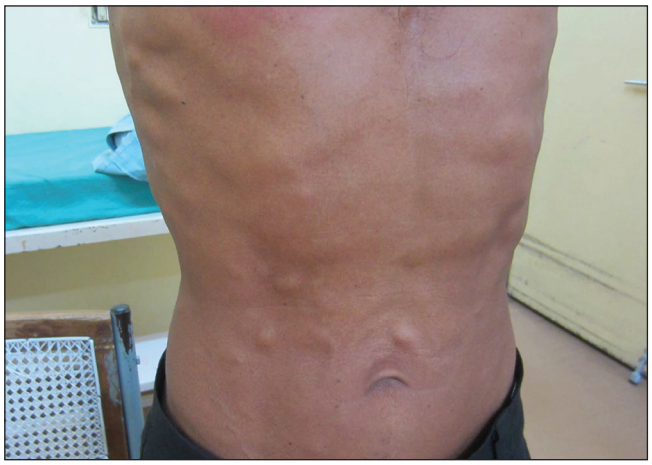

Figure 1: Subcutaneous nodules of neurocysticercosis

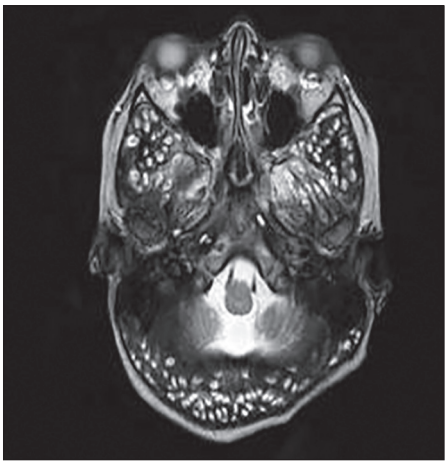

Figure 2: Axial section showing intraocular and intracranial lesions

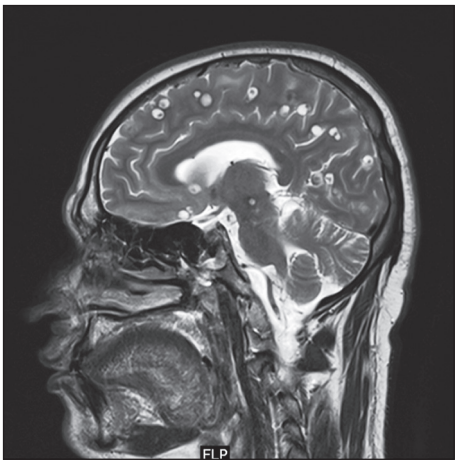

Figure 3: Sagittal section showing multiple neurocysticercosis lesions

PATIENTS AND METHODS

A prospective, hospital-based study conducted at, a Tertiary Referral Centre in India, from April 2012 to December 2013. Forty-three patients diagnosed with definite or probable NCC according to diagnostic criteria were selected for the study.[9]

A detailed history of demographic features, diet habits, raised intracranial pressure, fever visual symptoms behavioral problems, focal deficits,. subcutaneous nodules, muscle hypertrophy etc., were recorded. All patients underwent Hindi Mental State Examination and a battery of neuropsychological tests. In all patients, complete hemogram with absolute eosinophil

count, all mandatory investigations for patients with cognitive dysfunction, chest X-ray, stool examination for parasitic cysts, or ova were done.

MRI scan was performed in all patients and number of lesions, the location of lesions, proximity of lesions to the ventricular surface or cortex, perilesional edema, presence or absence of visualization of scolex was noted. Lumbar puncture was done in all patients, and cerebrospinal fluid (CSF) was analyzed for routine study, levels of acetylcholinesterase, and IL-10 and TNF-α was estimated in serum. Control CSF was taken from patients undergoing spinal anesthesia with informed consent.

Acetylcholinesterase was determined spectrophotometrically by the method of Ellman IL-10 and TNF-α assessed by enzyme-linked immune-adsorbent assay from serum. Interleukin levels from normal age and gender matched controls were compared with patients with NCC.

The following neuropsychological tests were used. Attention — assessed by digit vigilance test, fluency — assessed by animal naming test, working memory — assessed by N-back, planning, and execution — assessed by Tower of London, set shifting — assessed by Wisconsin card test, learning and memory — auditory verbal learning test (AVLT), parietooccipital function - assessed by complex figure of Rey.

