

The Emerging Alcoholic Liver Disease in China

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Over the past a few decades, the pattern of liver diseases in China has been changing. Alcohol abuse is a significant contributor to the global burden of disease and a leading cause of liver disease. Alcoholic liver disease (ALD) is associated with significant morbidity and mortality, which includes a spectrum of disorders from simple steatosis to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. In China, with the establishment and effective implementation of the Expanded Program on Immunization for HBV from 1992, the number of newly HBV-infected patients had a significant decline; whereas the number of patients with alcoholic and nonalcoholic fatty liver diseases is growing. The incidence of ALD will continue to upsurge in China. Due to significant differences in alcohol metabolism, genetics, drinking patterns, and eating habits and behaviors between the East and the West, the pathogenesis of ALD in Chinese population may be different from the well-characterized ALD in Western countries. In this article, we reviewed and discussed the epidemic trend, the occurrence and the development of ALD in China.

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Key Words: *alcohol liver disease, alcohol abuse, HBV, steatosis, steatohepatitis, fibrosis, cirrhosis hepatocellular carcinoma*

INTRODUCTION

Over the past a few decades, the pattern of liver diseases in China has been changing. With the establishment and effective implementation of the Expanded Program on Immunization for HBV from 1992, the number of newly HBV-infected patients had a significant decline; whereas the number of patients with alcoholic and nonalcoholic fatty liver diseases is growing. In contrast to HBV that has been received great attention in China over the past three decades, fatty liver diseases especially alcoholic liver disease (ALD) have received little attention from the government and private funding agencies, healthy policy makers, pharmaceutical companies despite their increasing economical and health burden. Alcohol abuse is a significant contributor to the global burden of disease and a leading cause of liver disease. ALD is associated with significant morbidity and mortality, which includes a spectrum of disorders from simple steatosis to steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. In 2010, alcoholic cirrhosis caused half a million deaths worldwide, accounting for 50% of all cirrhosis-related mortality. Moreover, alcohol related hepatocellular carcinoma caused an additional 80000 deaths.¹

The amount of alcohol consumption in Western countries has been maintained in a stable condition during the last thirty years; but in developing countries, there is a rising trend in alcohol consumption at an alarming rate. In China, social and

economic situation has experienced rapid development stage over the last three decades, resulting in a significant increase in the production and consumption of alcohol.²⁻⁴ According to the report from China National Bureau of statistics, compared to 1978, the amount of alcohol production increased by 21 times in 2006,^{5,6} and the average prevalence of weekly regular alcohol drinking in the Chinese population was increased by over 33% during 2004-2008.⁷ The global drinking database from the World Health Organization (WHO) described that the annual per capita consumption of alcoholic beverage in China has grown from 0.49L in 1961 to 10.61L in 2005.⁸ By 2013, China was ranked as the second heaviest drinking country next to the UK throughout the world.⁹ In addition, with the accelerating pace of economic development and an explosion of communication with the western world over the last three decades, the Chinese people had a dramatic transformation in their diet structures and life styles, resulting in a marked increase in nonalcoholic fatty liver disease.

In this article, we review and discuss the epidemic trend, the occurrence and the development of ALD in China.

EPIDEMIOLOGY

Despite a marked increase in alcohol consumption and the number of ALD in China, the nationwide large-scale epidemiological data on the prevalence of alcohol consumption and ALD have not been performed, and only some region-wide, relatively large-scale epidemiological surveys were conducted.¹⁰⁻¹⁵ In the general adult population, the habitual drinking rate ranges from 27.0% in 2000 to 66.2% in 2015 (**Table 1**); excessive drinking rate is elevated from

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0.21% in 1982 to 14.8% in 2000. In less than 20 years, the proportion of excessive drinking population has been raised by nearly 70 times. The prevalence of ALD has been increased from 2.27% in 2000 to 8.74% in 2015. There are quite obvious differences of drinking rate and the prevalence of ALD between male and female subjects with significantly higher levels in male subjects.

