Heavy Binge Drinking May Increase Risk of Stroke in Nonalcoholic Hypertensives Carrying Variant ALDH2*2 Gene Allele

Ching-Long Lai¹, Meng-Ta Liu²,³, Shih-Jiuin Yin¹, Jiunn-Tay Lee², Chun-Chung Lu², Giia-Sheun Peng²

Abstract-

Purpose: Epidemiologic evidence demonstrates that heavy drinking increases the risk of stroke. However, whether recent heavy drinking affects the incidence of acute stroke in nonalcoholic individuals with the variant allele ALDH2*2 has not been reported.

Case Report: Two previously nonalcoholic healthy men suffered from acute ischemic stroke after a single episode of binge drinking. Both patients had one risk factor for stroke (a history of hypertension) and were heterozygous for ALDH2*2.

Conclusion: The confluence of these factors with stroke has raised the possibility that heavy binge drinking increases the risk of acute stroke in hypertensives with the variant ALDH2*2 gene allele.

Key words: binge drinking, ALDH2, stroke, hypertension

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INTRODUCTION

Recent heavy drinking and even occasional drinking to intoxication can trigger an ischemic stroke⁴⁻⁵. Heavy drinking of alcohol may trigger stroke by precipitating cardiac arrhythmias or by raising the level of acetaldehyde, a potentially cardiotoxic byproduct of ethanol⁶⁻⁷. Most of the ethanol in blood is eliminated via oxidation to acetaldehyde and acetate, catalyzed principally by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)⁸⁻¹⁰. Both enzymes exhibit genetic polymorphism and ethnic variation⁸⁻¹⁰. The variant alleles ADH1B*2 and ALDH2*2 are the best known for their roles in ethanol metabolism and alcohol-related disorders⁸⁻¹⁰. The variant allele ADH1B*2 encodes the high-activity ADH isoform that accelerates the conversion of ethanol to acetaldehyde⁹⁻¹⁰, and the ALDH2*2 allele encodes the low-activity ALDH isoform that is functionally inactive, impairing the conversion of acetaldehyde to acetate⁹⁻¹⁰. The variant allele ADH1B*2 occurs in 80–90% of individuals in East Asian populations⁰⁻¹¹ and the variant allele ALDH2*2 is found almost exclusively in East Asian populations¹²⁻¹³. Among East Asian people, both the functional polymorphisms at the ADH1B and

From the ¹Department of Nursing, Chang Gung University of Science and Technology, Taoyuan. Departments of ²Neurology and ³Biochemistry, National Defense Medical Center, Taipei. ⁴Department of Internal Medicine, Hualien Armed Forces General Hospital, Hualien, Taiwan.

Correspondence to: Giia-Sheun Peng, MD. Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, No. 325, Cheng-Kung Rd Section 2, Taipei 114, Taiwan, Republic of China.
E-mail: penggs@ndmctsgh.edu.tw

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ALDH2 loci have been reported to be involved in alcohol metabolism, drinking behavior, and occurrence of alcohol-related disorders, but no report of the relevance of a binge drinking and variant allele ALDH2*2 in non-alcoholic hypertensive stroke patients. Herein we report two cases of acute ischemic stroke after a binge drinking in previously nonalcoholic hypertensive individuals genotyped as ADH1B*2/*2 and ALDH2*1/*2.

CASE REPORTS

Two previously healthy men (patients A and B) presented with acute stroke symptoms and were taken to our emergency department (ED). Patient A, 59 years old, had decreased consciousness, motor aphasia, and right-sided weakness 4 hours after attending a social activity where he became very drunk (blood ethanol concentration, about 108.3 mg/dl at the ED). Patient B, 57 years old, suffered from sudden right-sided limb numbness on getting up out of bed. The night before, he attended a wedding and got drunk after consuming about 400 ml of whiskey (equal to 170 g of ethanol).

Brain MRI in patient A (Fig. 1) showed multiple infarcts in the left frontal and parietal corona radiata (not shown) and basal ganglion, and a critical stenosis of the M2 segment of the left middle cerebral artery (MCA); brain MRI in patient B showed a large infarct in the left parietotemporal lobe and intact intracranial vessels. The findings of stroke screening tests, including blood routine, biochemistry, electrocardiogram and cardioechography, were unremarkable in both patients except for a history of hypertension. The determination of the ALDH2 and ADH1B allelotypes from an analysis of leukocyte DNA using the polymerase chain reaction – amplified product length polymorphism method showed both subjects were heterozygous for ALDH2*2 and homozygous for ADH1B*2/*2 (Fig. 2).

