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Pediatrics

IVERMECTIN AS AN ALTERNATIVE THERAPY IN SEVERE NEUROCYSTICERCOSIS CASES ,A STUDY

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ABSTRACT

INTRODUCTION: This study was carried out at Military hospital Jabalpur, Madhya Pradesh, Varanasi to evaluate the use of ivermectin in sever cases of neurocysticercosis patients from Jul 2011 To Jul 206.

MATERIALS AND METHODS: Patients included in this study were all confirmed cases of neurocysticercosis. Diagnosis was made by taking detailed history, Clinical examination, Computed tomography (CT) and or Magnetic Resonance Imaging scan & serology wherever indicated. Patients with active, transitional cysts and seizure were treated with steroids, albendazole and anticonvulsants. Seven children were given multiple courses of albendazole. Ivermectin was used in five children after three courses (28 days) of albendazole in each of them.

RESULTS: There were a total of 26 confirmed patients of neurocysticercosis who completed this study. Mean age of the presentation was 9.6 ± 4.9 years, 58% of the patients were female. The clinical profile of patients was as follows - partial seizures 63.3%, generalized seizures- 37.7%, headache - 67%, vomiting in 19 %, focal neurological deficit in 11% and combination of symptoms in 70% cases. Contrast CT brain showed a solitary lesion in 18 (71.1%) and multiple lesions in the rest. CT/MRI lesions were transitional in 64%, inactive in 21% and mixed in 36%, All the children were seizure free after two years of treatment and follow up). Ivermectin was used in five of the cases who did not respond to multiple courses of albendazole. All the cases received anticonvulsants phenytoin, carbamezapine and midazolam if required, steroids, & albendazole. Tab Ivermectin was used in seven of the cases with very good results.

CONCLUSION: Albendazole is effective in single as well as multiple ring enhancing lesions of neurocysticercosis in most of the cases, but in severe and new reappearing cases, Ivermectin is very promising and without any side effects

KEYWORDS : cysticercus, seizures, ring enhancing lesion, parenchymal lesion, albendazole, Ivermectin

INTRODUCTION

Ivermectin is an antiparasitic drug with a broad spectrum of activity, high efficacy as well as a wide margin of safety. It belongs to the family of Avermectins. It binds to glutamate-gated chloride iron channels, which are present in invertebrate nerve and muscle cells, and causes the paralysis and death of the parasite. Ivermectin is approved by the US Food and Drug Administration, and used worldwide to treat patients with onchocerciasis and strongyloidiasis. It is also used against a wide range of endoparasites (nematodes) and ectoparasites (insects, acarine) of animals and humans.

Cysticide treatment in neurocysticercosis has been controversial, because its efficacy is partial against vesicular and colloidal cystic forms in the face of the persistence of the parasite after a course of albendazole or praziquantel, the only two therapeutic options currently available. Ivermectin is a highly effective veterinary and human antiparasitic, safe, with occasional and minimal side effects, used for more than 25 years in endoparasitosis difficult to control, such as filariasis, onchocercasis, strongyloidiasis, etc., and also in ectoparasitosis, as pediculosis-capitis and myiasis. It acts in the myoneural junction on the receptors in the chlorine channel, increasing its permeability causing paralysis in adult worms, or by a mediated immune mechanism when acting on immature forms. Clinical cases. We present five patients previously treated with albendazole repeatedly with radiological evidence, demonstrating the persistence of viable vesicular or colloidal cysts and persistent epileptic seizures, who were given ivermectin 10 mg / day for 15 consecutive days or 10 mg / day, every other day for 30 days, with excellent clinical and radiological evolution.

Neurocysticercosis is the commonest parasitic central nervous infection world-wide.(3,4) and It is a public health problem in India with a wide distribution in the world and affects children as well as adults. (3,4,5).It is spread by fecal-oral contamination with *T. solium* eggs along with a poor hygiene practices in food handling by tape-worm carriers. Once exposed to gastric acid and bile, infective oncospheres are released in the upper small intestines of the human host, penetrate the intestinal wall, and disseminate throughout the body, including the CNS. (11,12,13). Seizures (50-80%), along with headache and impaired vision are common clinical presentations of NCC and leading causes of morbidity. Seizures can be partial /focal, generalized or rarely myoclonus and acquired epileptic aphasia , Dementia, learning difficulties and changes in cognition are often secondary sequelae in humans with NCC (2).

In this study we have tried to assess the efficacy of various treatment modalities with a trial of ivermectin in severe and resistant cases of neurocysticercosis and its outcome and follow-up of pediatric neurocysticercosis cases.

MATERIALS AND METHODS

The study was carried out in the Department of Pediatrics at Military hospital Jabalpur, Madhya Pradesh and Heritage Institute of Medical Sciences, Varanasi in children with seizure disorder in whom computed tomography brain scan had shown active or ring enhancing lesions or mixed lesions, All children outdoor and indoor having any combination of active, ring enhancing, or calcified were included in this study.