The prevalence of different disease stages among general population in China was reported as follows: 1.21%~6.23% mild ALD, 0.94%~3.74% alcoholic fatty liver, 0.42%~2.18% alcoholic hepatitis, and 0.11%~0.68% alcoholic cirrhosis¹⁰⁻¹⁵ (Table 2). Among excessive-drinking population, the incidence of different disease stages was approximately 50%, 10% and 10% in alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis, respectively.^{10,13} A multicenter study reported that the annual incidence of ALD among hospitalized patients with liver diseases in China was 2.7%, 2.9%, 3.0%, 3.6%, and 4.4% throughout 2000~2004, respectively. Two other studies revealed that among 902 patients who were diagnosed as ALD, there were 11.2% mild ALD, 22.6% alcoholic fatty liver, 28.8% alcoholic hepatitis, and 37.4% alcoholic cirrhosis.^{16,17} By analyzing approximately 2.3 million hospitalized patients between 2006 and 2010, a study

from hospitalization summary reports (HSR) in the 31 Grade 3A hospitals in Beijing found that hospitalization rates for viral hepatitis-related cirrhosis slightly declined by 10%; whereas rates for alcoholic cirrhosis inversely increased by 33%. For both types of cirrhosis, the male patients were predominant, accounting for 98% in ALD and 71% in viral hepatitis.¹⁸

The incidence and development of ALD are affected by many factors. The duration of alcohol intake and amount of ingested alcohol are the most important predictors.¹⁹ Other factors, such as coexistence of other liver diseases, obesity, metabolic syndrome, and cigarette smoking can also contribute to the overall risk of developing ALD.²⁰ Women are more prone to develop ALD at lower amounts of drinking alcohol and are more likely to progress to liver fibrosis than men.²¹ However, women in China has a much lower rate of ALD than man, this is probably because women in China drink much less alcohol than man. Dietary habits (such as high-fat diet) and drinking patterns (such as binge drinking) also influence the development and progression of ALD. In addition, some socioeconomic status, such as the levels of occupation, education, family income and marital status also affect ALD.

Table 1. Population-based epidemiological surveys on alcohol consumption in China.

	Year	Area	n	Age(years)	Habitual drinking (%)	Excessive drinking (%)
Li, et al	2000	Zhengjiang	18237 (M 66.0%)	38.3±12.3	27.0 (M —, F —)	14.8
Lu, et al	2000	Xian	3613 (M 60.6%)	36.0±13.0	35.2 (M 52.2, F 8.9)	—
Huang, et al	2005	Hunan	18828 (M 69.2%)	42.1±13.4	37.8 (M —, F —)	—
Chen, et al	2007	Liaoning	6598 (M 62.2%)	39.3±11.1	27.0 (M 38.3, F 5.6)	—
Wang, et al	2011	Shandong	7295 (M 48.2%)	44.7±13.9	42.76 (M 74.5, F 11.3)	—
Yan, et al	2015	Shanxi, Gansu, Xinjiang	2300 (M 75.0%)	38.1±13.3	66.2 (M 77.9, F 31.2)	—

Excessive drinking: alcohol consumption \geq 40g /day for over 5years; M: male; F: female; “—”: unavailable

Table 2. Population -based epidemiological surveys on alcohol liver disease in China.

	Year	n	Morbidity Rate of ALD (%)	ALD			
				MALD (%)	AFL (%)	AH (%)	AC (%)
Li, et al	2000	18237	4.34 (M 6.36, F 0.36)	1.21	0.94	1.51	0.68
Lu, et al	2000	3613	2.27 (only one female)	—	2.16	—	0.11
Huang, et al	2005	18828	4.36 (M 6.00, F 0.52)	1.21	0.97	1.50	0.68
Chen, et al	2007	6598	6.82 (M 9.75, F 2.00)	4.29		2.18	0.35
Wang, et al	2011	7295	8.55 (M 15.76, F 1.42)	6.23	1.71	0.42	0.17
Yan, et al	2015	2300	8.74 (M 10.08, F 4.70)	4.22	3.74	0.48	0.30

ALD: alcoholic liver disease; MALD: mild ALD; AH: alcoholic hepatitis; AC: alcoholic cirrhosis; “—”: unavailable

