Arq Neuropsiquiatr 1996, 54(1): 82-93

SEVERE FORMS OF NEUROCYSTICERCOSIS

TREATMENT WITH ALBENDAZOLE

SVETLANA AGAPEJEV, MARIA DORVALINA DA SILVA**, ANETE K. UEDA****

ABSTRACT - Study of 22 patients with the severe form of neurocysticercosis treated with albendazole (ABZ) administered in 6 different schedules ranging from 15 to 30 mg/kg/day for 21 to 60 days. Dextrochloropheniramine and ketoprofen were the adjuvant drugs. Multiple symptoms were observed in 90.9% of patients. Intracranial hypertension was manifested in 90.9%. Hydrocephaly occurred in 86.4%. Evolution was satisfactory in 10 patients, 8 died and 4 had sequelae. Tomographic studies showed the appearance of an isolated IVth ventricle in 9 patients, after ventriculoperitoneal shunt, before ABZ treatment in 3 of them, during in 5 and after treatment in one. Median clinical follow-up duration was 10 months for the patients who died and 3-4 years for survivors. In 3 patients there was an increase in cyst size during the administration of the 15 mg/kg/day ABZ dose, which was not observed in any patient when the 30 mg/kg/day dose was used.

KEY WORDS: cysticercosis, neurocysticercosis, severe forms, treatment, albendazole, dextrochloropheniramine, ketoprofen.

Formas graves da neurocisticercose: tratamento com albendazol

RESUMO - Estudo de 22 doentes, com a forma grave de neurocisticercose, tratados com albendazol (ABZ), administrado em 6 diferentes esquemas, que variaram de 15 a 30 mg/kg/dia, durante 21 a 60 dias. A dextroclorofeniramina e o cetoprofeno foram as drogas coadjuvantes. Múltiplos sintomas ocorreram em 20 doentes. Hipertensão intracraniana foi manifestação mais comum em 20. Hidrocefalia foi detectada em 19. A evolução foi satisfatória em 45,4%, faleceram 36,4% e 18,2% ficaram com sequelas. Na evolução tomográfica apareceu IV° ventrículo isolado em 40,9%, após derivação ventriculoperitoneal, em 3 deles antes do tratamento com ABZ, em 5 durante e, em um, após o tratamento. A mediana estatística do período de seguimento clínico foi 10 meses para aqueles que faleceram e 3-4 anos para os sobreviventes. Em 3 doentes houve aumento no tamanho dos cistos durante a dose de 15 mg/kg/dia de ABZ, não observado na vigência de 30 mg/kg/dia.

PALAVRAS-CHAVE: cisticercose, neurocisticercose, formas graves, tratamento, albendazol, dextroclorofeniramina, cetoprofeno.

The manifestations of neurocysticercosis (NCC) may be classified into benign and malignant, or severe, forms[5, 14]. In the first, the parasites usually are parenchymatous, non-cisternal corticomeningeal or, to a lesser extent, ventricular. This form represents the clinical expression of *Cysticercus cellulosae*. The patients may be asymptomatic or report headache and epileptic syndrome as predominant symptoms. Skull computed tomography (CT) reveals small lesions compatible with

Division of Neurology, Department of Neurology and Psychiatry and Department of Pathology, Botucatu School of Medicine, State University of São Paulo (UNESP). *M.D., Ph.D., Assistent Professor(Neurology); **M.D., Assistent Physician (Neurology); ***M.D.,Ph.D., Assistent Professor (Pathology). Aceite: 17-setembro-1995.

Svetlana Agapejev, M.D., Ph. D. - Department of Neurology and Psychiatry - School of Medicine. UNESP - P.O. Box 540 - 18618-000 Botucatu SP - Brasil.

vesicles, calcifications and/or granulomas distributed throughout the cerebral parenchyma. Prognosis is good, the therapeutic response is rapid, and survival is long. In the severe form the parasites are generally located in a cisternal or ventricular subarachnoid position. Vasculitis is frequent. Hydrocephaly is the most common manifestation and may result both from basal arachnoiditis and from the presence of intraventricular cysticercosis. This is the clinical manifestation of *Cysticercus racemosus*. There are multiple symptoms or manifestations of intracranial hypertension (ICH). Prognosis is bad, the therapeutic response is slow and poor, and survival is short. The high morbidity and mortality rates of NCC, specially when the clinical manifestation is ICH, reflect the severity of this neuroparasitosis. Surgical and symptomatic treatment has been most often indicated for the severe forms, specially in the presence of ICH[6, 28].

The objective of the present study was to report on the evolution of 22 patients with the severe form of NCC treated with ABZ plus dextrochloropheniramine and ketoprofen as adjuvants.

CASES AND METHODS

Of the 138 patients with NCC treated with ABZ from January 1985 to February 1993, were selected 22 who presented the severe form of the disease. The criterion of severity was based on the classification of Camargo Lima[5] and Estañol[14], with some modifications (Table 1). Patients with inflammatory cells in the cerebrospinal fluid (CSF) but with no clinical signs of ICH, patients with a clinical and tomographic picture compatible with benign ICH (pseudotumor cerebri), patients with hydrocephaly, derived or not, but without signs of ICH, patients with manifestations of ischemic cerebral vascular episodes without ICH, patients with a small or questionable isolated increase of the IVth ventricle, and all patients who abandoned follow-up at the outpatient clinic for a period of less than 2 years after the end of the therapeutic schedule proposed were excluded from the study.

Among the 22 patients who participated in the study, 15 (68.2%) were males and 7 (31.8%) were females, ranging in age from 15 to 62 years. All subjects were white.

Among the immunologic reactions for cysticercosis performed at the CSF Laboratory from 1984 to 1993, the complement fixation reaction (CFR) was not performed in $^{1}/_{5}$ to $^{2}/_{5}$ of the tests, and the immunofluorescence (IFC) reaction was not performed in ¾ of the tests.

