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	complete response emphasizes the need to develop more efficacious pharmacologic regimens, the association of albendazole sulfoxide concentrations with treatment response highlights the importance of optimizing existing therapeutic regimens. Additionally, the association of treatment response with parasite volume emphasizes the importance of early diagnosis.

Factors associated with cysticidal treatment response in extraparenchymal neurocysticercosis

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Abstract

Extraparenchymal neurocysticercosis is the most severe form of cysticercosis and response to treatment is suboptimal. We sought to determine how demographic and clinical characteristics, and albendazole sulfoxide concentrations were related to cysticidal treatment response. We conducted a longitudinal study of 31 participants with extraparenchymal vesicular parasites who received the same treatment, albendazole 30 mg/kg/day for 10 days with dexamethasone 0.4mg/kg/day for 13 days, followed by a prednisone taper. Response to treatment was determined by parasite volumes before and 6 months after treatment. Eight participants (25.8%) had a complete treatment response, 16 (51.6%) had a treatment response >50% but less than 100%, and 7 (22.6%) had a treatment response <50%. Complete treatment response was significantly associated with higher concentrations of albendazole sulfoxide (p=0.032), younger age (p=0.032), fewer cysts (p=0.049), and lower pre-treatment parasite volume (p=0.037). Higher number of previous cysticidal treatment courses was associated with a non-complete treatment response (p=0.023). Although the large proportion of participants with less than a complete response emphasizes the need to develop more efficacious pharmacologic regimens, the association of albendazole sulfoxide concentrations with treatment response highlights the importance of optimizing existing therapeutic regimens. Additionally, the association of treatment response with parasite volume emphasizes the importance of early diagnosis.

Keywords: Albendazole, Corticosteroids, Mexico, Neurocysticercosis, *Taenia solium*, Treatment.

Introduction

Neurocysticercosis (NC) is still the most frequent parasitic disease of the central nervous system (CNS), caused by installation of the larval form of the pork tapeworm *Taenia solium* in the CNS.[1] NC is a disease associated with poverty because the life cycle of the parasite requires outdoor defecation, free ranging pigs, poor sanitary control, and contaminated water. Due to this characteristic, NC is endemic in most of the countries of Latin America, Africa, and Asia.[2-4] Because of migration, NC is increasingly diagnosed in non-endemic countries, such as the United States and western Europe.[5,6] NC is clinically and radiologically heterogeneous and it is now recognized that two essentially different diseases can occur, depending on the location of parasites, i.e., parenchymal and extraparenchymal NC.[7] When the parasite is in the parenchyma, the main symptom is seizure, the parasite disappears or calcifies relatively easily after antiparasitic treatment with albendazole or praziquantel and prognosis is good with adequate seizure control with antiepileptic drugs. In the case of the extraparenchymal location of parasites (i.e., mainly basal subarachnoid and intraventricular), the situation is very different: parasites are larger, symptoms can be life-threatening (e.g., intracranial hypertension), severe vascular complications can occur, diagnosis requires specialized techniques, and response to treatment is often poor.[8] Although this form of NC is less common than parenchymal NC, its high morbidity and mortality warrants attention. A major problem in both clinical practice and research has been the difficulty of accurately diagnosing extraparenchymal NC. However, recent advances, such as assays for detection of

a secreted antigen in serum and cerebrospinal fluid (CSF),[9] 3D-MRI sequences (FIESTA, CISS),[10] and validated diagnostic criteria[11] have improved this situation.

The reasons for poor treatment response are not well understood and have not been studied in detail. Only one preliminary study in humans identified the possible relevance of the immunoinflammatory status of the host.[12] In swine cysticercosis, immunoinflammatory response appears to be relevant to treatment efficacy.[13] Other potentially relevant factors have not been examined.

Therefore, the aim of the present study was to identify different factors associated with the response to cysticidal treatment in extraparenchymal NC.

Methods

This study complied with all Mexican and international laws and regulations for ethical clinical research practice and the study protocol was approved by the ethical committee of Instituto Nacional de Neurología y Neurocirugía (INNN). All participants provided signed informed consent for their neurological and radiological information and stored plasma to be used for research purposes.

This was a longitudinal study conducted from June 2014 to April 2017 in which all patients with a confirmed diagnosis of vesicular extraparenchymal NC attending the INNN in Mexico City were invited to participate.