GENETICS

The genetic polymorphisms of the ethanol metabolizing enzymes is associated with the susceptibility to ALD development. Several studies from Taiwan, Beijing and Zhejiang found that the genetic polymorphisms of ADH2, ADH3 and ALDH2 among Han Chinese population are different from those in people from western countries, which

might explain the different incidence of ALD between Han Chinese from China and people from Western countries. Polymorphic ADH2, ADH3 and ALDH2 genes can affect the propensity for alcohol drinking in Chinese. The alleles of ADH2*2, ADH3*1 and ALDH2*2 most likely play a protective role against heavy alcohol consumption; however, ADH2*2 and ALDH2*2 may contribute to susceptibility for

ALD if the individuals with these polymorphisms drink heavily.²² By analyzing of ALDH2 polymorphisms in 450 patients with alcoholic cirrhosis and 683 patients with HBV-related liver diseases, we found that among drinkers with HBV infection, the gene polymorphism of ALDH2*1/*2 is associated with the incidence of HBV-related cirrhosis and HCC, and it is a risk factor for diseases progression from cirrhosis to HCC and from stage B to C or D in HCC. Among patients with alcoholic cirrhosis, the prevalence of the ALDH2*1/*2 is less than 5%, and patients with ALDH2*2/*2 were not found. In addition, Zhang *et al* found that the gene polymorphism for PsaI/PsaI restriction site of CYP2E1 was associated with susceptibility of ALD.²³ Finally, the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene polymorphism has been extensively characterized that predisposes towards more advanced alcohol-related liver lesions.²⁴ However, the association of PNPLA3 polymorphisms with ALD has not been studied in China.

CLINICAL PRESENTATION

Mild ALD can be asymptomatic; Moderate or severe alcoholic fatty liver can appear the clinical manifestations of chronic hepatitis, no specificity; Once for the development of alcoholic hepatitis, which can appear relatively obvious gastrointestinal symptoms and signs, such as loss of appetite, jaundice, liver area enlargement, liver tenderness, and *et al*. Long-term drinkers may develop to alcoholic liver cirrhosis, and even hepatocellular carcinoma (HCC). Because about 40% of Chinese population is ALDH2 genetic defects, even a small amount of alcohol consumption, may lead to facial flushing, heart palpitations and other discomfort due to the acetaldehyde metabolism disorders, which will reduce or stop alcohol intake. To a certain extent, the occurrence and progress of ALD will be prevented.

MANAGEMENT

Owing to the significant healthcare problems and prevalence of ALD, we need to find better and more powerful procedures to manage this disease. Management of ALD includes abstinence from alcohol, treatment of alcohol withdrawal, nutritional support, and treatment of cirrhosis-related complications. As for the patients with severe alcoholic hepatitis, most pharmacotherapy only improves short-time survival and has little beneficial effects for long-term survival in most trials. The important factors for six-month survival relate to abstinence and nutrition and then subsequently relate to the underlying cirrhosis and its complications. Drug treatments include drugs by improving alcohol metabolisms, antioxidants, drugs by anti-endotoxin, etc. New drugs are being developed, such as IL22 which has processed the stages of clinical trials. It is worth mentioning that traditional Chinese medicine (TCM) also played supporting roles in the treatment of ALD by improving the fat metabolism and anti-fibrosis. Patients with severe alcoholic hepatitis who fail medical therapy have very poor outcomes. New treatment agents for severe alcoholic hepatitis are under development, and the role of early liver transplantation in highly selected patients requires further study.²⁵ Liver transplantation is the best available option for patients with alcoholic cirrhosis as long as

they abstain from alcohol. There has been a gradual increase in the number of patients with end-stage ALD undergoing liver transplantation in mainland China over the last 10 years. In addition to medical treatment measures, compared to the patients with liver diseases related to viral hepatitis, ALD population needs more psycho-social supports from doctors, family members and the whole society. They need to build up the confidence of abstinence and cure for ALD, and to receive support and encouragement from their families and friends. In addition, Chinese government may further improve the systems and the laws related to the reduction of alcohol consumption.

FUTURE PERSPECTIVE

The incidence of ALD will continue to upsurge in China. Due to significant differences in alcohol metabolism, genetics, drinking patterns, and eating habits and behaviors between the East and the West, the pathogenesis of ALD in Chinese population may be different from the well-characterized ALD in Western countries. Thus, the researches on ALD in Chinese population should be carried out, such as the clinical diagnosis criteria of ALD, the characteristics of alcohol metabolism, and the clinical and pathological characteristics and prognosis in the Chinese patients with ALD.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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