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THE ALBENDAZOL TREATMENT'S EFFICACY IN HYDATID CYSTS

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Abstract. The evaluation of albendazol treatment's efficacy in hydatid cysts (CH) with different locations and the evaluation of treatment's efficacy based on: cysts' location, size, type and immunological status of patient. We performed a prospective study on 320 patients, during 5 years. We performed the drug-based treatment in cases of small and medium cysts sizes (< 7 cm). Statistics do not show a significant difference between the hepatic and pulmonary hydatic cysts' healing rates, $p > 0.05$ ($p = 0.5987$). Albendazol treatment's efficacy is higher in the case of hepatic localization than in other localizations. The efficacy of the albendazol therapy is significantly higher in the case of CH < 7cm in comparison with CH > 7cm, which requests a surgical treatment. The efficacy of the albendazol treatment is higher in the case of type 1 hydatic cysts than in the case of type 2 hydatic cysts. Patients with CD4 > 944 cells/mm3 responded better to treatment in comparison with the patients with CD4 < 944 cells/mm3. The efficiency of the albendazol treatment is lower for the patients presenting co-morbidities. Treating hidatid diseases with albendazol 800mg/day for 4 weeks, in repeated cures separated by free intervals of 2 weeks, had as a result the healing of 91.25% of the cases. The positive predictive factors of the albendazol treatment response were: hepatic or pulmonary localization of the hydatid cysts, small dimensions, below 7cm in diameter, presence of the type1 hydatid cists, absence of co-morbidities and unaltered immunological status (CD4 > 944 cells/mm^3).
Key words: hydatid cysts, albendazol, efficacy

Introduction

Hydatid disease is a worldwide health problem [1-3]. Unfortunately, realistic national or international figures do not exist for the total numbers of cases of cystic echinococcosis. The problem is that, the only basis for diagnosis was surgery, and few countries systematically reported cases. When they did report cases, uneven reporting occurred in different regions of countries. However, the increasing use of mass screenings with ultrasonography in endemic countries is generating important epidemiological data [4].

Two benzimidazolic drugs, mebendazole and albendazole, are the only anthelmintics effective against cystic echinococcosis. Albendazole and mebendazole are well tolerated but show different efficacy. Albendazole is significantly more effective than mebendazole in the treatment of liver cysts. Benzimidazole treatment alone requires prolonged administration over many weeks, with an unpredictable outcome in terms of response rates in individuals [5].

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Objectives

Primary: Evaluation of the albendazol treatment's efficacy in hydatid cysts with different locations,based to cysts' location, size, type and immunological status of patient.

Secondary: Predictive response factors to drug-based treatment.

Material and method

We performed a prospective study on 320 patients, diagnosed with hydatid cyst in Clinical Hospital of Infectious Diseases Constanta, Romania, during 5 years (2008-2013). We performed the drug-based treatment in cases of small and medium cysts sizes (< 7 cm) or in inoperable patients (severe chronic diseases) with cysts size >7cm, with multiple cysts (2 or more organs), peritoneal cysts, patients with multiple reoccurrences.

Administration protocol for the Albendazol therapy: 800mg/day , for 4 weeks, in repeated cures separated by free intervals of 2 weeks [1-2].

Examinations' calendar:

1. Initially, when included in the lot:
   - clinical examination;
   - APP (hydatid cyst, other chronic affections);
   - epidemiological context;
   - paraclinical evaluation: HLG, TGP, TGO,

serologic markers of the various types of chronic viral hepatitis (HBsAg, anti HCV, deltaAg, method - electrochemiluminescence (ECLIA), Roche Diagnostic, Switzerland;
- detection of anti Echinococcus granulosus antibodies (ELISA, NovaTec Immundiagnostica GmbH, Germany) through serologic reactions;
- Imaging evaluation - ECHO, x-rays, CT scans, MRI scans.

2. Monthly, during the treatment (before every therapeutic cure):
- clinical examination;
- paraclinical evaluation: hepatic toxicity;
- imaging evaluation – ECHO/x-rays (hydatic cysts' modifications due to treatment.

3. At the end of the treatment:
- clinical examination;
- paraclinical evaluation: HLG, TGP, TGO detection of anti Echinococcus granulosus antibodies (ELISA, NovaTec Immundiagnostica GmbH, Germany) through serologic reactions;
- imaging evaluation: ECHO/ x-rays, CT scan, MRI if needed.

4. ECHO/ X-rays and serological post-treatment surveillance, every 6 months for 2 years.

5. According to Gharbi classification (morphological classifications), we considered liver hydated cyst [6]:
a. Type I (CE1) - Pure fluid collection;
b. Type II (CE2) - Fluid collection with a detached membrane;
c. Type III (CE3) - Fluid collection with multiple septa and/or daughter cysts;
d. Type IV (CE4) - Hyperechoic with high internal echoes;
e. Type V (CE5) - Cyst with reflecting calcified thick wall.

