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

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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

Acta Neurol Taiwan 2012;21:39-43

INTRODUCTION

Recent heavy drinking and even occasional drinking to intoxication can trigger an ischemic stroke[1,2]. Heavy drinking of alcohol may trigger stroke by precipitating cardiac arrhythmias or by raising the level of acetaldehyde, a potentially cardiotoxic byproduct of ethanol[3,4]. Most of the ethanol in blood is eliminated via oxidation to acetaldehyde and acetate, catalyzed principally by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)[5]. Both enzymes exhibit genetic polymorphism and ethnic variation[6]. The variant alleles *ADH1B*2* and *ALDH2*2* are the best known for their roles in ethanol metabolism and alcohol-related disorders[7-9]. The variant allele *ADH1B*2* encodes the high-activity ADH isoform that accelerates the conversion of ethanol to acetaldehyde[10], and the *ALDH2*2* allele encodes the low-activity ALDH isoform that is functionally inactive, impairing the conversion of acetaldehyde to acetate[11]. The variant allele *ADH1B*2* occurs in 80~90% of individuals in East Asian populations[12] and the variant allele *ALDH2*2* is found almost exclusively in East Asian populations[13]. Among East Asian people, both the functional polymorphisms at the *ADH1B* and

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Received August 13, 2011. Revised October 21, 2011.
Accepted February 16, 2012.

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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 nonalcoholic 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[14] showed both subjects were heterozygous for *ALDH2*2* and homozygous for *ADH1B*2/*2* (Fig. 2).

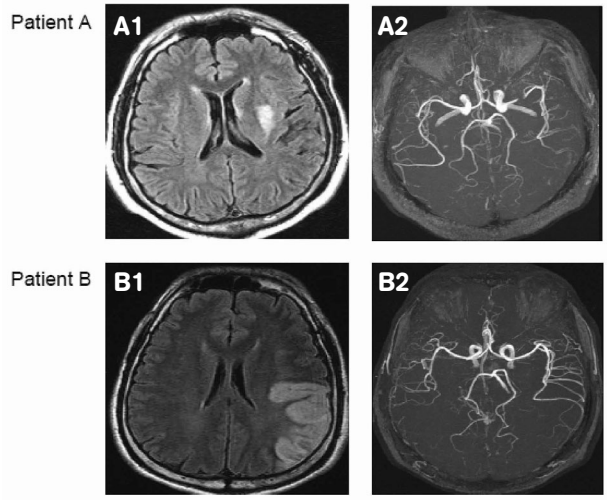

Figure 1. Brain images of two previously healthy men (patients A and B) who developed acute ischemic stroke after a drinking binge.
A1: Axial FLAIR image showing a hyperintense lesion in the left basal ganglia.
A2: Brain MRA image showing a critical stenosis in the M2 segment of the left MCA.
B1: Axial FLAIR image showing a large hyperintense lesion in the left parietotemporal lobe.
B2: Brain MRA image showing normal intracranial vessels.

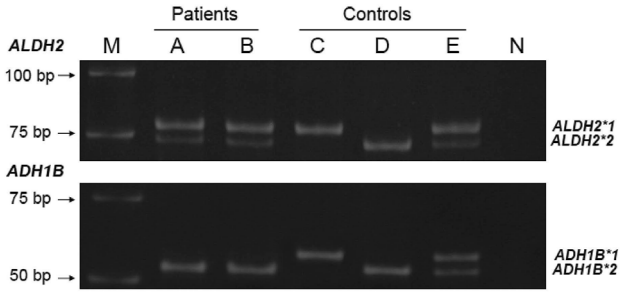

Figure 2. Genotyping of *ALDH2* and *ADH1B* by the polymerase chain reaction – amplified product length polymorphism method. Upper panel shows the genotyping of *ALDH2* and lower panel shows the genotyping of *ADH1B*. M, size marker; A and B, patients A and B with *ALDH2*1/*2* and *ADH1B*2/*2*; C, control subject with *ALDH2*1/*1* and *ADH1B*1/*1*; D, control subject with *ALDH2*2/*2* and *ADH1B*2/*2*; E, control subject with *ALDH2*1/*2* and *ADH1B*1/*2*; N, Blank.

DISCUSSION

Previous studies have shown that heavy drinking is one of the important risk factors for all stroke subtypes[1]. 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} β_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[4,22-24], 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.

ACKNOWLEDGEMENT

This work was supported by grants from the Tri-Service General Hospital (TSGH-C98-11-S01-04; TSGH-C99-11-S01-04; TSGH-C100-006-010-11-S01-03).

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