RESULTS

Total patients included for the study were 43. Approximately, two-thirds of the patients were men (n = 27; 62.8%) and one-third were women (n = 16, 37.2%). Most of the patients were from semi-urban area 22 (51.2%). The majority of the patients had primary education status 22 (50%).

Most of the patients were manual laborers followed by farmers and housewives History of pork consumption was obtained in 35 patients. Four were pure vegetarians. Initial symptoms were seizures 26 (60.5%), memory problems 12 (27.9%) depression 3 (7.6), and headache 2 (4%). Duration of symptoms varied from 1 month 15 (34.5%), 2 months 17 (39.5%), 3 months 10 (23.3%), and 4 months 1 (2.3%). Four patients had skin lesions/ subcutaneous nodules [Figure 1a].

CSF studies revealed normal values in 25 patients. Mononuclear pleocytosis was seen in eight patients. Pleocytosis with eosinophils was in four patients. Low glucose was seen in two patients. High protein was seen in four patients. Majority of lesions were in frontal lobes.

Neuropsychological scores of attention — digit vigilance test fluency — animal naming test working memory-N-back planning — Tower of London Wisconsin card test — set shifting AVLT, complex figure of Rey — parietooccipital function did not show any relation to the site of lesions [Tables 1 and 2]. More the number of lesions lesser the neuropsychological score with significant statistical correlation. The mean value of acetylcholinesterase, IL-10 and TNF-α in patients were 13.36, 21.37 and 176.72 respectively and median values were 9.39, 18.96, and 74.08, respectively. In controls, the mean value were 8.8, 11.76, and 53.49, respectively and median values were 8.71, 9.96, and 57, respectively. Acetylcholinesterase was increased in patients with a minimum value of 2.73 and a maximum

Table 1: Neuropsychological tests with site of lesions (N:I)

Site of lesions	Digit vigilance	Animal naming	N Back	Tower of london	Winconsin card	AVLT	Complex figure of ray
Frontal	7:01	7:01	7:01	8:00	8:00	7:01	8:00
Temporal	2:01	3:00	3:00	3:00	3:00	3:00	2:01
Parietal	1:00	1:00	1:00	1:00	1:00	1:00	1:00
Occipital	1:01	2:00	2:00	2:00	2:00	2:00	2:00
Frontal & temporal	2:00	1:01	1:01	1:01	1:01	2:00	2:00
Frontal & parietal	3:00	3:00	3:00	2:01	3:00	1:02	3:00
Frontal & occipital	4:00	4:00	4:00	4:00	4:00	4:00	4:00
Temporal & parietal	3:00	2:01	1:02	1:02	2:01	3:00	3:00

Table 2: Neuropsychological tests with site of lesions (part 2)

Site of lesions	Digit vigilance	Animal naming	N Back	Tower of london	Winconsin card	AVLT	Complex figure of ray
Temporal & occipital	1:00	1:00	1:00	1:00	1:00	1:00	1
Frontal, temporal & parietal	4:02	0:06	0:06	5:01	5:01	2:04	3:03
Frontal, temporal & occipital	1:02	0:03	1:02	1:02	1:02	2:01	2:01
Frontal, parietal & occipital	1:00	0:01	0:01	1:02	0:01	1:00	0:01
Frontal, temporal, parietal, occipital	2:03	1:04	1:04	2:03	3:02	2:03	2:03
Others	1	1	1	1	1	1	1
Total	43	43	43	43	43	43	43

value of 43.99 as against a minimum of 1.91 and a maximum of 17.36 in controls. The levels of IL-10 varied from 2 to 83.4 and TNF-α 5.09 to 1798.6 in patients. In controls, IL-10 varied from 0.76 to 51.3 and TNF-α 16.7 to 105.75. Mann-Whitney U-test was used to control the median of patients and controls [Tables 3 and 4]. *P* value of acetylcholinesterase-0.09 and IL-10-0.01 and TNF-α- 0.009. The acetylcholinesterase elevation in the CSF of patients was not statistically significant whereas the levels of proinflammatory cytokines in blood were highly significant. However, the raised interleukin level did not correlate with any site of lesions [Table 5].