Results

Different locations were encountered, but the most frequent occurrence was on the liver (67%), followed in frequency by the lungs (22%) . Other less frequent locations were the kidney, spleen, peritoneum, mediastinum, pericardium, brain, parotid gland, bone and muscle locations (1-3%).

Cysts dimensions between 3 and 7 cm were founded in most cases. The minimum cyst size was 1.1cm, while the maximum was 12 cm.

In most cases (90 patients), 6 therapeutic cures were necessary before the first healing signs appeared.

Patients' healing rate was 91.25% while the causes of treatment failure were: complications (overgrowth that required surgery in 12 cases), albendazole toxicity (3 cases), non-response to albendazole treatment (6 cases), decease (one case with multiple lung cysts).

We compared the cases of healed patients with hepatic cysts with the cases of healed patients with pulmonary cysts. Statistics do not show a significant difference between the hepatic and pulmonary hydatid cysts' healing rates (p = 0.5987) (Fig1).

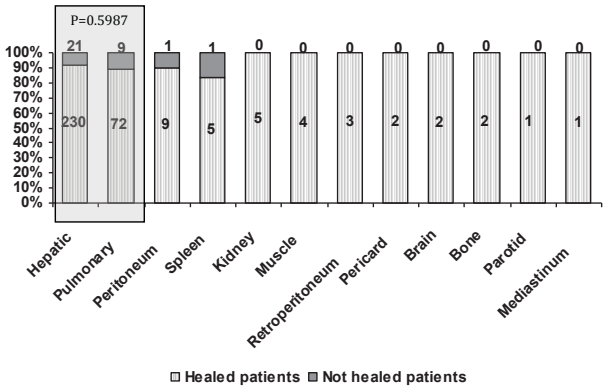

Figure 1.

The average of the cures followed for hydatid cysts with other localizations was 7.428571±1.886039.

Statistics show a significant difference between the hepatic or pulmonary and other locations hydatid cysts' healing rates. We can conclude that the Albendazol treatment's efficiency is higher in the case of hepatic or pulmonary localization than in other localizations. By this, we are saying that the hepatic and pulmonary localization represents a positive predictive factor for the therapeutic response (p = 0.009125) (Fig.2)

Most of the healed cases detained cvsts < 7cm in size.

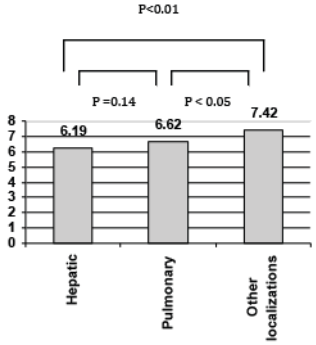

Figure 2. Number of cures

We can conclude that a dimension < 7 cm represents a positive predictive factor for the therapeutic response (Fig.3, Table I)

The average number of therapeutic cures administered

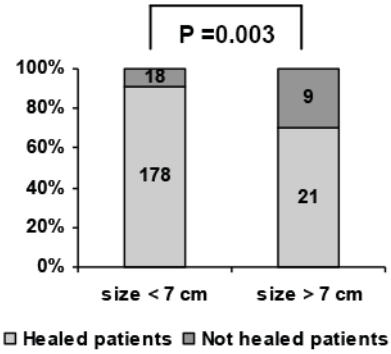

Figure 3.

to the patients with type 1 cyst was 6.739 ± 1.91, and for the cases of patients with type 3 cysts it was 8.181 ± 2.39. We compared the two results, and the outcome was that

DIMENSIONS		NUMBER OF HEALED CASES			
< 7 cm	< 3 cm	178	39	196	40
	3 – 4.9 cm		85		87
	5 – 6.9 cm		54		69
> 7 cm	7– 9.9 cm	21	17	30	22
	> 10 cm		4		8

Table I.

the number of therapeutic cures administered for the type 1 hydatid cyst (CE1) is significantly smaller than the number of cures administered for the type 3(CE3) hydatid cyst, thus the presence of the type 1 cysts being considered a positive predictive factor for the therapeutic efficiency ($p<0.01$, significant statistically).

The presence of comorbidities represented a negative predictive factor for the therapeutic response (Fig.4).

There were 2.8 % recurrences after a median delay of 16 months (12 – 24 months).

