Treatment of hydatid disease in childhood with mebendazole

A. Göçmen, M.F. Toppare, N. Kiper

ABSTRACT: The general characteristics of 56 childhood cases of cystic hydatid disease were analysed and the results of mebendazole therapy versus surgery were verified. Pulmonary radiograms and ultrasonography were used in the diagnosis. The cysts were localized primarily to the lungs.

Twenty seven patients were surgically-treated, with eight having recurrence after a mean period of 3.6 yrs. Thirty patients received regular mebendazole treatment, in a dose of 50 mg·kg⁻¹ with a mean duration of treatment of 11.7 months. Twenty one patients were cured and discontinued the therapy. Nine still use the drug, seven of whom have had dramatic improvement, while the other two have minimal radiographic changes but subjective improvement in general condition. The lung cysts vanished leaving minimal scars, whilst the liver cysts turned into inactive forms. The surgically-treated and drug-treated groups were similar in age, duration and severity of the disease.

The recurrence rate of drug-treated children (1 out of 20) was lower than that of the surgically-treated children (8 out of 27); however, this was not statistically significant.

Keywords: Children echinococcosis hydatid cyst mebendazole surgery

Material and methods

In this study, the general characteristics of 56 patients, who applied to the Department of Pediatric Chest Diseases, Hacettepe Children's Hospital, were analysed. There were 5, 26, 18 and 7 children in the 0–5, 5–10, 10–15 and 15–18 yr age groups, respectively. Two children had only liver cysts, 43 had only lung cysts, and 11 had lesions in both liver and lungs. Twenty seven patients were surgically-treated and 30 patients used mebendazole regularly (fig. 1).
The patients were questioned about close contact with dogs, if they had had previous hydatid cyst surgery, and whether their residences were urban. All patients had chest X-rays, abdominal ultrasonography and hepatic function tests. Patients were given mebendazole, 50 mg·kg\(^{-1}\) in three divided doses to be taken with fatty meals. The mean duration of symptoms, the number and diameter of the cysts, were noted for each child. The patients were examined every three months and drug therapy was halted when clinical and radiological cure was achieved. Patients were followed-up regularly at appropriate intervals.

At follow-up of the patients with hepatic hydatid cysts, ultrasonography was used. As it was reported that treated hepatic hydatid cysts do not usually disappear, cases of shrinkage and filling of cysts with cellular debris and/or calcification, were regarded as inactive (dead) cysts. All of the patients had a complete blood count and hepatic function tests within one to six months (mean 3.2 months) after starting the drug.

**Statistical analysis**

Mann-Whitney U-test was used in comparing the diameters of lung and liver cysts. Fisher exact chi-square test was used to analyse the significance of recurrence rates of surgically-treated and drug-treated patients. Mann-Whitney U-test was used to compare the mean duration of drug therapy for pulmonary and hepatic cysts, and to analyse the difference of mean cyst diameter per child, mean duration of symptoms, and mean age in the patients treated with or without drug therapy. Chi-square was used in comparing the number of cysts in the two groups.

**Results**

The overall age distribution of the 56 patients revealed that the predominant age group was the 5–10 yr olds, followed by the 10–15 yr group. The mean age was 9 yrs. All of the patients were under 18 yrs of age. Thirty five were from non-urban settlements. The overall age distribution of the 56 patients revealed that the predominant age group was the 5–10 yr olds, followed by the 10–15 yr group. The mean age was 9 yrs. All of the patients were under 18 yrs of age. Thirty five were from non-urban settlements.

Cough (57%) and fever (38%) were the predominant symptoms (table 1). In 26 of the patients (46%) there was a history of close contact with dogs. In majority of the patients physical examination was within normal limits; however, 16 (29%) had diminished breath sounds and/or tubular breath sounds, five had sonorous rhonchi-fine rales, five had hepatomegaly, five had dyspnoea and tachypnoea, and three had signs of accompanying disease. Two of the patients had neurological deficit due to intracranial cysts.

With the exception of one patient who did not receive mebendazole, all patients had normal hepatic function tests. The predominant appearance in pulmonary radiograms was an homogeneous ellipsoidal density in the right lung (table 2). Specific appearances, such as water lily sign (the cyst membrane floating in cyst fluid), and setting sun sign (partial appearance of the cyst on the diaphragm) were relatively rare. Seventy seven cysts were counted in 56 patients.