It was possible to submit all patients to a CT scan before and after ABZ treatment, but only 14 of them were submitted to a CT scan during treatment.

A definitive diagnosis of cysticercosis was made in 10 of the 22 patients (45.4%) by autopsy or biopsy.

A ventriculoperitoneal shunt (VPS) was implanted when clinical or tomographic evidence of hypertensive hydrocephaly was observed (19 patients). Except for 2 patients whose diagnosis of NCC was made postoperatively, craniotomy was indicated whenever maintenance of clinical signs and symptoms occurred (5 patients) after the end of ABZ treatment.

Patient evolution was studied in the presence of various schedules of ABZ treatment (Table 2) as an effort to define the best and efficacious dose. None of the patients was submitted to corticotherapy immediately before, during or after the use of ABZ. In cases in which clinical exacerbation of ICH occurred, no matter how mild, ketoprofen (150 to 300 mg/day), 20% manitol (5 to 10 ml/kg/day) and acetazolamide (250 to 500 mg/day) were administered at doses depending on the intensity of clinical manifestation. Patients with epileptic seizures received anticonvulsants. The antihistamine dextrochlorpheniramine (DCP) was administered (12 to 24 mg/day) to all patients and was maintained for 4 to 12 months after the end of the therapeutic schedule used. A new treatment with ABZ was performed for a period of 6 months (2 patients) to 1 - 2 years (2 patients) after the end of the first schedule due to the maintenance of clinical signs and symptoms.

The period of clinical observation covered the patients treated from January 1985 to February 1993, with follow-up at the outpatient clinic up to February 1995.

RESULTS

Clinical evolution

The clinical manifestations of NCC detected in the 22 patients with the severe form of the disease are listed in Table 3. Predominant symptoms were headache in 19 patients (86.4%), epileptic seizures in 14 (63.6%) and behavioral alterations with reduced memory or reasoning ability in 9 (40.9%). The association of headache and epileptic seizures was the major complaint in 7 cases (31.8%). None of the epileptic manifestations was primarily generalized. Among the neurological signs, papilledema was noted in 17 patients (77.3%), hyperreflexia in 13 (59.1%) and hemiparesis in 8 (36.4%). Cerebellar signs, cortical deafness, vestibular signs and amaurosis occurred in 2 patients each (9.1%).

Table 1. Distribution of the 22 patients with the severe form of neurocysticercosis according to the criteria of malignancy suggested by Camargo Lima and by Estañol, with some modifications.

Classification criteria	Authors	Nº of patients
Multiple symptoms	E	20
Presence of ICH	E / CL	19
Presence of hydrocephaly	E	19
Need for VPS	A	17
Presence of epilepsy	E	14
Need for VPS revision	A	9
Behavioural alterations	A	5
Presence of localizing signs	E	3
Ischemic cerebrovascular episode	A	2
Survival: 2 - 4 years	CL	2
< 2 years	CL	7
Typical CSF syndrome[28]	A	14
Pleocytosis	E	13
Racemose cysts	A	11
Isolated IVth ventricle	A	10
Parenchymatous cysts + infarction	E	3
Giant supratentorial cysts	E	1
Multiple granulomas + edema	E	0
Arachnoiditis + infarction	E	0

E, criteria adopted by Estañol et al.[14]; CL, criteria adopted by Camargo Lima[5]; A, criteria introduced by the authors of the present study; ICH, intracranial hypertension; VPS, ventriculoperitoneal shunt.

During treatment, severe ICH was observed only in one patient (Case 15) and hydrocephaly occurred in 2 (Cases 1 and 15, both with a history of more than one hospitalization due to meningitis). Epileptic seizures did not increase during ABZ treatment, but rather decreased in intensity and frequency.

All patients with hydrocephaly were submitted to VPS implantation at different times in relation to the therapeutic schedule with ABZ (Table 4). One patient (Case 13) was submitted to exeresis of a cystic tumor (biopsy = racemose cysts) in the right sylvian region before ABZ treatment (performed in another service) and 3 years after ABZ treatment for the removal of a left occipital cystic lesion (biopsy = degenerated and fibrotic cysticercus). Four patients (Cases 8, 9, 12, 19) were submitted to surgery on the posterior fossa to reach the IVth ventricle, where arachnoiditis of varying intensity was observed in 3 of them (Cases 9, 12, 19). In the case 8 who had been submitted to surgery before ABZ treatment, the cysts were racemose and were intact, and in another (Case 19), submitted to surgery approximately 10 months after the end of ABZ treatment, the cysts were degenerate. Of these 4 patients, only one survived (Case 8), although with paraparesis as sequelae.

The evolution (Table 2) was good in 45.5% (10:22) of patients, who were able to fully assume their normal activities. In these patients, the epileptic seizures were controlled with very low doses of anticonvulsants. The neurologic sequelae limited the normal activities of 18.2% patients (4:22). Patient mortality was 36.4% (8:22) : 3 (37.5%) of them (Cases 1, 2, 3) died during treatment with 15 mg/kg/day ABZ, and 5 (62.5%) after the end of treatment. Of these 5 patients, 80% (4:5) died within less than 36 months and only one (Case 9) died 6 years after the end of ABZ treatment. Of the 8 patients who died, 5 (62.5%) were males and 3 (37.5%) were females.

The racemose form of cysticercosis was observed in 11 patients (50%). Evolution was good in 5 of these patients (45.5%) and fatal in 6 (54.5%). One of the patients (Case 14), who had a good evolution, presented a new picture of ICH and meningoencephalitis, now associated with hypertensive hydrocephaly due to possible reinfection, again in the form of racemose cysticercosis, 5 years after the last treatment with ABZ (Fig 1). Of the 3 patients with multiple racemose cysticercosis who survived, one presented an increase in cyst size with the dose of 15 mg/kg/day ABZ, with full regression after a new therapeutic schedule of 30 mg/kg/day for 60 days (Fig 3, Case 10).

