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The natural history of cystic echinococcosis in untreated and albendazole-treated patients

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ABSTRACT

The World Health Organization (WHO) treatment protocols for cystic echinococcosis (CE) are based on the standardized ultrasound (US) classification. This study examined whether the classification reflected the natural history of CE in untreated and albendazole-treated patients. Data were collected during mass US screenings in CE endemic regions among transhumant populations, the Turkana and Berber peoples of Kenya and Morocco. Cysts were classified using the WHO classification. Patient records occurring prior to treatment, and after albendazole administration, were selected. 852 paired before/after observations of 360 cysts from 257 patients were analyzed. A McNemar-Bowker χ^2 test for symmetry was significant ($p < 0.0001$). 744 observations (87.3%) maintained the same class, and 101 (11.9%) progressed, consistent with the classification. Regression to CE3B occurred in seven of 116 CE4 cyst observations (6.0%). A McNemar-Bowker χ^2 test of 1414 paired before/after observations of 288 cysts from 157 albendazole-treated patients was significant ($p < 0.0001$). 1236 observations (87.4%) maintained the same class, and 149 (10.5%) progressed, consistent with the classification. Regression to CE3B occurred in 29 of 206 CE4 observations (14.1%). Significant asymmetry confirms the WHO classification's applicability to the natural history of CE and albendazole-induced changes. Regressions may reflect the stability of CE3B cysts.

1. Introduction

The natural history of cystic echinococcosis (CE), the natural evolution of the morphology of cysts over time, is still being defined (WHO-IWGE, 2003). CE is a geographically widespread, chronic, complex and neglected zoonosis caused by the larval stage of the taeniid cestode *Echinococcus granulosus*, which results in the development of fluid-filled cysts, usually located in the viscera, particularly the liver (Brunetti et al., 2011; Thompson and McManus, 2001; Craig et al., 2003). Actively developing cysts contain protoscolices (the larval stage of the tapeworm) contained in brood capsules (Brunetti et al., 2011; Thompson and McManus, 2001). The longest recorded survival time of a CE cyst in a human host was 53 years in a patient from Greece (Kern, 2003; Spruance, 1974); and studies indicate that cysts in the liver, regardless of size or class, can remain asymptomatic for over ten years (Kern, 2003). A percentage of cysts degenerate spontaneously and lose their biological viability over time (Kern, 2003). This degeneration is reflected by observable physical changes in cyst condition and morphology, and recent studies support the assertion that parasite viability is reduced in cysts displaying membrane detachment, daughter cyst rupture, increased cyst echogenicity, and other signs of degeneration of cystic material (Kern, 2003; Gil-Grande et al., 1993).

Albendazole, a benzimidazole-carbamate, was first recommended for the treatment of CE in 1983 (Saimot et al., 1983), and remains the current drug of choice for treating CE (Brunetti et al., 2010). Current recommendations are for constant administration, without monthly interruptions in treatment, as two oral daily doses for a total of 10–15 mg/kg/day (Brunetti et al., 2010). Albendazole-induced changes to the natural history of CE have recently been demonstrated. A randomized controlled trial of albendazole efficacy analyzed the

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viability of cysts in accordance with their physical characteristics and appearance, finding that ultrasound (US) was a highly specific indication of cyst viability with increased echogenicity suggesting non-viability (Gil-Grande et al., 1993). While the patients in this study were treated with albendazole, the physical changes they underwent were similar to those seen in untreated patients' cysts as they degenerate.

The complex variety of CE cyst classes seen on US led to the development of numerous classifications (WHO-IWGE, 2003). The first was developed by Gharbi in 1981, based on clinical studies (Gharbi et al., 1981), which was followed by approximately 30 other classifications for clinical or epidemiological natural history purposes (WHO-IWGE, 2003; Brunetti et al., 2011). Consisting of five categories, the Gharbi classification was widely adopted, but the question remained as to whether the classification accurately reflected the natural changes in cyst morphology over time: particularly, experts debated whether Gharbi classes II and III were ordered appropriately (WHO-IWGE, 2003; Brunetti et al., 2011). Among the other classifications was a classification developed by Caremani and colleagues, which was meant to reflect both natural and therapy-induced changes in cyst composition (Caremani et al., 1996, 1997). It describes seven cyst classes, for which all but one class had two subclasses (Caremani et al., 1996, 1997). Another classification was by Kjossev and Losanoff, who developed the TN(R)C formula (Kjossev and Losanoff, 2005, 1998). This system differentiated liver cysts by topographic location (T), nature of the cyst (N), cyst recurrence (R), and complications (C) (Kjossev and Losanoff, 2005, 1998).

This confusing situation led in 1994 to the World Health Organization (WHO) proposing the development of a WHO standardized US classification (WHO-IWGE, 2003). In 1995, the WHO Informal Working Group on Echinococcosis (WHO-IWGE) established a network of scientists to evaluate existing classifications of CE and decide on a standardized classification of US images. The first meeting was held in 1997 in Lisbon, the second meeting in Bariloche, Argentina, and the final meetings in 2000 in Arezzo, Italy, and 2001 in Kusadasi, Turkey, with the resulting classification published in 2003 (WHO-IWGE, 2003). The WHO classification was proposed from field epidemiological studies and aimed to more closely follow the natural history of CE, and would therefore be of value to clinicians treating patients with this disease and those conducting field epidemiological studies (WHO-IWGE, 2003; Macpherson and Milner, 2003).