Participant enrollment and treatment

The inclusion criteria were to have a diagnosis of vesicular extraparenchymal NC made using validated diagnostic criteria,[11] to accept the 15 days hospitalization and the medical treatment consisting of oral albendazole (30

mg/kg/day in three divided doses) for 10 days, administered with corticosteroids (IV dexamethasone 0.4mg/kg/day in three divided doses for 13 days, followed by oral prednisone 50 mg/day with a taper), to have not been treated with cysticidal drugs (albendazole, praziquantel, or ivermectin) and corticosteroids in the past 6 months before inclusion into the study, and to agree to attend follow-up appointments at 1 month and 6 months after treatment. The cysticidal treatment regimen used in this study has been used at the INNN for more than 10 years.[14] It is different from what is recommended in recent guidelines, i.e., to continue treatment until there is resolution of cystic lesions on neuroimaging studies;[15] however, there are no studies that support this recommendation.[16] Main adverse events of this regimen are reversible increase of liver enzymes and reversible alopecia in less than 10% of patients. Standard laboratory tests (complete blood count, liver and kidney function) were within normal limits at inclusion, at the end of treatment, and in the follow-up appointments. Glucose concentration was also within normal limits at inclusion in all the patients. Some participants developed hyperglycemia during dexamethasone treatment that required the use of antihyperglycemic agents. Individuals with uncontrolled metabolic diseases, neoplastic diseases, or other infectious diseases were excluded, as well as pregnant women.

Outcome: Evaluation of treatment response

All participants underwent a neurological evaluation and a cerebral MRI with FIESTA sequences[10] before initiating treatment and 6 months after completing the treatment. The evaluation of partial parasite volumes (pvol) in each of axial levels was done (Figure 1), and global parasites volume was determined using the

following formula: (pvol*1*+ pvol*2*+….+pvol*n*) x axial MRI slice thickness. Only volumes of parasites in vesicular stages were used (i.e., with a fluid intensity equal to the CSF intensity). This determination was made by two researchers, one neuroradiologist (RCM) and one neurologist (AF), both experts in NC. The volume index corresponding to the ratio between pre- and post-treatment volumes was calculated. Complete response was defined as all parasites disappearing after treatment (i.e., 100% reduction of parasite volume). Partial response was defined as a volume index greater than 2 (decrease of 50% or more of the parasite volume), and absence of response was defined as a volume index lower than 2 (decrease of less than 50% of parasite volumes). Inter-rater reliability for treatment response based on volume index was substantial between the two reviewers (Kappa 0.65, 95% confidence interval [CI]: 0.42-0.88). When there was disagreement, the two reviewers discussed the case together to reach consensus.

Evaluation of factors possibly involved in treatment response

Demographic variables

Age, sex, place of residence, education level were ascertained by direct interview of participants at study inclusion.

Radiological characteristics

In addition to the determination of parasite volume (described above), location of parasites (ventricular, subarachnoid, or both), number of parasites and presence of a ventriculoperitoneal shunt were assessed in all the participants on pre-treatment MRI.

Cerebrospinal fluid characteristics

Lumbar punctures to evaluate CSF cellularity (cells/mL), protein count (mg/dL), and glycorrhachia (mg/dL) were performed in 28 participants (90.3%) before treatment and in 27 participants (87.1%) 6-months after treatment.

Measurement of albendazole sulfoxide concentrations in plasma.

In order to measure through plasma steady state concentration, a blood sample was obtained at day 10, immediately before the administration of the last dose in 22 of the participants (71%). Determination of albendazole sulfoxide plasma concentrations was done using a fully validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method as follows: An aliquot of 100 μL of plasma sample was mixed with 100 μL of carbamazepine (concentration 800 ng/mL, internal standard). A volume of 5 mL of ether:dichloromethane:chloroform (60:30:10) was added and samples were vortex-shaken for 5 minutes. Samples were centrifuged at 3 000 rpm for 20 minutes and frozen at -70°C for 20 minutes. The organic phase was evaporated to dryness at 45°C with a nitrogen stream, samples were reconstituted with 50 μL of methanol:5 mM formic 70:30 (v/v), and 10 μL were injected into the chromatographic system. The LC system consisted on an Agilent 1100 quaternary pump and autosampler (Palo Alto, CA, USA). The chromatographic separation was carried out on a Gemini C18 analytical column (150 x 4.6 mm, 5 μm, Phenomenex, Torrance, CA, USA) with a pre-column (Phenomenex C18 ODS). Mobile phase was composed of methanol:formic acid 5mM (70:30, v/v) at a flow rate of 0.7 mL/min. Mass spectra was obtained on an ABSciex 3200 QTrap linear ion trap quadrupole mass spectrometer (ABSciex, Darmstadt, Germany). Quantification was performed using multiple reaction

