

Treatment of cystic echinococcosis: a combination of general goals and rules, individual decisions and indications

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The four papers published in this issue of the Netherlands Journal of Medicine on cases of cystic echinococcosis (CE)¹⁻⁴ remind us of several important points: 1) CE/hydatid disease, due to the larval development of *Echinococcus granulosus*, is less benign than often claimed; 2) its surgical treatment may be at the origin of dissemination and complications; 3) CE should be evoked for a variety of presenting signs and symptoms when the patient comes from an endemic area; 4) the treatment of CE complications needs to adapt the individual condition of the patient while following general rules that aim at removing or inactivating the parasitic cysts and preventing parasite recurrence.^{5,7} Both clinical cases of CE presentation, with aching hands and urticaria in an 18-year-old girl,⁴ and with gastrointestinal symptoms in a Kyrgyz 44-year-old veterinarian,² well illustrate the variety of presenting signs and symptoms. The observation of a quite unusual hydatid cyst location with complete obstruction of the pulmonary artery and destruction of the lung¹ fully supports both the risk of surgery and the usefulness of an appropriate surgical procedure combined with chemotherapy to treat CE complications. It is likely that the first surgical operation on the liver cyst was responsible for the pulmonary embolism. A description of the first operation (type of operation, possible mistakes) could have explained the occurrence of protoscolex and/or cyst fragment migration from the hepatic veins to the pulmonary arteries through the cardiac right cavities.

Surgery has long been considered the only treatment for all cases of hydatid cysts. In 1996, treatment guidelines published by the WHO-*Informal Working Group on Echinococcosis (IWGE)* stated that the therapeutic strategy should consider combined or alternative treatments.⁸ Since then, results of long-term evaluation have been made available and updated guidelines are currently being

discussed by the WHO-IWGE and should be published soon. There are very few available controlled trials designed to assess CE treatment. A recent meta-analysis aimed at finding 'evidence-based' answers to the main questions about treatment strategy in cystic echinococcosis.⁹ The main results, graded according to the Cochrane system, were as follows: 1) chemotherapy is not the ideal treatment for uncomplicated hydatid cysts of the liver when used alone; 2) the level of evidence is too low to help decide between radical or conservative treatment; 3) omentoplasty associated with radical or conservative treatment is efficient in preventing deep abscesses; 4) drug treatment associated with surgery requires further studies; 5) the laparoscopic approach is safe; 6) percutaneous drainage associated with albendazole therapy is safe and efficient in selected patients; 7) the level of evidence is low concerning treatment of complicated cysts. Thus, several key questions regarding CE treatment are obviously not answered.

The objective of surgery is to remove parasitic cysts and fluid completely, a major advantage compared with other types of treatment. However, when discussing surgery regard should be given to cyst location in the liver, lung and/or other organs, number of cysts, presence of other cysts in other organs, anatomical/clinical complications, clinical status of the patient, but also surgical facilities, expertise of the surgical team and quality of follow-up.⁸ Controversies still exist about the preferred operating technique. Many operations and variants have been published.^{5,7,10-13} Hepatic resection is usually only recommended for central cysts of a left lateral segment. Liver transplantation has been exceptionally performed in patients with acute Budd-Chiari syndrome and secondary biliary cirrhosis.¹⁴ Various types of cystectomy, with or without pericystectomy, permit the complete removal of the parasite. A modified technique of endocystectomy vs

pericystectomy has recently been evaluated in one of the very rare randomly controlled surgical trials which showed the advantage of the former for cysts ≤ 8 cm in diameter.¹⁵ Total subadventitial cystectomy has also recently been proposed to excise the laminated membrane intact, by following the virtual gap which exists between the inner and outer fibrous layer surrounding the cyst.¹⁶ Such a procedure might have prevented entry of parasitic material into hepatic veins in the case described by Aribas *et al.*¹ In order to avoid spillage of the cyst content, the peritoneal cavity must be carefully protected and the cyst content and germinal layer sterilised by protoscolicides: 3% hydrogen peroxide, 80 to 95% alcohol, 15 to 20% saline solution, 0.15 chlorhexidine/1.5% cetrimide and/or 10% polyvinyl pyrrolidone iodine.¹⁷ Formalin and $>20\%$ hypertonic saline should not be used because of the risk of sclerosing cholangitis. Despite the high number of hydatid cysts surgically removed worldwide, few large reviews of surgical cases with a significant follow-up are available, and the number of recurrences is generally underestimated. It ranges from 2 to 25%, depending on the size, location, number, or peroperative rupture of the cysts, as well as expertise of the surgical team.¹¹⁻¹³ The high number of repeated operations in a single patient in most of the published reports is indirect evidence for the frequency of recurrence; of course, the authors often stress that the first operation was performed 'elsewhere'. This emphasises the necessity of long-term follow-up.