Table 2. Distribution of the 22 patients with the severe form of neurocysticercosis according to schedule of albendazole treatment, general characteristics (sex, age) and clinical evolution after treatment.

ABZ dose	Case	Sex	Age	Evolution		
mg/kg/day			(years)	good	sequelae	death
15 during:18 days	1	M	34	-	-	ICH
21 days	2	F	62	-	-	ICH
15 days	3	F	30	-	-	ICH
15 → 20 → 25	4	M	31	yes	-	-
21 days each dose	5	M	26	-	-	BCP
	6	M	30	yes	-	-
	7	M	34	yes	-	-
15 → 20	8	M	28	-	paraparesis	-
21 days→30 days	9	F	56	-	-	PEb
	10	M	53	yes	-	-
	11	M	37	yes	-	-
	12	M	15		-	ICH
15 → 30	13	M	46	yes	-	-
21 days →30 days	14	M	39	yes	-	-
	15	M	38	yes	-	-
	16	F	24	-	paraplegia	-
	17	F	44	-	hemiparesis	-
15 → 30	18	M	38	-	-	BCP
21 days → 60 days	19	M	30	-	-	V
	20	F	30	yes	-	-
	21	F	67	-	dementia	-
30 during 60 days	22	M	37	yes	-	-

M, male; F, female; good, evolution without sequelae + return normal life; sequelae, presence of sequelae that partially or fully limited routine activities; ICH, intracranial hypertension; BCP, bronchopneumonia; PEb, pulmonary embolism; V, ventriculitis; →, an one week interval without albendazole.

Ventricular localization of the parasites was suggestive in 10 patients (45.4%), on the basis of the appearance of an isolated IVth ventricle in 8 of them, and as observed during surgery in 2 (Cases 8, 19). Of these, 3 (30%) had a good evolution, 3 (30%) died and 4 (40%) evolved with sequelae (Table 2). In one of the patients with an isolated IVth ventricle (after VPS), the appearance of the angulo-ponto-cerebellar region syndrome was observed during treatment with 15 mg/kg/day ABZ, with regression within approximately 2 years after the use of 30 mg/kg/day ABZ for 60 days (Fig 3; Case 20).

Of the 8 patients who died, 3 (Cases 2, 5, 12) were not submitted to autopsy, although their deaths were clinically attributed to pulmonary infection or ICH. Of the 5 patients submitted to autopsy, 40% (2:5) had pulmonary problems as the causa mortis, and in the remaining ones (3:5), the direct cause of death was ICH. Autopsy of the cases who had used a maximum of 15 mg/kg/day ABZ (Cases 1, 2) revealed intact and degenerating cysts (Fig 2; Case 1). In the patients who had used 30 mg/kg/day of the drug for 60 days, the cysts were degenerated or calcified (Fig 2; Case 18).

The period of clinical observation of these 22 patients with the severe form of NCC up to February 1995 ranged from 2 to 10 years (median = 3-4 years) for survivors and from 15 days to 6 years (median = 10 months) for those who died. The onset of the first symptoms ranged from 1 month to 26 years (median = 2 years) and

Table 3. Clinical and laboratory characteristics of the 22 patients with the severe form of neurocysticercosis, treated with albendazole.

Case	Clinical picture	VPS	CSF	CT				
				Rc	Hc	iIVth	pc	cc
1	ICH + ME + EP	1 + 1r	syndr	2	during	-	-	-
2	ICH + EP	1	syndr	1	before	-	>2	-
3	ICH + EP + BA	1 + 1r	syndr	3	before	-	-	-
4	ICH + EP	1 + 2r	syndr	-	before	-	-	-
5	ICH + EP	1 + 1r	syndr	-	before	-	>2	-
6	ICH + EP + BA	1 + 2r	syndr	-	before	-	-	-
7	ICH + EP	-		-	-	-	1 giant	-
8	ICH	1		-	before	post-VPS	-	-
9	ICH + ME	1 + 1r	syndr	-	after	post-VPS	-	several
10	ICH + EP	1	syndr	2	before	-	>2	-
11	EP	-		1	-	-	-	several
12	ICH + ME	2 + 6r	syndr	-	after	post-VPS	-	-
13	EP	-		2	-	-	>2	several
14	ICH + ME	1	syndr	1	after	-	>2	several
15	ICH + ME	1 + 1r	syndr	-	during	post-VPS	-	-
16	ICH	1		-	before	post-VPS	-	-
17	ICVE + EP	1		-	before	post-VPS	-	several
18	ICH + EP + BA	1 + 1r	syndr	2	before	-	>2	several
19	ICH + EP + BA	1 + 2r	syndr	2	after	-	>2	-
20	ICH + ME	1		-	before	post-VPS	-	-
21	ICH + EP + ICVE	1		-	before	post-VPS	-	-
22	ICH + ME + BA	1	syndr	2	before	post-VPS	-	-

ICH, intracranial hypertension; EP, epilepsy; ME, meningoencephalitis; BA, behavioural alteration; ICVE, ischemic cerebrovascular episode; VPS, ventriculoperitoneal shunt; r, number of revisions of the VPS system CSF, cerebrospinal fluid; syndr, typical CSF syndrome of neurocysticercosis[28]; CT, skull computorized tomography; Rc, racemose cysts; Hc, appearance of hydrocephaly in relation to the albendazole treatment; iIVth, appearance of an isolated fourth ventricle; pc, parenchymatous cysts; > 2, more than 2 cysts; cc, calcifications.

clinical worsening ranged from 5 days to 54 months (median = 2 months). Survival time (Table 5) either starting from the first symptoms or from clinical worsening and/or treatment with ABZ was more than 4 years, including one death in 59.1% of patients.

