CLINICAL AND GENETIC CHARACTERISTICS OF KOREAN MALE ALCOHOLICS WITH AND WITHOUT ATTENTION DEFICIT HYPERACTIVITY DISORDER

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Abstract — Aims: To examine the clinical and genetic characteristics of Korean male alcoholics with and without attention deficit hyperactivity disorder (ADHD). Methods: The present study included 85 male alcoholics who were diagnosed as having DSM-IV alcohol dependence. A total of 28 (32.9%) alcoholics were diagnosed as having DSM-IV ADHD with ongoing symptoms in adulthood. For the evaluation of their psychiatric conditions, the alcohol dependence scale (ADS), Beck depression inventory (BDI), Beck anxiety inventory (BAI), Barratt impulsiveness scale (BIS), brief anger-aggression questionnaire (BAQ), overt aggression scale (OAS), codependence test, and obsessive compulsive drinking scale (OCDS) were administered. The genotype frequencies of the dopamine type 2 receptor gene (DRD2), aldehyde dehydrogenase type 2 gene (ALDH2), functional polymorphism in the regulatory region of the serotonin transporter gene (5-HTTLPR), and catechol-O-methyltransferase gene (COMT) polymorphisms were examined.

Results: Compared with alcoholics without ADHD, the mean ages for the onset of pathological drinking and alcohol withdrawal hallucinations were significantly earlier in alcoholics with ADHD. There was also a significant difference in the history of antisocial behaviour between the two groups. Compared with alcoholics without ADHD, the mean scores of the ADS, BDI, BAI, OAS, and OCDS were significantly higher in alcoholics with ADHD. With regard to the codependence test results, the mean scores of the interpersonal problem, low self-esteem and anxiety/fear subscales, and the mean total score of the codependence test were significantly higher in alcoholics with ADHD when compared with those without ADHD. There were no significant differences in the genotype frequencies of the DRD2, ALDH2, 5-HTTLPR, and COMT polymorphisms between alcoholics with and without ADHD. Conclusions: The results of this study suggest that the comorbidity of alcohol dependence and ADHD in this Korean sample forms a distinct clinical phenotype that shows an increased severity of alcohol-related symptoms and behavioural/emotional problems and that ADHD is associated with an increased risk for the early onset of alcohol dependence in Korean male alcoholics.

INTRODUCTION

Several recent studies have suggested that attention deficit hyperactivity disorder (ADHD) is an important risk factor for the development of alcoholism (Biederman, 1998; Wilens, 2002), and the results from several follow-up studies done on ADHD children and adults have revealed a high prevalence of alcohol abuse and/or dependence in these subjects (Biederman et al., 1997, 1998; Ercan et al., 2003). Biederman et al. (1995) have reported that the risk of substance use disorders was twice as high for those subjects with ADHD, and it was four times as high for the ADHD subjects having a comorbid conduct disorder when compared with the normal population.

Alcohol and substance use disorders tend to appear at an earlier age for adults with ADHD when compared with those without ADHD (Wilens et al., 1997). In addition, the adults with alcohol use disorders exhibit an increased severity of substance use problems, when ADHD is combined with their drinking problems, and the presence of ADHD has been suggested to accelerate the transition from substance abuse to dependence (Wilens, 1998). ADHD and alcohol or substance dependence occur together more frequently than would be expected by chance (Kaminer, 1991; Ercan et al., 2003). Approximately 40% of ADHD adults have been reported to exhibit alcohol or substance use disorders (Biederman et al., 1995) and, conversely, in those adults with substance use disorders, the rates of ADHD range from 15 to 25% (Wilens, 1998).

There have been many familial and genetic studies showing that hereditary factor is important in the mechanism of ADHD or alcohol-dependence development (Faraone and Doyle, 2001; Fan et al., 2004), and there is a possibility that the two disorders might share overlapping sources of genetic liability (Johann et al., 2003). The candidate genes associated with alcohol dependence have been mentioned in several genetic studies (Dick and Foroud, 2003). These genes include the dopamine type 2 receptor gene (DRD2), aldehyde dehydrogenase type 2 gene (ALDH2), serotonin transporter gene (5-HTT), serotonin 1B receptor gene, and catechol-O-methyltransferase gene (COMT), and most of these genes, interestingly enough, are also the candidate genes associated with ADHD (Bobb et al., 2005).

The results of the above-mentioned studies have well documented the close relationship between ADHD and alcohol dependence. However, most of these studies have been conducted on Western populations, and the genetic data between the alcoholics with and without ADHD have rarely been compared in previous studies. Therefore, the aim of this study was to examine the clinical and genetic characteristics of Korean male alcoholics with and without ADHD.

SUBJECTS AND METHODS

Subjects

The present study included 85 male alcoholics (41.5 ± 3.4 years), aged 29–50 years, who were hospitalized at the Department of Psychiatry of the Gyeongsang National University Hospital and the Hannaeum Hospital in Korea, and who agreed to participate in the study. All the subjects were
Clinical assessment

The diagnostic interview schedule for children-IV (DISC-IV)-ADHD module-whole life version (Shaffer et al., 2000) was the tool used for the diagnosis of ADHD in the present study. It is a structured interview tool designed to evaluate the severity of the ADHD symptoms, and it also evaluates the current state and the affected state throughout the lifetime of the subject according to the DSM-IV criteria. The diagnoses were made by face-to-face interviews that were conducted by two board-certificated psychiatrists. The DISC-IV interviewers underwent intensive training regarding the instrument, the diagnostic classification, and the use of the DISC-IV. A total of 10 subjects were randomly selected for examining the inter-rater reliability testing, and this resulted in a high level of inter-rater reliability (0.90) for the diagnosis of ADHD. Of the 85 alcohol-dependent subjects, 28 (32.9%) were diagnosed as having ADHD with ongoing symptoms in their adulthood.