The children along with their parents and witnesses were interviewed separately with the help of a predesigned questionnaire. All the parents and legal guardians of children enrolled for the study, confirmed participation freely and voluntarily. A questionnaire to interview every child, their parents and witnesses was prepared and followed. Written permission for the same was taken in writing from the parents. Permission was also obtained from the ethical committee of the institute.

To begin with 26 children whose history, signs, symptoms , clinical examination and investigation confirmed them to be suffering from neurocysticercosis were selected for the study. After 2 years, only 21 children could be followed-up as the rest dropped out. We followed the diagnostic criteria by Del Brutto *et al*, in this study. (11) According to this criteria, either one absolute criteria or a combination of 2 major, 2 minor and 1 epidemiologic criterion are necessary for the definitive diagnosis.(Table-1). Probable diagnosis is made by 1 major plus 2 minor or 1 major plus 1 minor plus 1 epidemiologic criterions or 3 minor plus 1 epidemiologic criterion.

MRI brain was done only in multiple lesion cases (06 in number)

already detected by CT scan brain. Number of lesions were counted in CT scan and the disease activity was classified as active (appearance on CT as hypodense cyst without enhancement), transitional (appearance of a ring or nodular shadow with contrast enhancement) and inactive (calcified lesions) based on the viability of the parasite as proposed by Carpio *et al*.(12)

Patients with active, transitional or mixed cysts and seizure were treated with oral albendazole (15 mg/kg/day) in two divided doses with the maximum dose 800 mg/day, for total duration of 28 days as definitive therapy for active and transitional cysts.(1,2). All patients who were started on albendazole therapy, irrespective of any features of raised intracranial tension (ICT) were given oral Prednisolone (1 mg/kg/dose with the maximum dose of 50 mg/day) 48 hours before starting albendazole therapy as seizure could be precipitated by the introduction of albendazole because of inflammatory reaction by the breakdown of cysts.(1,2,3). Prednisolone was continued for a total period of 15 days, i.e., two days before and thirteen days after the start of albendazole therapy. Five of the children were given tab ivermectin 10 mg per day orally. The drugs used for the control of seizure were midazolam, carbmezapine and phenytoin. Praziquantel was not used in this study Once the patient's condition was stabilized , they were placed on oral carbmezapine (20-30 mg/kg), which was continued for 2 yrs or more. In children with recurrent seizures, persistent lesions and in seizure-free patients with calcification of cysts, carbmezapine was continued for a longer period. Out of this, eight children required multiple courses of albendazole of 28 days each, as the symptoms persisted in the form of vomiting, headache seizures and appearance of new lesions on CT/MRI. Follow up protocol was in the form of regular clinical evaluation, repeat CT scan at intervals of 06 weeks 03 months, 06 months and 24 months along with, This was a prospective observational study . Permission from the parents and institutional ethical committee for trial of ivermectin was obtained.

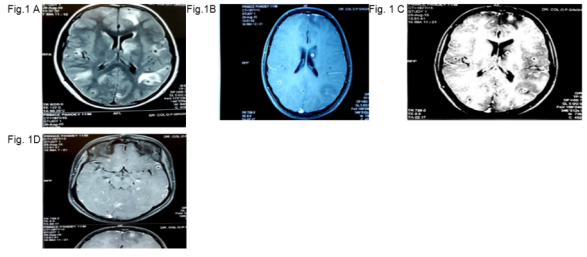


Figure 1. CT scan showing multiple neurocysticercosis (A,B,C,D)

Fig-2A

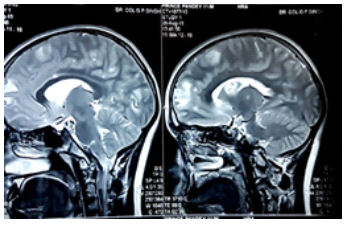
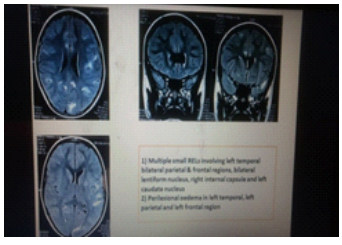


Fig-2A



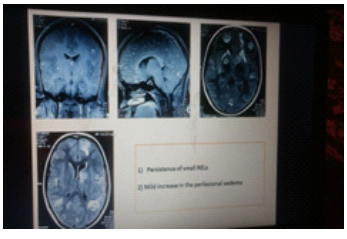


Fig -2-C

Fig 2 A,B & C ---Noncontrast axial T1-weighted scan showing small, circular cyst with cerebrospinal-like fluid and a small eccentric scolex seen as intramural nodule, isointense rim suggestive of cyst wall, and hypointense areas surrounding the cyst suggestive of perilesional edema. (B) T2-weighted axial scan showing the same cyst with cerebrospinal-isointense fluid, intramural nodule, hypointense rim suggestive of cyst wall, and hyperintense perilesional edema. (C) FLAIR axial section showing the same hypointense cyst with hyperintense scolex, thin cyst wall, and hyperintense perilesional edema. The presence of scolex is pathognomonic of neurocysticercosis.