Evolution of CSF

Examination of the CSF of punctured patients showed variable alterations (Table 6) depending on the time of collection.

Before ABZ treatment, negativity of immunologic reactions was observed in 2 cases. CSF exacerbation occurred in 50% (9:18) of the patients submitted to CSF puncture before, during and after ABZ treatment.

During ABZ treatment, cellularity increased in 33.3% (6:18) of the patients, eosinophils were detected in 33.3% (6:18) of the patients, 4 of whom died, plasmocytes were observed in 27.8% (5:18), 4 of whom died. Hyperproteinorrachia was detected in 38.98% (7:18) and hypoglucorrachia in 38.9% (7:18). Of the immunologic reactions for cysticercosis, CFR became positive in 15.4% (2:13) of the examinations and IFC in 42.9% (3:7).

Table 4. Distribution of the 16 patients with the hydrocephalic form of neurocysticercosis treated with albendazole, according to the ventriculoperitoneal shunt (VPS) implantation time in relation to the therapeutic schedule with albendazole and to the number of deaths.

VPS implantation time	Nº of patients	Nº of deaths
Before	10	2 (20%)
During	4	3 (75%)
After	2	1 (50%)
Total	16	6 (38%)

Table 5. Distribution of the 22 patients with the severe form of neurocysticercosis by onset of first symptoms, clinical worsening and occurrence of death in relation to time.

Time	Onset of 1st symptoms	Clinical worsening*	Deaths
> 4 years	13 (59.1%)	13 (59.1%)	1 (12.5%)
2 - 4 years	5 (22.7%)	2 (9.1%)	0
< 2 years	4 (18.2%)	7 (31.8%)	7 (87.5%)

**The clinical worsening was coincident with the beginning of albendazole treatment.*

After the end of ABZ treatment, in a variable time interval, the last CSF samples in the medical records showed decreased cellularity in all patients, an increase in eosinophilorrachia in 16.7% (3:18), 2 of whom died, elevation of proteinorrachia in 44% (8:18) and a decrease in glucorrachia in 27.8% (5:18). The only patient who presented plasmocytorrachia also died. As to the reactions for cysticercosis, CFR remained positive in 46.2% (6:13) and IFC became positive in 25% (2:8).

Tomographic evolution

Skull CT before ABZ treatment was altered in all patients. The lesions observed were associated with one another in 86.4% (19:22) and were single in 13.6% (3:22). Among these 3 patients with a single lesion, diffuse cerebral edema occurred in 2 (Cases 12, 15) and a single giant cyst in one (Case 7). Among the associated lesions, hydrocephaly was the most common (16:22), followed by the presence of racemose cysts (11:22). These, in turn, were multiple (2 to 3) in 81.8% of cases (9:11) and localized in the sylvian region (unilateral in 5 patients and bilateral in 3), in base cisternae (7 patients), in the median frontal region (Cases 1, 3, 18) and around the brain stem (Case 1). The topography of the racemose cysts present at a single location was left parietal lobe(Case 11) and in the IVth ventricle (Case 8). Calcifications (6:22) and multiple parenchymatous cysts (8:22) were associated with several aspects of the lesion and did not appear as single lesions.

During treatment with ABZ, CT showed that the parenchymatous cysts decreased in size or disappeared during the final phase of the 15 mg/kg/day ABZ schedule. Hydrocephaly decreased spontaneously in 1 patient (Case 14), appeared in 3 (Cases 1, 2, 15) and worsened in 1 (Case 22). An isolated IVth ventricle occurred in 2 patients without previous hydrocephaly and in 3 patients with previous hydrocephaly corrected by VPS. Cerebral edema appeared in 1 patient, remained unchanged in 4 and regressed in 3. The number of calcifications increased in 2 patients and remained unchanged in the other 6. Of the 11 patients with racemose cysts, only 5 were submitted to CT during treatment, and an increase in the cysts was observed in 2 of them (Fig 2; Case 1, Fig 3; Case 10). In a patient with VPS due to previous hydrocephaly, a previously undetected giant cystic lesion occurred in the left angulo-ponto-cerebellar region in addition to an isolated IVth ventricle (Fig 3; Case 20).

At varying periods of time after ABZ treatment, the last skull CT showed that 4 patients (Cases 4, 5, 6, 19) maintained universal hydrocephaly despite VPS. An isolated IVth ventricle appeared in 1 patient (Case 12) and remained in 5 (Cases 8, 16, 17, 20, 21). Parenchymatous cysts were no longer observed in any patient. Diffuse cerebral edema was unchanged in one (Case 19). New calcifications appeared in 3, including 2 with the single racemose form. The multiple racemose cysts disappeared.

Table 6. Distribution of the patients with the severe form of neurocysticercosis treated with albendazole, according the observed alterations on cerebrospinal fluid (CSF) and the period of use of the cysticide.

Period	Before			During			After		
CSF alterations	nº	Δ	M	nº	Δ	M	nº	Δ	M
Cells / mm³ ↑	15	15 - 680	128	13	20 - 760	54	9	12 - 170	48
% neutrophils	11	1 - 96	3	5	1 - 63	7	4	2 - 26	4
% eosinophils	13	2 - 65	6	10	1 - 63	6	7	1 - 37	10
% plasmocytes	9	1 - 25	5	5	1 - 14	3	3	2 - 4	3
Proteins ↑ mg/100ml	18	30 - 510	85	16	56 - 3200	119	17	29 - 360	138
Glucose ↓ mg/100ml	11	3 - 39	24	13	0 - 36	13	11	3 - 37	31
Normal CSF	2			3			2		
Not performed	2			3			3		
Total	20			19			19		

nº· number of patients; Δ, lower and higher value verified; M, statistical median; ↑, increase; ↓, decrease. Note- Lymphocytes percentages variable depending on the percentages values of other founded cells. No macrophage presence was verified.