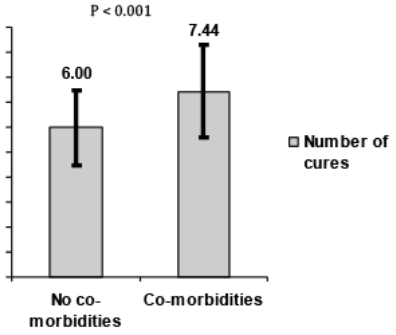

Figure 4.

We performed CD4 count after therapy, for 20 responsive patients versus 19 non-responsive patients. Median CD4 for the two groups was 944 cells/mm3. Patients with CD4 > 944 cells/mm3 responded better to the treatment in comparison with the patients with CD4 < 944 cells/mm3 ($p < 0.01$). We conclude that CD4 represent a positive predictive factor for the therapeutic response.

Discussion

Constanta is an endemic area for Hydatidosis and the Infectious Diseases Clinic has a long experience in therapy with albendazole. In the absence of systematic national reporting there is no recently epidemiological study and there are no reports about the effectiveness of therapy with albendazole in Romania. An international study conducted in 2009 from six centres (five countries including Romania, 711 treated patients) reported that 1-2 years after the initiation of benzimidazole treatment, 75% of hydated cysts were classified as inactive, but the study was restricted to liver and peritoneal cysts [7]. Other authors have reported rates similar or lower than our study (91.25%): Gil-Grande 1993 – 94% [8], Teggi 1993– 77.9% [9], Franchi 1999 - 82.1% [10] and Keshmiri 2001 – 82% [11].

A recent study (Cappello E et al) on 30 patients with hepatic hydatid cyst notified a cure rate of 76.6% and relapses were more frequent in patients treated with albendazole before 2005. Co-morbidities were observed in 17 (53.1%) patients (hypertension, chronic pulmonary diseases, hepatitis B and hepatitis C) and as in our study , they were a negative predictive factor for the therapeutic response and complications were observed in six patients (18.8%) these being cyst rupture, and bacterial infection [12].

In another study, albendazole was the most frequently used agent, the median duration of antihelminthic therapy was 6 months, as in our study, (range 0.7-144 months) and there were 17% recurrences after a median delay of 2 years (range 0.4-17 years). The presence of multiple visceral organ involvement increased the odds of recurrence by 5.4 (95% CI 3.1-9.4) [13]. In our study we reported only 2.8 % recurrences, but after a median delay of 16 months (10 – 24 months), in our protocol, we have recorded post-treatment surveillance every 6 months for 2 years. Only a Peruan study reported a low effectiveness of albendazole HCE therapy compared with the efficacy reported in clinical trials, 34% per patient and 40% per cyst after 3.8 ± 2.5 years [14].

In another chinese study, of 196 cases enrolled with liver hydatid cysts, after a long period with albendazole treatment (6 to 30 months) 32.7% were considered to be cured, 49% were improved, 14.3% remained unchanged, and 4.1% cases became aggravated. Patients with CE3 cysts needed a longer treatment course for cure (26.4 months), compared to cases with CE1 (20.4 months) or CE2 type (9 months) [15]. In our study the average number of therapeutic cures administered to the patients with CE1 cysts was 6.739 ± 1.91, and for the cases of patients with CE3 cysts it was 8.181 ± 2.39, more less than chinese study.

In relation to the role of CD4 in therapeutic response, in the last years, several studies have shown that genetic and immunologic host factors are responsible for the treatment resistance. Also in the adventitial layer surrounding the regressive and involutional hydatid cysts, infiltrating lymphocytes were composed mostly of CD4+ cells [16]. In our study CD4 was evaluated after treatment and probably a correct prediction analysis related to CD4 would have been possible if this value could have been measured prior to the initiation of therapy. We consider that CD4 counts can be a predictive factor for a response to treatment in patients, influencing the choice of optimal therapeutic intervention method.

Conclusions

Treating hydatid diseases with albendazol 800mg/day for 4 weeks, in repeated cures separated by free intervals of 2 weeks, had as a result the healing of 91.25% of the cases (Fig.5-7).

The treatment has a similar efficacy in the hepatic and pulmonary hydatic disease (91.63%, respectively 88.88%).

The efficacy of the albendazol treatment is higher in the case of hepatic and pulmonary hydatic disease than in other localizations.

The positive predictive factors of the Albendazol treatment response were: hepatic or pulmonary

localization of the hydatid cysts, small dimensions, below 7cm in diameter, presence of the type1 hydatid cysts, absence of co-morbidities and unaltered immunological status (CD4 > 944 cells/mm^3).

Figure 5. Hydatid cysts before albendazol treatment

Figure 6. Hydatid cysts after 3 cures of albendazol treatment

Figure 7. Hydatid cysts after 6 cures of albendazol treatment

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