Organized by degree of cyst activity/viability, the WHO CE US classification scheme consists of six classes (CL and CE1–CE5), each of which exhibits a different subset of distinguishing (but not necessarily pathognomonic) characteristics (Fig. 1) (WHO-IWGE, 2003).

A cystic lesion (CL) is an undifferentiated simple cyst, the etiology of which is unclear; but, if CE, it is thought to be an active, early cyst (WHO-IWGE, 2003). CE1 and CE2 cysts are active and usually fertile with viable protoscoleces (WHO-IWGE, 2003). A typical CE1 cyst is a round, unilocular cyst, recognized on US as an anechoic region surrounded by a clearly-defined laminated membrane (WHO-IWGE, 2003). If shifted, floating broodcapsules and small calcifications may be seen as echoes within the cyst, a feature known as "hydatid sand" or "snow flake sign (WHO-IWGE, 2003)." Daughter cysts may form within a unilocular mother cyst from this viable material (Lewall, 1998). CE2 cysts contain daughter cysts without any apparent degeneration, and are sometimes described as having a "rosette-like" or "honeycomb-like" appearance (WHO-IWGE, 2003). Although not officially incorporated as part of the WHO CE US classification, cysts of the CE2 class can be subcategorized as either CE2A (a mother cyst septated or partially filled with daughter cysts) or CE2B (a mother cyst entirely filled with daughter cysts) (WHO-IWGE, 2003). For the purposes of this study, this subcategorization has been applied. The CE3 cyst class is viewed as transitional between active and inactive classes (WHO-IWGE, 2003). While a CE1 cyst may develop daughter cysts, thus progressing to the CE2 stage, it may alternatively progress to the CE3A stage (Brunetti et al., 2010): the hallmark of a CE3A cyst is laminated membrane detachment from the cyst wall of a CE1 cyst, appearing as a wavy membrane floating within a unilocular anechoic region (WHO-IWGE, 2003). Due to this derivation, CE3A cysts are interpreted as early cysts transitioning to the inactive stage, and are as likely to be viable as inviable (Brunetti et al., 2016; Brunetti and Junghanss, 2009). A CE3B cyst typically contains both intact and ruptured daughter cysts, as well as solid, degenerated materials which appear increasingly echogenic (WHO-IWGE, 2003). Viewed as the transitional stage between CE2 and CE4 cysts, CE3B cysts are typically viable due to the presence of intact daughter cysts, and therefore may be considered to fall more on the active side of the transitional range (Brunetti and Junghanss, 2009). US features of CE1, CE2, and CE3 cysts are pathognomonic for CE (WHO-IWGE, 2003).

CE4 and CE5 cysts are viewed as inactive (WHO-IWGE, 2003). The CE4 class appears as a heterogeneous and hyperechoic region, sometimes with small calcifications, or as a spiral resembling a "ball of wool."[1] Most CE4 cysts are infertile (WHO-IWGE, 2003; Gil-Grande et al., 1993). A CE5 cyst has a thick wall of calcification producing a dark cone-shaped shadow beneath the cyst (WHO-IWGE, 2003). Although suggestive of CE, morphological features of CE4 and CE5 cysts are not pathognomonic (WHO-IWGE, 2003).

The WHO US classification of CE proposes that degeneration of cysts moves in the CL to CE5 direction (WHO-IWGE, 2003). For example, collapse of the endocyst in a CE1 cyst is postulated to result in the observation of a CE3A cyst; and the disappearance of daughter cysts from within a CE2 or CE3B cyst is anticipated to result in the observation of a solid CE4 cyst (Brunetti et al., 2010; Stojkovic et al., 2014). The primary exception to this forward trajectory is the observed "reactivation" of CE4 cysts via the reappearance of daughter cysts, more frequently occurring within months after treatment with benzimidazoles (Stojkovic et al., 2014).

Despite its goals to 'facilitate both the uniform reporting of results from field epidemiological studies as well as in clinical studies

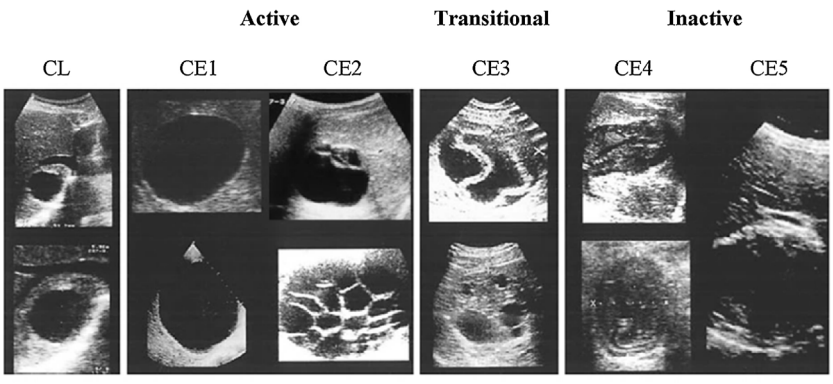

Fig. 1. WHO-IWGE ultrasound classification of cystic echinococcosis (WHO-IWGE, 2003, 2017; Brunetti et al., 2010) (adapted).