DISCUSSION

As old as the knowledge of the existence of cysticercosis (Aristophanes, ca. 400 b.C.)[21] are the attempts at treatment of the teniasis/cysticercosis complex. Treatment of teniases with an extract of male wild fern roots (Theophrastus, ca. 330 b.C.)[20] was only replaced with synthetic antiparasitic agents in 1960[20]. When an option must be taken between surgical indication and pharmacological therapy[4,6,12,18,27,30,33], controversy still exists, specially when the cyst is of ventricular or subarachnoid localization[9,11,19,24,29]. Even so, a common consensus can be reached about the fact that the therapeutic conduct should be individualized for each patient[1,8,9,33], since the serum and CSF levels of cysticides present a wide individual variation[17] not related to age, sex, presence of an inflammatory process or therapeutic efficacy, but depending on the individual pharmacokinetic differences.

However, when pharmacologic therapy is chosen, further controversy arises, now related to the concentration of the cysticide, to time of treatment, localization of the parasite and clinical form of manifestation[1,3,11,13,27,31,33]. On the other hand, there are no longer any doubts about the fact that ABZ is more effective than praziquantel[8,26,31], also because it better penetrates the subarachnoid space[17].

Although technological advances such as ELISA in CSF and neuroimaging became available in our service only in 1994, we only included in our series the patients treated until 1993 because we felt that a follow-up of less than 2 years may give a falsely favorable impression, or even an unfavorable impression, as well demonstrated by the evolution of our patients, among whom there was only one death after this follow-up period (Case 9). Furthermore, the appearance of fatal episodes (Cases 1, 2, 3, 5, 12, 18, 19) or of complications (Cases 10, 13, 19, 21) is more frequent during this period[1,5,6,14,22].

A point common to most reports on the treatment with cysticides, either albendazole or praziquantel, is the exclusion of patients with signs of ICH[3,27,31] and the diversification of treatment schedules. The presence of localizing neurological symptoms has also been a criterion for exclusion of pharmacological treatment[4,6,27,30]. However, for us these were the criteria for patient inclusion in the present study. Thus, an attempt at comparing our data with those of any other study in the literature becomes quite difficult. Consequently, the conclusions can only be personal, although based on rigorous observation over a period of more than 10 years.

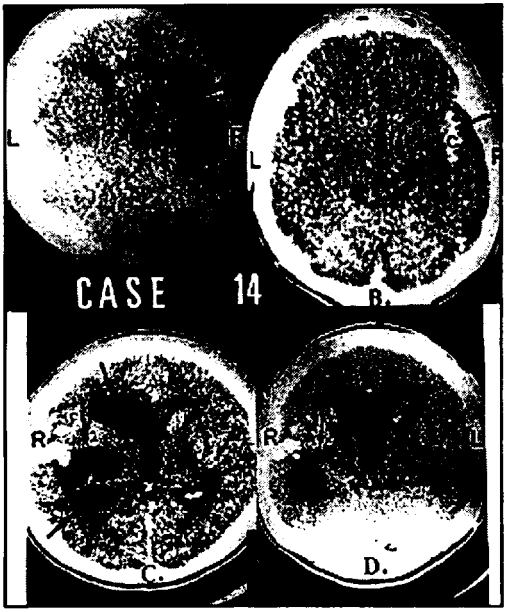

Fig 1 Case 14. A (before treatment with ABZ): cystic lesion surrounded by an area of edema (arrow) showing a deviation of the interhemispheric midline by the mass effect. B (24 months after the use of ABZ): calcifications (c, arrow) at the site of the lesion shown in A. C (4 years after ABZ): cystic lesions (arrows) close to the lesion described in A (recurrence?). D (2 months after the use of 30 mg/kg/day ABZ for 60 days, as a 2nd treatment): observe the reduction of cysts and the increase in hydrocephaly.

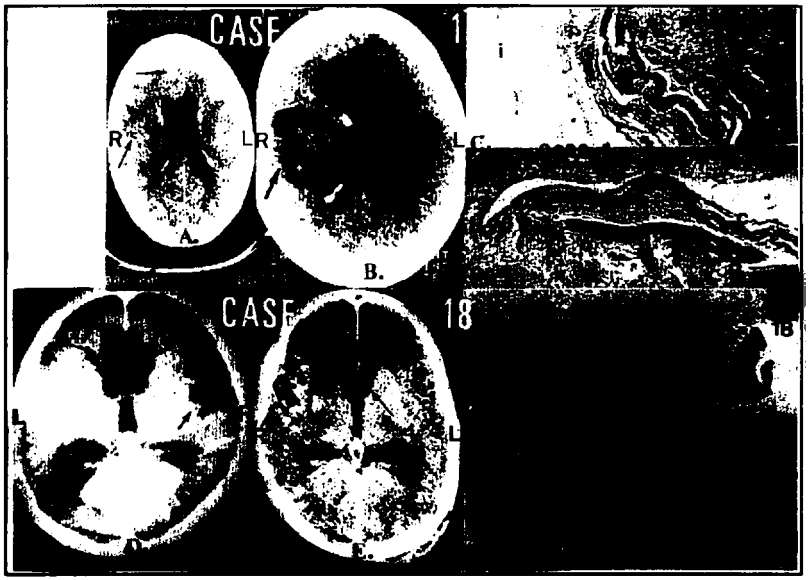

Fig 2. Case 1. A (before treatment with ABZ): questionable cystic lesions (arrows) in a paramedian frontal region and in a right sylvian region. B (during treatment with 15 mg/kg/day ABZ): observe the increase in the lesions. C: aspect of the various cysticerci detected at autopsy, in different stages of degeneration. [i, intact; d, degenerating; c, beginning of calcification; p, parenchyma. Staining with hematoxylin-eosin; original magnification 31x. R, right; L, left.] Case 18. D (before ABZ treatment): note the similar topography of the parasites compared to Case 1. E (2 days after the end of treatment with 30 mg/kg/day ABZ for 60 days): the cystic lesions are reduced (arrows) and frontal areas suggesting encephalic infarction are present (la). F: uniform aspect of degeneration of the cysticerci (Cs, in green) detected at autopsy. [fb, fibrosis; v (arrow), vasculitis; p, parenchyma. Staining with CALLEJA; original magnification 6.6x. R, right; L, left.].