DISCUSSION

Forty-three drug naive patients with NCC were clinically and neuropsychologically evaluated. The number of lesions, location of lesions, acetylcholinesterase levels in CSF, IL-10 and TNF-α levels were compared with neuropsychiatric impairment in patients. The levels of biological markers were controlled with normal CSF and blood samples. It was found that proinflammatory cytokines were high to highly significant levels compared to controls. It correlated with severity of cognitive impairment. Acetylcholinesterase levels were mildly elevated in patients compared to controls, but

Table 3: Acetyl chlinesterase interleukin 10 and TNF alpha in patients

Patients	Acetyl chlinesterase nmol/min/ml	Interleukin 10 (pg/ml)	TNF alpha (pg/ml)
Number	43	43	43
Mean	13.36	21.37	176.72
Median	9.39	18.96	74.08
Mode	7.18	2	5.09
Std deviation	10.24	16.33	334.31
Minimum	2.73	2	5.09
Maximum	43.99	83.4	1798.6

Table 4: Acetyl chlinesterase interleukin 10 and TNF alpha in controls

Controls	Acetyl chlinesterase nmol/min/ml	Interleukin 10 (pg/ml)	TNF alpha (pg/ml)
Number	35	36	36
Mean	8.86	11.76	53.49
Median	8.71	9.96	57
Mode	9.25	0.76	57
Std deviation	3.43	9.61	18.58
Minimum	1.91	0.76	16.7
Maximum	17.36	51.3	105.75

Table 5: Correlation of neuropsychological scores with number of lesions in magnetic resonance imaging

Tests	Number of lesions	Frontal	Temporal	Parietal	Occipital	Others
Digit vigilance test						
Correlation	−0.025	−0.198	−0.003	−0.104	−0.181	−0.073
Significance	0.872	0.294	0.987	0.507	0.245	0.640
n	43	43	43	43	43	43
Animal naming test						
Correlation	−0.640	−0.560	−0.649	−0.568	−0.167	−0.152
Significance	0.001	0.001	0.003	0.001	0.285	0.331
n	43	43	43	43	43	43
N-back						
Correlation	−0.625	−0.4810	−0.657	−0.568	−0.133	−0.063
Significance	0.001	0.001	0.002	0.002	0.394	0.689
n	43	43	43	43	43	43
Tower of London						
Correlation	−0.466	−0.287	−0.0436	0.396	−0.108	−0.024
Significance	0.002	0.062	0.001	0.015	0.492	0.878
n	43	43	43	43	43	43
Wisconsin card test						
Correlation	−0.398	−0.287	−0.395	−0.293	−0.152	−0.152
Significance	0.009	0.062	0.009	0.056	0.331	0.330
n	43	43	43	43	43	43
AVLT						
Correlation	−0.394	−0.395	−0.189	−0.458	−0.065	−0.053
Significance	0.009	0.009	0.225	0.002	0.679	0.734
n	43	43	43	43	43	43
Complex figure of Rey						
Correlation	−0.370	−0.299	−0.301	−0.456	−0.190	−0.114
Significance	0.015	0.052	0.052	0.002	0.222	0.466
n	43	43	43	43	43	43

AVLT – Auditory verbal learning test

it was statistically not significant and did not correlate with the degree of impairment in neuropsychological tests. The number of lesions correlated with cognitive impairment but not the location.

Most patients with impaired neuropsychological tests had lesions in colloid/colloid vesicular stages.

Patients with raised IL-10 and TNF-α were mostly having vesicular lesions. Patients with raised IL-10 were not having any preference for site of lesion.

CONCLUSION

Cognitive impairment is present in patients with NCC. There is statistically significant correlation of cognitive impairment with the number of lesions in MRI probably due to the absolute loss of brain volume. The type of neuropsychological tests and score does not correlate with the site of lesions.

Patients with impaired scores in neuropsychological tests had the majority of lesions in the vesicular stages in MRI.

The increase in the level of interleukins is statistically significant and correlates with vesicular stages. It is likely that cognitive impairment is more due to inflammation triggered degeneration resulting in breaking of synapses which exposes the neurons to apoptosis.

The researchers were not blinded to the cases and controls. Inflammatory markers were estimated in blood only and follow-up to know the course of cognitive impairment once inflammation subsides is likely to be useful. Our study reveals cognitive dysfunction in patients with NCC could be due to infection associated inflammatory changes, and anti-inflammatory drugs could be tried for the cognitive dysfunction associated with NCC.

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Conflicts of interest
There are no conflicts of interest.

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