monitoring (MRM) of the following transitions: *m/z* 282 → 240 for albendazole sulfoxide, and *m/z* 237.2 → 194.1 for carbamazepine. The assay range was between 125 and 3500 ng/mL (r^2 = 0.998). The quantification limit was 125 ng/mL. The precision of the intra-day assay was between 4.2 and 9.6%, while for the inter-day assay it was between 5.6 to 11.6%. The accuracy results showed that the deviation with respect to the nominal concentrations ranged from 1.4 to 7.0% for the intra-day assays and for the inter-day experiments it was from 2.4 to 6.9%.

Other variables

Time from diagnosis to inclusion and number of previous cysticidal cycles were also determined by direct participant interview and evaluation of medical records.

***Statistical analysis*.**

We first computed descriptive statistics (counts, percentages, means with standard deviation, and medians with ranges, where appropriate) and then compared variables by treatment response (<50%, 50% to <100%, 100%) using Fisher's exact tests for categorical variables or Kruskall-Wallis tests for numeric variables. Spearman correlation coefficients were also computed for key variables of interest (i.e., pre-treatment number of cysts and volume of parasites; age and volume index with albendazole sulfoxide concentration). Wilcoxon signed-rank sum tests were used to determine if there were significant differences in pre-/ post-treatment CSF characteristics and parasite volume. Correction for multiple comparisons was not done because the risk of type II error outweighed the risk of type I error, as our sample size was small. Data analysis was done using SAS 9.4

(SAS Institute, Inc., Cary, NC) and a 2-sided alpha level of 0.05 was used to determine statistical significance.

Results

Inclusion of participants

During the period of the study, approximately 500 patients with NC were received care at the INNN. Of them, 45 individuals met all the inclusion criteria and 43 of them agreed to participate in the study. Twelve patients were further excluded during the study. The causes were death due to infectious complications (necrotizing fasciitis) in one patient, neurosurgical treatment in 2 patients, interruption of cysticidal treatment in one patient, and incomplete follow-up in 8 patients. It is relevant to mention that 17 of the 31 participants included in this study were also included in another large, published study.[7]

Description of the sample

Among the 31 participants enrolled, the mean age was 48.5 years, more than half (58.1%) were male, more than half (61.3%) resided in an urban area, and about half (51.6%) had a primary school education or less (Table 1). The majority of participants had subarachnoid cysts (74.2%), with a median of 4 cysts. Mean pre-treatment parasite volume was 8570.9 mm^3 and was not significantly different between men and women (p=0.548). Although volume was higher for cysts in the subarachnoid compartment (8246.2±10137 mm^3) than those located in the ventricular system (4350.6±5210 mm^3), this difference was not significantly different (p=0.14). There was a significant correlation between pre-treatment

number of cysts and volume of parasites (rho=0.59, p<0.001). For most participants, quite some time had passed since their initial diagnosis of NC and the inclusion in this study, with a median of 2 years. The cysticidal treatment evaluated in this study was the first such treatment for 13 treatment-naïve participants (41.9%). The other participants had received cycles of albendazole, albendazole + praziquantel, or albendazole + ivermectin at least 6 months before inclusion. Complete responder participants previously received albendazole alone, while partial and non-responder participants had received the three types of therapeutic regimens. Overall most of the participants presented with intracranial hypertension that required the collocation of a ventriculoperitoneal shunt before treatment (67.7%). Other pre-treatment symptoms were headaches (8, 25.8%), cognitive alterations (5, 16.1%) and seizures (3, 9.7%). Pre-treatment CSF was mostly inflammatory although this was variable, as shown in Table 1.