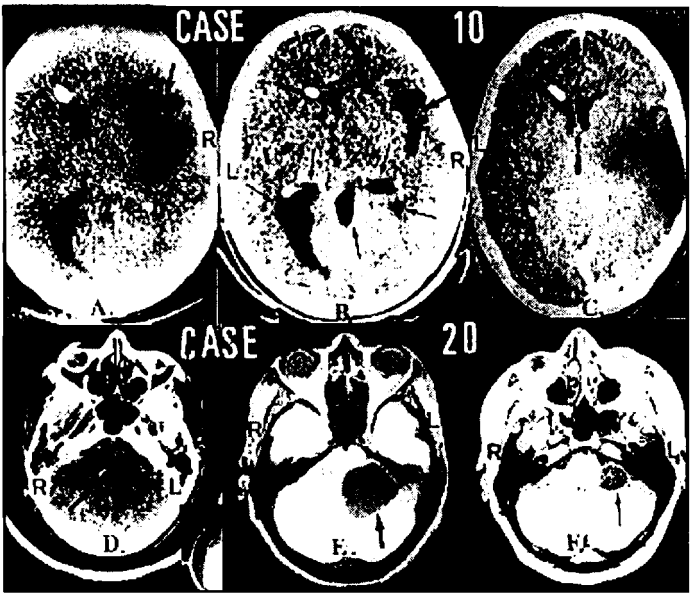

Fig 3. Case 10. A (before the 1st ABZ treatment): multiple hypodense lesions (arrow) suggesting racemose cysticercosis. B (5 months after the 1st ABZ treatment): observe the appearance of cysts not detected in A (arrows) and a decrease of the cyst previously present. C (28 months after the use of 30 mg/kg/day ABZ for 60 days): disappearance of the cysts.[R, right; L, left.] Case 20, D (before ABZ treatment): a medium to small isolated IVth ventricle (arrow), apparently without lesions in an angulo-ponto-cerebellar region. E (during the 3rd week of 15 mg/kg/day ABZ): observe the appearance of a cystic lesion in this region (arrow). F (20 months after the ABZ schedule): an encapsulated cystic area continues to be present in the same region, although smaller in size. [R, right; L, left].

Cases 1 and 18 (Fig 2), very similar in clinical, CSF and tomographic terms, differed in the ABZ schedule used, in the causa mortis and in the aspect of the cysticerci detected. In Case 1, who received doses of up to 15 mg/kg/day for a shorter period of time, the immediate cause of death was ICH and the parasites were intact and in different stages of degeneration; in addition there was an increase in racemose cysts during treatment. In contrast, in case 18, who received higher doses and for longer periods of time, the immediate cause of death was not neurological and all parasites were in an equally advanced phase of degeneration. On the other hand, one should keep in mind the good evolution of Cases 20 (Fig 3) and 22, and of Case 10, who presented an increase of the cysts while taking a lower dose of the drug over a shorter period of treatment; further treatment was needed, and only then did the patient show good recovery (Fig 3).

The study of these patients supports the use of high doses of ABZ over a prolonged period of time, especially in severe cases, although Del Brutto[10] and Sotelo[27] stated that better results are not obtained with higher doses or longer treatment.

The presence of hydrocephaly is, of itself, sufficient to qualify as severe the form of manifestation of cysticercosis in the CNS[14]. And when it occurs as the first manifestation, the prognosis is worse[32]. This was clearly demonstrated by our series, in which all patients who died had hydrocephaly.

With respect to the best time for the installation of a ventricular CSF shunt, we believe that signs of hypertensive hydrocephaly should not be the only indicative factors. In NCC, even when

clinical manifestations of ICH are absent but tomographic signs of periependymal edema are present, hydrocephaly should be relieved as soon as possible and pharmacological treatment should be instituted immediately after (Table 4). This conduct has greatly improved patient prognosis and decreased the number of revisions of the shunt system.

On the other hand, when an isolated IVth ventricle occurred, our experience in approaching the posterior fossa with or without the previous installation of a VPS system was disastrous (Cases 9, 12, 19). This highly negative experience may perhaps have been due to the fact that surgery was carried out after pharmacological treatment in all 3 patients. This treatment, by being effective, led to arachnoiditis which, of itself, is a contraindication of an approach to the IVth ventricle[6, 24]. Perhaps, if this approach had been carried out before clinical treatment, the evolution might have been different. However, the hypertensive hydrocephaly of these patients was detected only after the use of ABZ, representing one more factor of prognostic worsening. In the remaining cases with an isolated IVth ventricle, VPS was performed before ABZ treatment, except for Case 15 whose VPS was installed during clinical treatment. After 4-5 years had passed without the need for revision of the VPS system, spontaneous regression of the IVth ventricle occurred in this patient (Case 15). The remaining patients with this type of ventricular lesion have not yet completed 4 years of follow-up at the outpatient clinic.

Although men presented a higher incidence of the severe form of NCC (68.2%), a fatal evolution or an evolution with sequelae was more common among women. Among female patients, 42.8% (3:7) died or survived with sequelae at the same proportion. One woman (Case 16) also had the spinal form of cysticercosis. This prevalence of the pathology in the male sex and the higher fatal outcome among women have been widely discussed in the literature[2,21].

