

COMMENTARY

## Association between local alcoholic beverages and amoebic liver abscess in the Indian subcontinent: Weird but true!

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Amebiasis is caused by *Entamoeba histolytica* (EH), a protozoan that is endemic in third-world tropical countries due to poor sanitation and overcrowding. It is currently the third most common cause of death from parasitic disease. Amoebic liver abscess (ALA), the most common manifestation of invasive amebiasis, accounts for <10% of all cases of amebiasis. In a recently published longitudinal study from Sri Lanka involving 346 patients with ALA, all patients had a positive history of consumption of alcohol, and the majority (79.2%) consumed a local alcoholic drink consisting of fermented palm juice known as toddy and arrack<sup>1</sup>. The incidence of ALA was the highest in the dry season, matching the toddy seasons and total toddy sales in the local area. The consumption of local alcohol (toddy and arrack) was identified as an independent risk factor for the development of ALA (odds ratio –4.5, 95% confidence interval: 1.94–11.96). Subjects who consumed alcohol 4–6 times in a week or daily had far greater risk of ALA than those who consumed 2–3 times in a week or less. Marked male predominance (98.4%) observed in this study was attributed to the differences in alcohol consumption between the two genders. Interestingly, when multiple toddy samples were collected from the area where most of the patients consumed the drink and then subjected to culture as well as microscopic examination, none of them demonstrated EH cyst or trophozoites, suggesting that toddy was not the source of the infection. If toddy was not the source of infection, then what was this association about? Possibly, toddy could have increased the virulence of EH by some unknown mechanism. In fact, the association between toddy consumption and ALA has been known for a long time; however, it has received only little attention so far. Hai *et al.*, in early 90s, reported the profiles of 220 cases of ALA, where 85% of patients had a history of significant consumption of toddy<sup>2</sup>. The peak incidence of ALA correlated with the peak toddy season (April–July). Since then, several other studies were published from the Indian subcontinent where a strong linkage was documented between consumption of local alcohol, particularly toddy, and occurrences of ALA (Table 1). In a study by Raja *et al.*, 80% of ALA patients had a history of consuming local alcohol, and these patients had longer duration of symptoms, larger size of abscess, and more frequent requirements for radiological intervention<sup>5</sup>. In a recent study from Bihar, India, where 80% of 95 ALA patients were toddy consumers, toddy drinkers had larger-sized abscesses, greater complication rates, and delayed resolution of abscess.<sup>4</sup> Menon *et al.*

reported that the proportion of alcohol consumption, especially toddy, was significantly higher in patients with ALA than with pyogenic liver abscess (91 vs 54%,  $P = 0.01$ ).<sup>6</sup>

The burden of amebiasis and toddy consumption is considerable in the Indian subcontinent. Toddy is prepared by the fermentation of the sap of various species of the palm tree. In India, Palmyra palm and coconut palm are commonly used to prepare toddy. The alcohol content of toddy is <5%. Toddy is commonly consumed by people belonging to low socioeconomic groups. The National Sample Survey Office consumption data 2011–2012 of India indicated that toddy was the most popular drink for rural India, followed by country liquor. The most common manifestation of toddy-induced liver disease appears to be ALA, which is clearly in contrast to the spectrum of liver diseases among chronic consumers of commercially prepared alcohol, such as alcoholic hepatitis and cirrhosis. This difference may be due to the fact that toddy has a relatively lower percentage of alcohol (<5%), and there is a possibility of microbial contamination due to a lack of distillation process and unhygienic practices during preparation and storage. The nonalcoholic content of toddy might affect the virulence of latent EH. Moreover, toddy consumers belong to lower socioeconomic status and have unhygienic lifestyles, which predispose them to high parasitic burden.

We have enough data to support an association between indigenous alcohol and ALA; however, the basis of this relationship is not yet clear. A nondetection of EH in local alcoholic preparation in the recent study refutes the presumption of these preparations being the source of infection transmission. Moreover, even in the target population, the occurrence of ALA mostly among consumers of local alcohol, and more so during toddy seasons, may suggest a role of toddy in influencing the virulence of EH. The most likely explanation appears to be that toddy creates some kind of environmental changes in the gut of individuals with asymptomatic amebiasis, which switch pre-existing latent EH to virulence. Asymptomatic amebiasis is prevalent in tropical third-world countries because of poor sanitation.