Outcome: Evaluation of the radiological response to treatment

Response to treatment was determined by comparing pre- and post-treatment parasitic volumes, evaluated by volumetry from 3D MRI sequences. Figure 2 shows the evolution of parasite volumes, which were significantly reduced after treatment (p<0.001), although in most of the participants (74.2%) the response was not complete. It should also be noted that pre- and post-treatment volumes, and volume indexes were variable among participants (Table 1). Eight participants (25.8%, 95% CI: 11.9-44.6) had complete disappearance of parasites, 16 (51.6%, 95% CI: 33.1-69.9) a partial decrease ≥50%, and 7 (22.6%, 95% CI: 9.6-41.1) a partial decrease <50%. In this latter group, 3 participants presented an

increase in the parasite volume after treatment (volume index <1). At a clinical level, 7 of 8 participants with complete response (87.5%), 9 of the 16 with partial response (56.2%) and 3 of the 7 with response <50% (42.8%) had an improvement of their symptoms. Main persistent symptoms were headaches and cognitive alterations. It is relevant to note that one of the participants had a stroke one week after the end of albendazole treatment, although she was receiving high oral prednisone doses (1mg/kg/day). As sequelae, she had a slight limitation in fine movement in the right arm.

Main results: Factors associated with the radiological response to treatment

Differences in these variables between the groups of participants with complete response, 50-99% response, and <50% response to treatment were evaluated (Table 1).

Demographic factors

The variables significantly associated with treatment response were age (p=0.032), with younger participants more likely to have complete treatment response. There were no statistically significant associations between treatment response and sex, place of residence, and education level. It is, however, relevant to note that volume indexes were higher for women (mean: 902.6, median: 20.5) than men (mean: 435.9, median: 4.1) showing a better treatment response in women, but this only bordered on statistical significance (p=0.072).

Radiological factors

The variables significantly associated with treatment response were number of cysts (p=0.049) with those with fewer cysts more likely to have complete

treatment response, pre-treatment volume (p=0.037), and post-treatment volume (p<0.001), with participants who had lower pre- and post-treatment volume more likely to have complete treatment response. Pre-treatment volumes in participants with a complete response (mean 2430.2±1339.0) were significantly lower than those of participants with partial response (mean 10706.9±12264.3, p=0.013). The same relationship was found comparing pre-treatment number of parasites between participants with complete response (mean 2.6±1.6) and participants with partial response (mean 6.7±5.2, p=0.014).

Location of cysts (subarachnoid vs. ventricular) was not significantly different between the three groups of participants.

Cerebrospinal fluid characteristics

Pre-treatment lumbar punctures were done in 28 of the 31 participants (90.3%) and 6-month post-treatment lumbar punctures were done in 27 of them (87.1%). There were no statistically significant differences in the pre-treatment cells, glucose, and proteins in the CSF of the 3 groups of participants (Table 1); however, there was a non-significant lower pre-treatment cell count among those with <50% treatment response relative to the other two groups.

Overall, there were no statistically significant pre-/post-treatment differences in CSF cells (p=0.824), glucose (p=0.325), or proteins (p=0.472, data not shown in tables). When data were stratified by treatment response a significant increase in CSF glucose was found for those participants with a complete treatment response vs. all other participants (mean difference: 18.2±18.1, median 12.4, range -5.0 to 41.0; p=0.031).

Albendazole sulfoxide concentrations

Steady-state albendazole sulfoxide concentrations in plasma were significantly associated with response to treatment. Higher concentrations were associated with greater likelihood of complete response (p=0.032, Table 1, Figure 3). Mean steady-state plasma albendazole sulfoxide concentrations were 1625.0 ng/mL, with no statistically significant differences between men and women (p=0.570) and a negative, though nonsignificant, correlation with age (rho=-0.35, p=0.110). Concentrations were lower among participants with ventricular cysts (mean 1236.5±760.8 ng/mL) than those without ventricular cysts (mean 1739.2±751.1 ng/mL), but this difference was not statistically significant (p=0.196).

There was a significant correlation between albendazole sulfoxide concentration and volume index (rho=0.580, p=0.004), showing a higher treatment response at higher plasma concentration. Mean albendazole sulfoxide concentration was also significantly lower in the 3 participants with an increase of parasite volume post treatment (639.2±389.7 ng/mL) compared with the other participants (1780.6±692.8 ng/mL), p=0.009.

Other factors

The number of previous cysticidal cycles was associated with response to treatment (p=0.023), with those with more cycles associated with a treatment response <50%. There were no statistically significant associations between treatment response and time from diagnosis to inclusion in the study, and placement of ventriculoperitoneal shunt.