### Table 1. – Symptoms of the 56 patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>32</td>
</tr>
<tr>
<td>Fever</td>
<td>21</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>10</td>
</tr>
<tr>
<td>Chest pain</td>
<td>8</td>
</tr>
<tr>
<td>Expectoration of cyst contents</td>
<td>6</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6</td>
</tr>
<tr>
<td>No symptoms related to cyst</td>
<td>5</td>
</tr>
<tr>
<td>Neurological deficit</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
</tr>
</tbody>
</table>

(Abdominal pain, headache, etc).

### Table 2. – Characteristics of pulmonary radiograms from 56 patients

<table>
<thead>
<tr>
<th></th>
<th>L lung</th>
<th>R lung</th>
<th>Bilateral</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogeneous ellipsoidal</td>
<td>13</td>
<td>14</td>
<td>6</td>
<td>33 (59)</td>
</tr>
<tr>
<td>Pleural sign</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Air - fluid levels</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>11 (19)</td>
</tr>
<tr>
<td>Water lily sign</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Setting sun sign</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Normal radiograms</td>
<td></td>
<td></td>
<td></td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Total 21 25 8 56

(%) : % of 56 patients.

Two patients had liver cysts only, 43 had lung cysts only, while 11 children had lesions in both organs. In the latter group, two had cerebral and two had splenic cysts. Cyst diameters in the lungs ranged from 1–18 cm (mean 5.7 cm), and in the liver from 1–8 cm (mean 5.6 cm), with no significant differences in the mean diameters.

Twenty seven patients were surgically-treated. Eight of these patients had recurrences at 8 months to 7 yrs after surgery (fig. 1). These eight patients were later given mebendazole. Twenty eight patients were given only mebendazole treatment. One patient had a history of expectoration of cyst contents and chest X-ray revealed a perforated cyst. After two years, in which he could not be followed, he was seen again, on this occasion chest X-ray was clear and he was presumed to have had a spontaneous recovery.

Since 1982, a total of 36 patients were give mebendazole, 30 of them receiving the drug in appropriate dosage and duration. Twenty one of these patients completed the therapy and the drug was stopped. Mean duration of drug usage was 11.7 months (range 7–24 months). Nine patients are still receiving the drug. While seven had dramatic reduction in cyst size, in two patients only minimal changes were observed. However, these two stated subjective improvement. The 20 patients who completed the
therapy were followed for between 16–50 months (mean 29.9 months). One patient was lost to follow-up after obtaining a cure of an hepatic cyst. One patient who had regularly used mebendazole for 11 months and was thought to be cured, had recurrence after an interval of 6 months; after using the drug for an additional seven months the residual cyst vanished. The 27 surgically-treated children were comparable to the second group of 30 children who used mebendazole regularly: a) mean age 8.3 versus 8.8 yrs (p>0.05); b) duration of symptoms 2.4 versus 2.2 months (p>0.05); and c) mean cyst diameters 5.8 versus 5.6 cm (p>0.05). The number of cysts (40 versus 39 (p>0.05)) was also similar in the two groups. However, in the surgically-treated group two patients had both intracranial and intrahepatic cysts, and one of them died after successive operations.

All of the patients except one had nearly clear chest radiograms with a minimal fibrotic band when drug treatment was over. The first radiological changes were evident 15–20 days after starting the drug and somewhat earlier in perforated cysts (fig. 2). In 13 out of 23 patients with isolated lung cysts, therapy was completed with a mean drug usage of 11.2 months (range 4–24 months). In ultrasonographic follow-up of hepatic cysts, it was noted that in one patient the cyst vanished with a residual fibrotic scar, and in seven cysts were filled with cellular debris and became ecogenic (inactive) (fig. 3).

Fig. 2. — Serial chest radiograms of a case: A) before treatment; B) three months later; C) after completion of the treatment with mebendazole.

Fig. 3. — A) first hepatic sonogram; B) after completion of the treatment with mebendazole.
Two inactive cysts had calcifications. Patients with liver cysts used the drug for an average of 11.8 months (range 8–18 months). No significant difference in the mean time of cure was observed between lung and liver cysts (p>0.05). The recurrence rate of hydatid cyst in children treated with mebendazole was lower than the group treated surgically, although this difference did not reach a statistically significant level, 1 out of 2 versus 8 out of 27 (p>0.05).

During the therapy, no patient experienced leucopenia or deterioration of hepatic function and no case of alopecia, urticaria or anaphylaxis was encountered. Three children had haemoptysis after 2–6 months of drug therapy; one of them necessitating admission to the hospital but needed only supportive measures.