Abbreviations: *MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.*

RESULTS

The patients who completed this study, the mean age of onset of symptoms was 8.4 years with a range of 4-15 years. 15 patients were female while 11 were male. All of these children were from a rural background and the parents were defense forces personal.

Seizure was the commonest presenting symptom in all the cases. Simple partial seizure was seen in 63.33% of cases at presentation, complex partial seizure in 37.77% (Table-2)

Table-1- Lesions, site, Type & nature

Total number of cases- 26 Lesion (number, location ,type)	Absolute number- -26
Type of lesion Single multiple	 26 18 08
Site of lesion Frontal Parietal Temporal, Occipital	 05 14 05 01
Nature of lesions Active Transitional Inactive	 17 06 05

Table 12: Clinical Profile of 26 patients completing the study

Symptoms at presentation	Total no=26 . (F-09, M-06)
Simple partial seizure	14(63.33%)
Complex partial seizure	3(13.33%)
Mixed	10(40%)
Headache	26(100%)
Vomiting	25(93%)
Neuropsychiatric presentation	3(13.33%)
Cranial nerve palsy	3(13.33%)
Fundal edema	5(20%)

Table 2. Table depicting treatment regimes used

Children who received single course of albendazole for 28 days (15 mg/kg) body weight	26
Children who received multiple courses of albendazole for 28 days (15 mg/kg) body weight	13
Children who received Ivermectin 10 mg daily for 15 days	5

Table 3. Table depicting response to treatment

Regression of lesions/reduction in size with albendazole single course 15 mg/kg body weight x 28 days	7
Regression of lesions/reduction in size with albendazole, multiple courses 15 mg/kg body weight x 28 days	13
Regression of lesions/reduction in size with ivermectin, 10 mg/day x15 days	5

Symptoms of raised intracranial tension like headache with or without vomiting was there in many of the cases at initial presentation. Children who dropped out, the CT scan brain revealed active lesion in three patients, transitional lesion in 02 cases. Total 26 lesions were detected from CT scan at the presentation, fourteen of which were noted in the parietal lobe, five each in the frontal lobe and temporal lobe and one in the occipital lobe. Five of them never turned up at six weeks of follow-up, rest all came for follow up regularly. Out of the 21 patients who attended after 6 weeks 13 had persistence of symptoms and increase in the number of lesions . They were subjected to repeat courses of albendazole (three cycles of 28 days each). Reassessment

was done with repeat MRI where eight patients responded but five patients showed new lesions. These patients were subjected to tab Ivermectin 10 mg/day daily for 15 days. None of these five children had any side effect of the drug.

At sixteen weeks of follow-up seizures disappeared in less than half of the cases included in this study. They were seizure free till the end of 24 months. To begin with all children presented with headache with or without vomiting, after 6 months of follow up ,headache was present in only three cases. This also resolved after 2 years. three cases had focal neurodeficit in the form of sixth cranial nerve paresis. At the end of two years of follow up this also recovered. Only three children had abnormal behavior in the form of violent attitude, irrelevant talking and forgetfulness and poor performance at school, but at the end of mean of 2 year they also recovered completely.

DISCUSSION-

Ivermectin in the treatment has not been published in India and most of the world except by J.A. Diazgrandos -Sanchez et al(1). We have used Ivermectin in five cases who failed to respond to multiple dosage of albendazole .The results have been very encouraging as the signs & symptoms improved and there was clearance of cysts on repeat CT scan.

No adverse effect were observed in any of the five cases. Partial seizure was the commonest presentation in our study unlike most other literatures worldwide.(3,7,14,15) Incidences of status epilepticus or convulsive crisis were less than 6% in our observation, Headache and vomiting were observed in 19 % and 11% in our study group. Singhi *et al* recorded almost 33% incidences of headache and vomiting.(3,5) Kalra and Sethi cited 44% incidences of headache because of raised intracranial tensions.(3,15)

Indian Academy of Pediatrics recommends at least 12-18 months of therapy for convulsion. Some authors also advocate continuation of anticonvulsants until the resolution of lesions(3,39) However, if seizures are recurrent or associated with calcified lesions treatment should be continued for 2-3 years before any attempt to wean from anticonvulsants. Carbamazepine and phenytoin are the commonly used anticonvulsants.

Albendazole in the treatment of pediatric neurocysticercosis in the context of resolution of active or transitional cysts and better clinical progress is a controversial subject. There are proponents of no albendazole therapy, short course therapy (7 days) and 28 days course of full dose albendazole therapy.(18) Use of multiple cycles of albendazole or even higher dosage 25 mg/kg is a established fact in treatment of neurocysticercosis. However, Albendazole or other anticysticercal drugs are contraindicated for spinal and ocular involvement as drug induced inflammation may result in irreversible damage to the respective organs. Ivermectin is the new promising drug in the management of neurocysticercosis. No studies for the trial of this drug are available in India except the present one.

CONCLUSIONS

Albendazole is effective in single as well as multiple ring enhancing lesions of neurocysticercosis but in severe and in disseminated cases ivermectin is very promising and without any side effects. Ivermectin was effective and lacked adverse events when treating these five patients resistant to conventional treatment with albendazole.

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