Discussion

Extraparenchymal NC is the most severe form of the disease, and is associated with even worse outcomes than parenchymal NC because response to treatment is suboptimal. In our study, we found that more than 75% of the participants (24/31) did not have complete disappearance of all vesicular parasites with the standard treatment. This result is consistent with a previous report showing that 36% of individuals with this form of NC had persistent parasites after two treatment cycles.[8] These data demonstrate the importance of the treatment failure and the relevance of trying to understand contributing factors.

We observed that steady-state plasma concentrations of albendazole sulfoxide were associated with response to treatment, in a plasma concentration-response manner. Although previous studies showed that plasma albendazole sulfoxide concentrations were higher when higher doses of albendazole were administered,[14] the relationship between administered doses and treatment response has not been previously studied, perhaps because of a lack of adequate tools to evaluate treatment response. For the first time, we used volumetric studies (FIESTA sequence of MRI) to compare the parasitic volumes before and after the treatment. This technique has been demonstrated to be the most sensitive for the visualization of parasites in these locations.[10] Our results support why the dose of 30 mg/kg is more efficient in this location than the dose of 15 mg/kg, which is the dose typically used in case of parenchymal NC. For ethical reasons, we did not evaluate the albendazole sulfoxide concentrations in CSF at the end of treatment. Indeed, as lumbar puncture is invasive, it would have been excessive to repeat it 10 days after the pretreatment lumbar puncture. This information would surely

have been of interest, although previous studies have shown that there is a positive and significant correlation in albendazole sulfoxide concentrations between the CSF and plasma.[17] Our result shows the importance to use strategies to increase the concentration of albendazole sulfoxide in plasma. In particular, it has been shown that the intake of albendazole with a high fat content meal (traditional Mexican breakfast) increased the plasma concentration of albendazole sulfoxide 7-fold.[18] This practice should be systematically applied to patients receiving this treatment.

Another result of interest was the significantly better response to treatment in younger participants. Although the factors involved in this result are not well understood, we can hypothesize that two parameters could be involved. First, the decrease of reactivity against the parasite with age, that has been previously shown, could be implicated.[19,20] Likewise, age of the parasites could also be relevant. Although we do not know when participants were infected, it is possible that older participants have a longer infection time than younger participants. In this context, in an *in vivo* study using the murine model of cysticercosis by *Taenia crassiceps* (a parasite showing broad similarities with *T. solium*), it was shown that the efficacy of cysticidal drugs (albendazole and praziquantel) decreased with increasing time of infection.[21] Thus, it is possible that parasites that have more time in the CNS of patients respond less than parasites with less time.

Another interesting finding was the association of the lower pre-treatment parasite volumes and the better treatment response (p= 0.037, Table 1). This shows the importance of an early diagnosis, when parasites are still small. Indeed, since the extraparenchymal space is large, parasites can grow for a long time

before they begin to cause symptoms. Early detection strategies by using a rapid diagnostic test to assess the presence of parasitic antigen, as recently suggested, could help in this regard.[22]

The finding that a greater number of previous cysticidal treatments was significantly associated with poor response to treatment could reflect the heterogeneity of treatment response. The presence of a group of patients that does not respond to treatment, despite repeated courses, shows the need to develop new therapeutic regimens.

Although we did not find significant differences between men and women in treatment response, it is important to note that 62.5% of the participants in the group with total response to treatment were women, while in the case of partial response or non-response, 34.8% of the participants were women. Also, volume indexes were higher in women than men showing a better treatment response in women, bordering on statistical significance (p=0.072). This trend is consistent with previously published results showing that women have a greater reactivity than men against parasites.[19,23] The mechanisms involved in these differences are not known, but we can hypothesize that endocrine differences between sexes, as well as immunoendocrine interactions could be involved. It should be noted that profound hormonal changes associated with NC have been described,[24] showing the relevance of studying this topic in more detail.

We did not find significant associations between CSF characteristics (cells, proteins, glucose) and the response to treatment. This result does not corroborate previous preliminary studies showing the relevance of the immunoinflammatory state in the response to treatment.[12] It is, however, relevant to note that the CSF

parameters evaluated in this study are very general and studies evaluating more precise markers (cytokine, phenotype of cells, in particular) are necessary to understand the relevance of this aspect.

There are some limitations that bear to mention. First, our sample size was small and thus our statistical power was limited, precluding multivariable analysis. Future work driven by hypotheses from the present study should seek to clarify and determine the independence of associations. Second, the majority of the participants in our study had subarachnoid cysts (23/31) and relatively few had ventricular cysts (8/31), therefore, some questions regarding generalizability remain. Finally, some of the participants received previous cysticidal treatment, so we cannot completely rule out the possibility of some contamination in the treatment effect. However, this possibility is unlikely as 6 months with no treatment was required for inclusion in the study. Also, our results do not support this possibility because the number of previous cycles of treatment was higher in the participants with low response to treatment compared with participants with adequate response to treatment.