DISCUSSION

Previous studies have shown that heavy drinking is one of the important risk factors for all stroke subtypes. Genetic variation in alcohol metabolism is one of the biological determinants that can significantly influence
drinking behavior and the development of alcohol-induced disorders (7,8). The relevance of recent heavy drinking to the occurrence of acute stroke in people with variant allele ADH1B*2 or ALDH2*2 has not been reported. Only two population-based surveys on Japanese residents revealed that ADH1B*1 allele and ALDH2*1 allele were significantly associated with the prevalence of cerebral infarction (15,16). However, neither study elucidated the relationship between these genes and drinking behavior nor how they influence vulnerability to the acute stroke.

From pharmacokinetic and pharmacodynamic studies in Han Chinese with the allele ALDH2*1*1 and the variant allele ADH1B*2 (which encodes a high-V_{max}, \( \beta_2 \) subunit that may increase alcohol elimination rates), ADH1B*2 per se did not lead to an appreciable increase in blood levels of acetaldehyde and thereby to increased cardiovascular sensitivity after intake of moderate amounts of ethanol (17). By contrast, the variant ALDH2*2 allele appeared to lower liver ALDH2 activity. However, combined genotype-phenotype studies demonstrated that homozygous ALDH2*2/*2 individuals responded to even a single dose of alcohol with increased acetaldehyde level and pronounced cardiovascular effects. Heterozygotic ALDH2*1/*2 individuals, regardless of their ADH1B genotype, also showed a similar phenotype after consuming a low to moderate amount of ethanol (17).

In general, the adverse reaction of individuals with variant ALDH2*2 alleles to alcohol reduces the frequency and quantity of alcohol use and episodic binge drinking (18) thereby providing innate physiological protection against excessive drinking and the development of alcoholism (19,20).

Most of strokes are ischemic. Approximately 30% of ischemic strokes are caused by cerebral embolism originating elsewhere in the circulation, most frequently in the heart. Excessive drinking and binge drinking can cause heart problems including cardiomyopathy and cardiac arrhythmia, leading to embolic stroke. The LIFE study (21) indicated that high alcohol intake will increase the risk of stroke in hypertensive patients with left ventricular hypertrophy. However, recent studies demonstrated that transgenic overexpression of ALDH2 or activation of ALDH2 with agonist appears to reduce ischemic damage to the heart (8,22-24), possibly more ALDH2 activities by increasing the metabolism of toxic biogenic and environmental aldehydes and metabolic activation of nitroglycerin. Jo et al. (24) also found that inactive form of variant ALDH2*2 allele is an independent risk factor for myocardial infarction in elderly Korean men. It seems that ALDH2 plays a role in cardioprotection against occasional adverse events.

The only risks of stroke in patients A and B were history of hypertension and binge drinking. In patient A, blood ethanol remained high even more than 4 hours after binge drinking. They were genotyped as ADH1B*2/*2 and ALDH2*1/*2. Theoretically, variant ADH1B*2 and ALDH2*2 alleles will make them have high blood acetaldehyde concentration through the increased alcohol elimination rates and the slowed conversion of ethanol-derived acetaldehyde to acetate and significant cardiovascular consequences after ethanol consumption. Therefore, the speculation of cardioembolic stroke in both cases could well have been circulatory and cardiac rhythm disturbances triggered by hypertension and alcohol intoxication.

Approximately one billion people in East Asia carry the variant ALDH2*2 allele. Our cases highlight the issue of whether binge drinking in individuals with variant ALDH2*2 and thus low ALDH2 activity have greater vulnerability to stroke caused by alcohol-induced cardiovascular effects (19,20). Further studies are needed to clarify how drinking behavior influences the occurrence of stroke in such individuals.

In conclusion, the risk of acute ischemic stroke in hypertensive Asians with variant ALDH2*2 allele after binge drinking might increase cardiovascular stress due to prolonged elevation of blood ethanol and acetaldehyde levels.

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