Since 1986, Puncture Aspiration Injection Reaspiration (PAIR) has been proposed as an alternative to surgery.¹⁸ After percutaneous puncture under ultrasonographic guidance, a complete aspiration is performed; the residual cavity is then filled with a protoscolicide, usually ethanol, reaspired 10 minutes later. Detailed practical guidelines have been published after a careful evaluation of the technique by the WHO-IWGE.¹⁹ Long-term follow-up of patients is now available.^{20,21} A meta-analysis has established the efficiency, safety and usefulness of the procedure in selected indications.²² A very limited number of anaphylactic shocks and secondary dissemination, lower than after surgery in most series, have been reported.¹⁰ PAIR can be proposed for type CE1, and selected cases among CE2, and CE3 cysts according to WHO classification.²³ It is contraindicated if there is a communication between the cyst and the biliary tree. Deep location in the liver is not, per se, a contraindication to PAIR since in such cases surgical dissection of the cyst is difficult and may lead to peroperative parasitic embolism in the vessels or damage to the bile ducts. Drainage may be associated with PAIR in large cysts.²¹ To treat cysts with numerous daughter cysts, a PAIR-like technique using larger tubes and vacuum aspiration through a small surgical incision was first described in a huge series of cases in western China;²⁴ similar procedures have then

been published in European countries.^{25,26} Laparoscopic treatment of the cysts is also feasible but, however, more frequently associated with spillage and recurrence.²⁷

Treatment of complications and recurrences is always difficult and needs a multidisciplinary approach to define the best option adapted to the patient's condition. With multiple cysts and multiple initial locations, recurrence in multiple organs and especially in the peritoneum represents a good indication of chemotherapy alone,²⁸ which may also be the first step before a hazardous operation in complicated cases. Albendazole is usually preferred at an average daily dosage of 15 mg/kg/day; it must be given continuously, without those treatment interruptions which were recommended in the past. Blood count and transaminases must be checked every week for the first month and every month thereafter.^{7,8,28} Combination of chemotherapy and surgery or PAIR is increasingly being used. Presurgery treatment with albendazole may facilitate a complete removal of the germinal layer, as shown in this issue by Genetzakis *et al.*³ A recent report of 52 CE cases treated with surgery and pre- and postsurgery albendazole showed the efficacy of chemotherapy to prevent recurrence, assessed within a 5 to 92 month follow-up.²⁹ Praziquantel, which is protoscolicidal but has no efficacy on germinal layer cells, may be added, especially after surgery when the risk of spillage is high.²⁸ However, no controlled long-term studies have ever evaluated chemotherapy efficacy to prevent recurrence after surgery, as well as the optimal schedule before and after surgery or PAIR and the risk/benefit of a combined treatment with praziquantel. Depending on the team, duration of albendazole therapy ranges between one and eight days before and one and three months after PAIR. It is noteworthy that in the four papers published in this issue, the schedule and duration of albendazole treatment were quite variable: only after surgery for an unknown duration,¹ three sequences of 28 days, with treatment interruptions, before PAIR, and apparently no treatment after the puncture despite the failure of fluid aspiration and ethanol reinjection,² 28 days, only before surgery,³ and six months, only after surgery.⁴ This clearly indicates the absence of consensus and the need for guidelines.

Assessment of treatment efficacy relies mainly on the morphology and size of the cyst(s), appreciated by repeated ultrasound examinations. A major endpoint is the disappearance of the cyst; however, persistence of ultrasound or CT-scan image may well be associated with parasite death and thus response to the treatment. Serology is of little use to assess cyst viability; specific IgG4 could be good indicators of treatment efficacy but are not widely available.¹⁵

The search for new drugs is ongoing. Attempts at increasing serum concentrations of albendazole have given promising results.^{30,31} Amphotericin B was proposed as salvage treatment in alveolar echinococcosis, due to

Echinococcus multilocularis, but does not seem to work in CE.³² The parasitocidal effect of nitazoxanide was recently proven *in vitro* but has never been tested in human CE.³³ New therapeutic approaches such as radiothermal ablation are currently under investigation.³⁴ However, what is most urgently needed in order to make progress in the treatment of this disease, which still occurs frequently worldwide, is to construct controlled studies aimed at more clearly specifying the respective place of the various treatment options, including a 'watch and wait' attitude for asymptomatic cysts which may be cured spontaneously.^{35,36}

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