Conclusions

Our study shows interesting results that will help to improve the pharmacological treatment of these severe patients. Particularly, the significant association between plasma concentration of albendazole sulfoxide and response to treatment is of great relevance. Indeed, this result must motivate future studies to find strategies to correct the poor absorption of albendazole. Also, the better treatment response for smaller parasite volume is of high relevance, demonstrating

the need of developing new tools permitting an earlier diagnosis of this severe forms of NC.

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Data-Sharing Statement: Data presented in this manuscript cannot yet be shared as the study remains in progress. All data sharing agreements are subject to ethics committee review. For any questions, please contact: afleury@biomedicas.unam.mx

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Figure titles

Figure 1. Example of volume determination in one axial level of FIESTA MRI (left: pre-treatment; Right: post-treatment)

Figure 2. Comparison of pre- and post-treatment parasite volumes (in mm3) among the 31 participants

Figure 3. Plasma albendazole sulfoxide (ABZSO) concentrations and its relationship with treatment response. Data are presented as mean and SD.

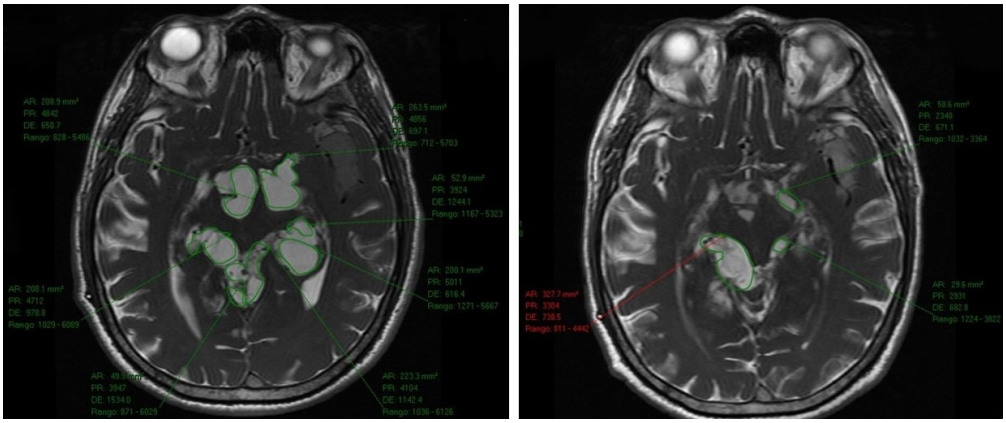

Figure 1. Example of volume determination in one axial level of FIESTA MRI (left: pre-treatment; Right: post-treatment)

326x135mm (96 x 96 DPI)