Discussion

In hydatid disease surgical treatment carries a high recurrence rate. Wilson et al. [12] reported that recurrence after surgery of pulmonary cysts may be even higher. With successive operations, the mortality rate could be as high as 20% [13]. As the potential dangers of surgical interventions and possible organ resections are evident with a growing organism, it is vital to have a non-surgical treatment for this disease in children. The report of Öztaşkent and Amato [14] showed that 32% of the patients are under 20 yrs and the disease is also significant in childhood.

The epidemiological data in our study are in accordance with the literature in age distribution, symptoms and physical findings of childhood patients [15, 16]. In agreement with our results, several reports indicate that the main localisation in children is in the lungs [15, 17, 18]. The possible reason for this is that in children oncospheres are carried through the periduodenal and perigastric lymphatics to mediastinal vessels and through the thoracic duct to the lungs [19]. They are mostly in the right lung. Our finding of accompanying liver cysts in approximately one fifth of pulmonary lesions is also in accordance with the classical knowledge [20].

It was surprising that, after an average period of 3.6 yrs, about one third of the surgically-treated patients had recurrences. In adult series, recurrence rate is reported to be 1–14% [3, 21, 22]. In the conditions existing in Turkey, hydatid cyst operations are common and surgical experience is adequate. Therefore, rather than inadequacy of surgical interventions it should be considered that the actual recurrence rate may be higher in children, or that small cysts may be unnoticed at the time of operation.

There has not been a general agreement on the dosage and duration of mebendazole treatment. Wanggo et al. [23] claimed 200 mg·kg\(^{-1}\) dosage to be most effective in mice, however, comparative studies in human beings are required. At this dosage gastrointestinal side-effects may occur. Fatty meals enhance absorption of the drug and raise plasma levels [24], therefore, patients are advised to ingest mebendazole with fatty meals. Side-effects and complications, such as neutropenia, alopecia, hepatotoxicity and fungal superinfections, have been reported in the adult series but were not encountered in our patients. This indicates that the daily dose of 50 mg·kg\(^{-1}\) is safe in childhood [8, 13, 25].

Duration of treatment in our patients was generally longer than in the adult series. Bekhti et al. [7], who were among the first users of mebendazole, reported that 30 days of treatment resulted in the loss of vitality of cysts which then regressed completely within 4–13 months. Kayser [8] gave mebendazole to his patients for less than three months. Kummerer and Schantz [26] used a six week high dose, followed by a three month low dose regimen, while Karpathhos et al. [27] gave the drug for 10–12 weeks, and Bryceeson et al. [9] continued treatment for 4–11 months in inoperable patients. Messaritakis et al. [28] reported the effectiveness of high dose and short course mebendazole therapy in children with hydatid disease. In our series, the duration of treatment varied between 7 and 24 months, with a mean of 12 months. This may be due to failure of parents to give the drug to the child regularly, or to rapid microsomal inactivation in childhood. Romig et al. [29] found that the rate of cyst growth is faster in the 5–15 yr age group than in other age groups. This may explain, in part, the long duration of drug treatment. Even in patients with minimal radiographic changes, drug therapy was accompanied by improvement in general condition and disappearance of complaints of anorexia and malaise.

Although the treatment period for isolated lung cysts was somewhat shorter than that of liver cysts, the difference was not significant. The lung cysts all vanished leaving a minimal fibrotic density, in one patient, while liver cysts tended to transform from a cystic structure to a homogeneous one, by filling with cellular debris. This observation was also reported by Brendimarte et al. [30] and Singhcharoen et al. [31], who demonstrated, by histopathological methods, that the cysts were non-vital. The reason why hepatic cysts persist, even though inactive, was poorly understood. Richards et al. [32] demonstrated that pulmonary cysts had some structural differences from hepatic cysts. The high macrophage activity in lung tissue may also contribute to the process.

Many researchers feel that objective criteria that indicate the success or failure of the treatment in a definite period [9, 33] are lacking. All paediatric patients, except those with intracranially or paraspinally localised cysts, are recommended to have mebendazole therapy lasting for 9–18 months, including those patients who showed striking objective improvement at the beginning of the therapy. This long duration of drug therapy seems to be a prerequisite for precluding recurrences that may occur up to 7 yrs later [34, 35]. Mebendazole is the drug of choice for treatment in children, due to its lack of side-effects, the low risk of recurrence, and the fact that all of the patients benefited from the therapy, with the majority eventually obtaining a cure.
MEBENDAZOLE IN CHILDHOOD HYDATID DISEASE

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References