In 1984, when we started the study of ABZ in NCC, we used to combine dexamethasone as an adjuvant in the first 3 patients. However, severe uncontrollable complications such as arterial hypertension and diabetes which arose in these 3 patients led to the need to replace the glucocorticoid with the antihistamine. This replacement was based on knowledge about the immunoallergic mechanisms[7, 15] of the manifestations of this neuroparasitosis and on the notion that glucocorticoids do not inhibit the antigen-antibody reaction and the consequent release of histamine and other active substances[22], whereas antihistamines compete with histamine in their receptors and therefore impair its action[16]. Thus, encouraged by the good clinical response observed in the first 3 patients and those who followed, we abolished the corticoid and introduced the antihistamine as an adjuvant in the cysticidal schedule.

Ketoprofen (KP), a non-hormonal anti-inflammatory agent (NHAI), was first used only as an analgesic. However, in some patients presenting pleocytosis and headache, we observed, in addition to the decrease or disappearance of headache, a discrete decrease in CSF cellularity. In view of this possible passage through the blood brain barrier[23], KP is being administered as a first-choice drug in the presence of headache, before manitol, in the presence or absence of concomitant pleocytosis in the CSF, with good results.

Replacement of corticosteroids with the routine use of an antihistamine and an NHAI over the last 10 years was only unable to prevent the onset of signs of severe and fatal ICH in 3 patients (Cases 1, 2 and 3), all of them with a previous history of clinical worsening in the presence of corticotherapy. In the remaining Cases, clinical exacerbation occurred between the 1st and 5th day of ABZ use and did not last more than 3 days, regressing satisfactorily with the use of KP, acetazolamide and manitol. Although it is known[34] that epileptic seizures are better controlled after the use of ABZ in patients with parenchymatous cysts, we noted that in patients with the severe form of cysticercosis this control is even higher during the use of ABZ, suggesting a possible antiepileptic action of the cysticide. However, experimental studies are needed to confirm this clinical observation.

The study of the CSF of these patients with the severe form of NCC suggests that elevations above the statistical median of the percentage of eosinophils and plasmocytes during and after ABZ treatment may be considered as factors for a poor prognosis, since this worsening of the prognosis

does not occur when these percentages decrease or do not increase during and after the use of the cysticide. In other words, the more prolonged the immunoallergic response to treatment, the worse the prognosis seems to be. Consequently the study of the CSF in clinical treatment is of high prognostic value in the evaluation of the survival of these patients.

We do not think that cyst number or size is important to define the time of treatment, as suggested in the literature[33]. The localization and mainly the form of presentation of these cysts seems to better define the therapeutic schedule to be used.

Our observations over a period of more than 10 years of ABZ treatment of the severe form of NCC permits us to suggest that:

1) the therapeutic conduct, clinical or surgical, should be individualized;

2) in the presence of hypertensive hydrocephaly, even without clinical signs of ICH, evolution is better when the patients are submitted to a ventricular CSF shunt immediately before the specific pharmacological schedule;

3) the approach to the posterior fossa, specifically to the IVth ventricle, is contraindicated after cysticidal treatment;

4) the presence, or the simple suspicion, of parenchymatous cysticerci appears to render a little more benign the clinical course of the patients;

5) the simple parenchymatous forms respond well and rapidly to a dose of 15 mg/kg/day of ABZ for a period of 20-30 days;

6) the multiple racemose forms of ventricular and/or subarachnoid localization seem to evolve better when treated with 30 mg/kg/day of ABZ for 60 days;

7) when the presence of racemose cysts of any localization or of single cysts of ventricular localization and mainly in the IVth ventricle is suspected or confirmed, the dose of 15 mg/kg/day should be avoided to permit the short- or long-term growth of these cysts probably by slowing down their degeneration process;

8) in the patients studied, the 30 mg/kg/day dose of ABZ, in combination with DCP and KP, did not cause short- or long-term side effects and minimized the effects of clinical and laboratory exacerbation commonly occurring during the first week of cysticidal treatment;

9) since these are severely ill patients, a minimum time of 4 years of follow-up is needed to reach any conclusions;

10) these cases require constant rigorous vigilance since, no matter how small an interfering event may be, intervention should be as prompt as possible to insure a better evolution.

Note - Since February 1993, for the severe forms of NCC we have been using a schedule of 30 mg/kg/day ABZ for 30 days to not racemose forms or 60 days to the racemose forms, whether the cysts are of ventricular, subarachnoid or parenchymal localization.

Acknowledgments - The authors are grateful to the Discipline of Tropical Diseases, specially in the person of Professor Domingos Alves Meira, M.D., for their collaboration and encouragement that permitted the start and the maintenance of the study on treatment of neurocysticercosis. They are also grateful to Mrs. Elettra Greene for revising the English text.

REFERENCES

1. Agapejev S, Meira DA, Barraviera B, Machado JM, Pereira PCM, Kamegasawa A, Ueda AK. Neurocysticercosis: treatment with albendazole and dextrochloropheniramine. Trans R Soc Trop Med Hyg 1989; 83:377-383.
2. Agapejev S. Incidence of neurocysticercosis at the University Hospital, Faculty of Medicine of Botucatu, State University of São Paulo (Abstract). Thesis, Ribeirão Preto, 1994. Arq Neuropsiquiatr 1995; 53: 170-171.
3. Andrade AS Fº, Galdino GS, Mattos GR, Moreno OA, Ancilon M, Rollemberg JC Fº. Albendazol em neurocisticercose: relato de 5 casos. Rev Bras Neurol 1991; 27:115-120.
4. Araújo LP, Silva MN. Formas císticas da neurocisticercose: considerações sobre o tratamento cirúrgico. Arq Bras Neurocirurg 1994, 13:173-180.