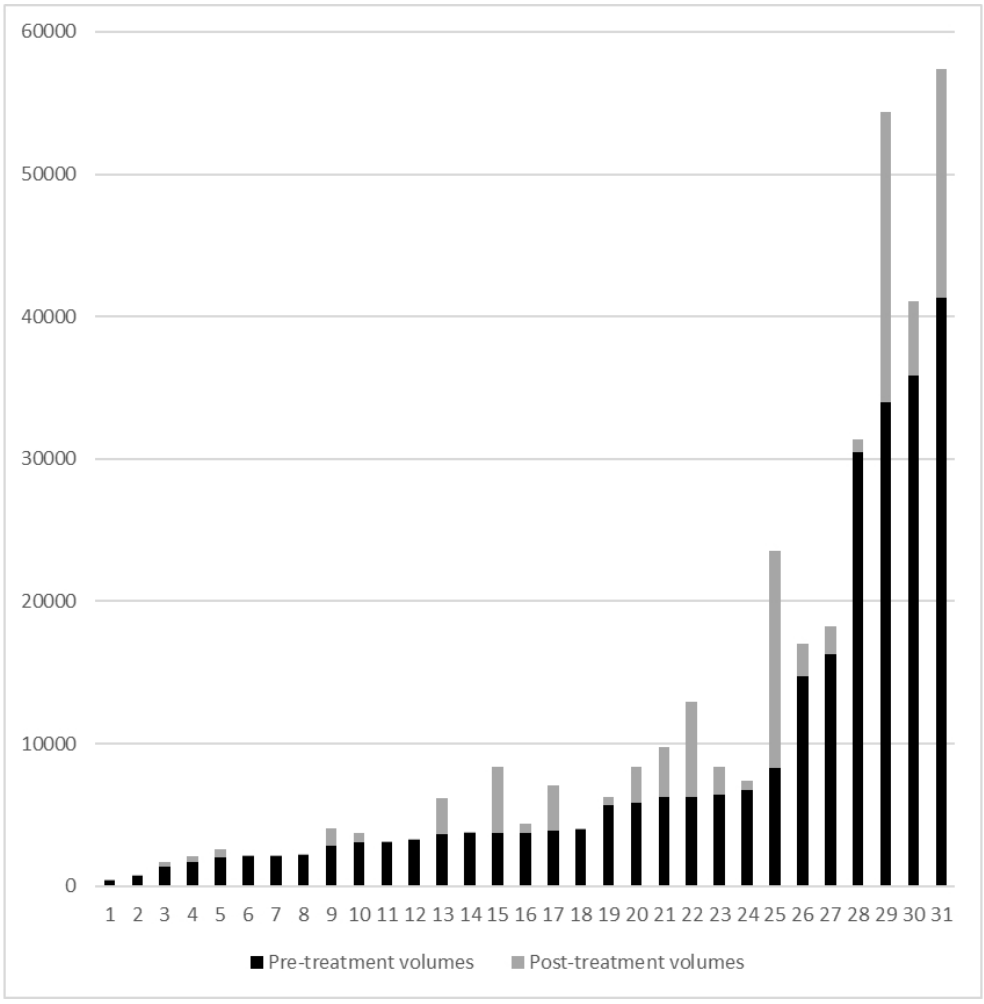

Figure 2. Comparison of pre- and post-treatment parasite volumes (in mm3) among the 31 participants

228x226mm (96 x 96 DPI)

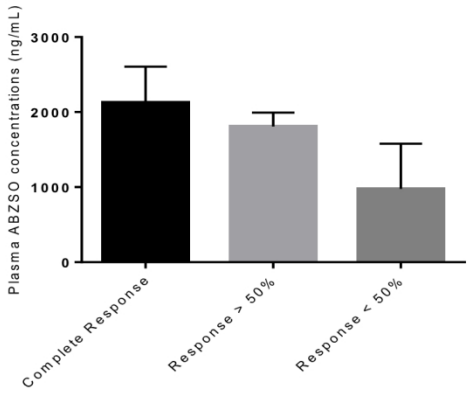

Figure 3. Plasma albendazole sulfoxide (ABZSO) concentrations and its relationship with treatment response. Data are presented as mean and SD.

279x215mm (144 x 144 DPI)

Table 1. Demographic, pre- and post-treatment disease characteristics, and plasma albendazole sulfoxide concentrations overall and by treatment response

		Overall N=31	Treatment response <50% N=7 (22.6%)	Treatment response 50%-<100% N=16 (51.6%)	Complete treatment response N=8 (25.8%)	P-value
Demographic characteristics						
Age	Mean (SD)	48.5 (8.6)	53.3 (7.5)	49.4 (6.6)	42.6 (10.4)	0.032*
	Median (range)	49.0 (32.0-63.0)	56.0 (37.0-59.0)	50.0 (36.0-61.0)	40.5 (32.0-63.0)	
Sex (Male)		18 (58.1)	5 (27.8)	10 (55.6)	3 (16.7)	0.398**
Place of residence (Urban)		19 (61.3)	6 (31.6)	8 (47.4)	4 (21.1)	0.385**
Education level (Primary school or less)		16 (51.6)	3 (18.8)	9 (56.3)	4 (25.0)	0.895**
Radiological characteristics						
Cyst location						0.131**
	Subarachnoid	23 (74.2)	3 (13.0)	14 (60.9)	6 (26.1)	
	Ventricular	3 (9.7)	1 (33.3)	1 (33.3)	1 (33.3)	
	Both	5 (16.1)	3 (60.0)	1 (20.0)	1 (20.0)	
Pre-treatment number of cysts						0.049*
	Mean (SD)	5.6 (4.9)	6.0 (3.4)	7.0 (5.9)	2.6 (1.6)	
	Median (range)	4.0 (1.0-24.0)	7.0 (1.0-10.0)	5.0 (1.0-24.0)	2.5 (1.0-6.0)	
Pre-treatment parasite volume, mm^3						0.037*
	Mean (SD)	8570.9 (11148.0)	9431.9 (10959.0)	11264.6 (13095.0)	2430.2 (1339.0)	
	Median (range)	3758.0 (374.4-41334.9)	6240.0 (3639.4-33974.6)	5779.5 (1398.4-41334.9)	2651.5 (374.4-3985.2)	
Post-treatment parasite volume, mm^3						<0.001*
	Mean (SD)	2974.0 (5098.1)	8033.6 (6985.8)	2246.9 (3903.2)	1.0 (0.0)	
	Median (range)	679.9 (1.0-20382.7)	4660.9 (2528.2-20382.7)	797.6 (102.4-16076.7)	1.0 (1.0-1.0)	
Volume index						<0.001*