There can be various mechanisms by which toddy could influence EH virulence. The resident microbial flora in human colon is an important determinant of survival and virulence in EH. Alcohol consumption is known to induce intestinal bacterial dysbiosis, which may in turn alter the activity of EH. Undistilled local alcoholic beverages contain a large number of microorganisms that might have more propensity to cause intestinal

**Table 1** Studies published from the Indian subcontinent demonstrating an association between local alcoholic beverages and amoebic liver abscess

Study	Year	Country	n	All alcohol consumption (%)	Local alcohol consumption	Remarks
Kannathasan <i>et al.</i> <sup>1</sup>	2018	Sri Lanka	346	100	79.2% Toddy and arrack	<ul style="list-style-type: none"> <li>• 98.4% male</li> <li>• EH not found in toddy</li> <li>• Peak incidence during dry session</li> </ul>
Hai <i>et al.</i> <sup>2</sup>	1991	India	220	85	85% Toddy	<ul style="list-style-type: none"> <li>• Peak incidence during toddy season (April–July)</li> </ul>
Alam <i>et al.</i> <sup>3</sup>	2014	Bangladesh	90	79	79% NS	<ul style="list-style-type: none"> <li>• Complicated ALA was more common in alcoholic than nonalcoholic drinks</li> </ul>
Sinha <sup>4</sup>	2017	India	95	80	80% Toddy	<ul style="list-style-type: none"> <li>• Toddy drinkers had larger-sized abscesses, greater complications, and delayed resolution of abscess</li> </ul>
Raja and Karthick <sup>5</sup>	2014	India	108	94	79.6% NS	<ul style="list-style-type: none"> <li>• Alcoholics had larger abscess and more complications</li> </ul>

ALA, amoebic liver abscess; EH, *Entamoeba histolytica*; NS, not specified.

dysbiosis. EH lacks mitochondria and obtains its energy from the fermentation of glucose. EH alcohol dehydrogenase 2 (EHADH2) is a key enzyme in this pathway<sup>7</sup>. Thus, expression of EHADH2 is required for the growth and survival of EH trophozoites in human. A study has found that alcohol increases virulence of *S. Pneumonia* by upregulating its alcohol dehydrogenase<sup>8</sup>. In a similar manner, it could increase the virulence of EH. Moreover, EHADH2 is an 'iron-activated' enzyme, and experimental studies have demonstrated that iron promotes growth and in-vivo invasiveness of EH. Makkar *et al.* have suggested that high content of iron in habitual consumers of alcohol may predispose patients to invasive amebiasis, leading to ALA.<sup>9</sup> Authors demonstrated that the liver tissue of most patients with ALA had higher grades of iron deposition than the liver tissues of non-ALA cases. Alcohol is known to increase the intestinal absorption of iron and hepatic deposition of iron. Notably, iron content of traditional fermented beverages is known to be much higher than commercially prepared alcoholic beverages. Raja *et al.* have suggested that the invasive capacity of EH is facilitated by alcohol due to increases in intestinal permeability<sup>5</sup>. Ghosh *et al.* have reported that alcohol suppresses the function of Kupffer cells in the liver, which has the important role of clearing the amoeba.<sup>10</sup> Thus, the mechanism involved in the increasing virulence of EH seems to be related to both the alcoholic and nonalcoholic contents of toddy.

Experimental studies on these aspects are needed to shed more light and to help better understand the relationship between local alcoholic beverages and ALA. Because the linkage appears to be strong enough, creating greater awareness among the people who are at risk would be helpful in order to eliminate the disease. By avoiding consumption of local alcohol in areas where amebiasis is endemic, the magnitude of ALA can be substantially decreased. In addition, it would be interesting to see whether the

use of antiamebic drugs can prevent the development of ALA in toddy consumers with asymptomatic amebiasis.

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