5. Camargo-Lima JG. Cisticercose encefálica: aspectos clínicos. Thesis, Escola Paulista de Medicina São Paulo, 1966.
6. Colli BO, Martelli N, Assirati JA Jr, Machado HR, Salvarini CP, Sassoli VP, Forjaz SV. Cysticercosis of the central nervous system: I.Surgical treatment of cerebral cysticercosis - a 23 years experience in the Hospital das Clínicas of Ribeirão Preto Medical School. Arq Neuropsiquiatr 1994; 52:166-186.
7. Correa D, Dalma D, Espinoza B, Plancarte A, Rabiela MT, Madrazo I, Gorodezky C, Flisser A. Heterogeneity of humoral immune components in human cysticercosis. J Parasitol 1985; 71: 535-541.
8. Cruz M, Cruz I, Horton J. Albendazole versus praziquantel in the treatment of cerebral cysticercosis : clinical evaluation. Trans R Soc Trop Med Hyg 1991; 85:244-247.
9. Davis LE, Kornfeld M. Neurocysticercosis: neurologic, pathogenic, diagnosis and therapeutic aspects. Eur Neurol 1991; 31:229-240.
10. Del Brutto OH, Sotelo J. Neurocysticercosis:an update. Rev Infect Dis 1988; 10:1075-1087.
11. Del Brutto OH, Sotelo J. Albendazole therapy for subarachnoid and ventricular cysticercosis. J Neurosurg 1990; 72:816-817.
12. Del Brutto OH, Sotelo J, Aguirre R, Díaz-Calderón E, Alarcón JA . Albendazole therapy for giant subarachnoid cysticerci. Arch Neurol 1992; 49:535-538.
13. Escobedo F, Penagos P, Rodriguez J, Sotelo J. Eficacia de albendazol en el tratamiento médico de la cisticercosis cerebral: estudio controlado tomográficamente. Invest Méd Internat 1988, 15(Supl): 23-26.
14. Estañol B, Corona T, Abad P. A prognostic classification of cerebral cysticercosis : therapeutic implications. J Neurol Neurosurg Psychiatry 1986; 49:1131-1134.
15. Flisser A, Perez-Monfort R, Larralde C. The immunology of human and animal cysticercosis : a review. Bull WHO 1979; 57:839-856.
16. Gilman AG, Goodman LS, Rall RW, Murad F. The pharmacological basis of therapeutics.Ed 7. New York: Macmillan 1980: 627-629.
17. Jung H, Hurtado M, Sanchez M, Medina MT, Sotelo J. Plasma and CSF levels of albendazole and praziquantel in patients with neurocysticercosis. Cl Neuropharmacol 1990; 13:559-564.
18. Livramento JA, Machado LR, Spina-França A. Immunology of neurocysticercosis. In Fejerman N, Chamoles NA (eds). New trends in pediatrics neurology. Amsterdam: Elsevier, 1993; 307-312.
19. Lobato R, Lamas E, Portillo JM, Roger R, Esparza J, Rivas JJ, Muñoz MJ. Hydrocephalus in cerebral cysticercosis: pathogenic and therapeutic considerations. J Neurosurg 1981; 55:786-793.
20. Malagón F. Elementos del binomio taeniasis/cisticercosis: una sintesis. In Flisser A, Malagón F (eds). Cisticercosis humana y porcina: su conocimiento e investigación en México. Ciudad de México: Limusa, 1989: 3-6.
21. Moreira EL. Neurocisticercose. Clínica, patologia e tratamento da forma ventricular bloqueante. **Thesis,**. Faculdade de Medicina de Ribeirão Preto. Ribeirão Preto, 1984.
22. Miller O. Curso de corticoterapia. J Bras Med 1978. (ed esp): 7-11.
23. Netter P, Lapique F, Bannwarth B, Tamisier JN, Thomas P, Royer RJ. Diffusion of intramuscular ketoprofen into the cerebrospinal fluid. Eur J Clin Pharmacol 1985; 29:319-321.
24. Salazar A, Sotelo J, Martinez H, Escobedo F. Differential diagnosis between ventriculitis and fourth ventricle cyst in neurocysticercosis. J Neurosurg 1983; 59:660-663.
25. Sotelo J, Marin C. Hydrocephalus secondary to cysticercotic arachnoiditis. a long-term follow-up review. J Neurosurg 1987; 66:686-689.
26. Sotelo J, Escobedo F, Penagos P. Albendazole vs praziquantel for therapy for neurocysticercosis: a controlled trial. Arch Neurol 1988: 45:532-534.
27. Sotelo J, Del Brutto OH, Penagos P, Torres B, Rodriguez-Carbajal J, Rubio-Donnadieu F. Comparison of therapeutic regimen of anti-cysternal drugs for parenchymal brain cysticercosis. J Neurol 1990; 237:69-72.
28. Spina-França A. Síndrome liquórica da neurocisticercose. Arq Neuropsiquiatr 1961; 19:307-314.
29. Spina França A. Cysticercosis of the central nervous system. In Chopra JS et al (eds). Advances in neurology. Amsterdam Elsevier, 1990: 283-291.
30. Stepien L, Choróbski J. Cysticercosis cerebri and its operative treatment. Arch Neurol Psychiat 1949; 61:499-527.
31. Takayanagui OM, Jardim E. Therapy for neurocysticercosis. Comparison between albendazole and praziquantel. Arch Neurol 1992; 49:290-294.
32. Torrealba G, Del Villar S, Tagle P, Arriagada P, Kase CS. Cysticercosis of the central nervous system: clinical and therapeutic considerations. J Neurol Neurosurg Psychiatry 1984; 47:784-790.
33. Vasconcelos D, Cruz-Segura H, Mateos-Gomez H, Zenteno-Alanis G. Selective indications for the use of praziquantel in the treatment of brain cysticercosis. J Neurol Neurosurg Psychiatry 1987; 50:383-388.
34. Vazquez V, Sotelo J. The course of seizures after treatment for cerebral cysticercosis. N Engl J Med 1992; 327: 696-701.