	Mean (SD)	631.6 (1257.0)	1.2 (0.5)	8.1 (8.0)	2430.2 (1339.0)	
	Median (range)	6.3 (0.5-3985.2)	1.2 (0.5-1.8)	5.9 (2.3-33.3)	2651.5 (374.4-3985.2)	
CSF characteristics						
Pre-treatment						
Cells	Mean (SD)	95.4 (111.2)	69.0 (61.1)	96.0 (132.7)	110.8 (97.8)	0.854*
	Median (range)	43.0 (9.0-512.0)	29.0 (22.0-149.0)	36.0 (9.0-512.0)	108.0 (12.0-277.0)	
Glucose	Mean (SD)	34.0 (26.6)	35.6 (36.1)	39.7 (25.7)	22.4 (20.7)	0.240*
	Median (range)	24.5 (2.0-95.0)	16.0 (10.0-95.0)	46.0 (2.0-92.0)	14.0 (2.0-57.0)	
Proteins	Mean (SD)	568.9 (1144.0)	755.4 (1391.0)	673.3 (1369.0)	256.5 (175.7)	0.992*
	Median (range)	204.5 (24.0-5440.0)	117.0 (72.0-3240.0)	143.0 (24.0-5440.0)	312.0 (26.0-510.0)	
Post-treatment						
Cells	Mean (SD)	103.2 (160.4)	33.3 (23.1)	139.6 (190.8)	55.8 (99.0)	0.239*
	Median (range)	48.0 (0.0-624.0)	20.0 (20.0-60.0)	81.5 (0.0-624.0)	23.5 (6.0-299.0)	
Glucose	Mean (SD)	38.8 (22.3)	34.3 (14.6)	38.8 (26.5)	40.6 (16.5)	0.804*
	Median (range)	39.0 (5.0-92.0)	36.0 (19.0-48.0)	38.0 (5.0-92.0)	43.0 (8.0-62.0)	
Proteins	Mean (SD)	307.2 (365.2)	287.0 (383.7)	287.6 (402.0)	353.9 (321.4)	0.545*
	Median (range)	131.0 (25.0-1410.0)	71.0 (60.0-730.0)	110.5 (25.0-1410.0)	292.0 (28.0-912.0)	
Steady-state plasma albendazole sulfoxide concentrations, ng/mL						0.032*
	Mean (SD)	1625.0 (765.9)	977.3 (600.6)	1808.1 (672.3)	2430.2 (1339.0)	
	Median (range)	1600.0 (287.1-3196.9)	864.2 (287.1-1945.9)	1863.3 (648.3-3196.9)	2651.5 (374.4-3985.2)	
Other characteristics						
Time from diagnosis to inclusion in the study (years)						0.814*
	Mean (SD)	3.9 (4.3)	4.7 (4.7)	3.9 (4.6)	3.4 (3.7)	
	Median (range)	2.0 (0.0-13.0)	4.0 (0.0-12.0)	1.5 (0.0-13.0)	2.0 (1.0-12.0)	
Number of previous cysticidal cycles						0.023*
	Mean (SD)	1.2 (1.5)	2.9 (2.0)	0.6 (0.8)	1.0 (1.3)	
	Median (range)	1.0 (0.0-5.0)	3.0 (0.0-5.0)	0.0 (0.0-2.0)	1.0 (0.0-4.0)	
Placement of VPS		21 (67.7)	6 (28.6)	10 (47.6)	5 (23.8)	0.601**

*Kruskall-Wallis test. **Fisher exact test.