For the evaluation of psychiatric conditions, the alcohol dependence scale (ADS) (Skinner and Allen, 1983; Lee et al., 2000), Beck depression inventory (BDI) (Beck et al., 1961; Lee and Song, 1991), Beck anxiety inventory (BAI) (Beck et al., 1988; Yook and Kim, 1997), Barratt impulsiveness scale (BIS) (Lee, 1992; Patton et al., 1995), Brief anger-aggression questionnaire (BAQ) (Maiuro et al., 1987), overt aggression scale (OAS) (Yudofsky et al., 1986), codependence test (Kitchens, 1991; Kim et al., 1999), and obsessive compulsive drinking scale (OCDS) (Anton, 2000) were administered to the subjects. The Korean versions of all the instruments used in this study are known to have good validity and reliability. The ADHD testing or other tests administered had not been influenced by withdrawal symptoms or craving of the subjects.

Genotyping

**DRD2 Taq1A allele genotype.** Genomic DNA was extracted from blood lymphocytes using Genomic DNA Extraction kit (Bioneer, Korea). The polymerase chain reaction (PCR) method determining Taq1A DRD2 alleles has been previously described by Grandy et al. (1989). Two alleles were obtained: uncleaved 310 bp A1 and cleaved (180 and 130 bp) A2.

**ALDH2 genotype.** For the PCR genotyping of the ALDH2 polymorphism, the method developed by Tu and Israel (1993) was used.

**5-HTTLPR genotype.** The 5-HTTLPR of the 5-HTT gene regulatory region was amplified by the PCR method described elsewhere (Heils et al., 1996). The 484 bp fragment was designated as S allele and the 528 bp fragment as L allele.

**COMT genotype.** COMT genotypes were determined by restriction fragment length polymorphism (RFLP) analysis, as described by Lachman et al. (1996). Two alleles were obtained: L allele (96/83/20/18 bp) and H allele (114/83/20 bp).

Statistical analysis

Allele frequencies were estimated by counting, and the Hardy–Weinberg equilibrium was calculated based on these allele frequencies by the goodness-of-fit $\chi^2$-test. The estimation of allele frequencies and the test for Hardy–Weinberg equilibrium were conducted for the genotypes of all subjects.

Group differences in the clinical variables involving continuous data were computed using the independent two sample $t$-test. Between-group comparisons involving categorical data were assessed using the $\chi^2$-test. Significance level was set at $P = 0.05$ (two-tailed).

RESULTS

**Comparison of the demographic and alcohol-related characteristics between the alcoholics with and without ADHD**

The mean age of the alcoholics with ADHD was 43.1 ± 13.2 years, which was not significantly different from that of the alcoholics without ADHD (42.5 ± 11.8 years) (Table 1). Significant differences were seen in the marital status and education level ($P < 0.05$). There were no significant differences in the socioeconomic status, history of depression, or history of other substance between the two groups. Compared with alcoholics without ADHD, the mean age of onset of pathological drinking, as manifested by four or more problem drinking days a week that lead to clinically significant impairment in a person, was significantly earlier in alcoholics with ADHD. The percentage of those having experienced pathological drinking before the age of 30 was significantly higher ($P < 0.05$) in alcoholics with ADHD when compared with alcoholics without ADHD. There were no significant differences in the mean age of onset of alcohol withdrawal symptoms and the percentage of those having experienced alcohol withdrawal hallucinations once at least since the onset age of drinking between the two groups. However, the mean age of onset of alcohol withdrawal hallucinations was significantly earlier ($P < 0.01$) in alcoholics with ADHD when compared with those without ADHD. There was a significant difference ($P < 0.05$) in the history of antisocial behaviour between the two groups.
A comparison of the ADS, BDI, BAI, BIS, BAQ, OAS, OCDS, and codependence test results between alcoholics with and without ADHD

Comparison of the ADS, BDI, BAI, BIS, BAQ, OAS, OCDS, and codependence test results between the alcoholics with and without ADHD

Compared with alcoholics without ADHD, the mean scores of the ADS, BDI, BAI, OAS, and OCDS were significantly higher ($P < 0.05$, $P < 0.01$ for the ADS and BDI profiles) in alcoholics with ADHD (Table 2). No significant differences were found between alcoholics with and without ADHD in the BIS or BAQ results. With regard to the codependence test results, the mean scores of interpersonal problem, low self-esteem and anxiety/fear subscales, and the mean total score of the codependence test were significantly higher ($P < 0.05$, $P < 0.01$ for the interpersonal problem profile) in alcoholics with ADHD when compared with those without ADHD.

Comparison of the genotype frequencies between alcoholics with and without ADHD

The distribution of genotypes for the DRD2, ALDH2, 5-HTTLPR, and COMT polymorphisms were in agreement with the expected values of the Hardy–Weinberg equilibrium. There were no significant differences in the genotype frequencies of the DRD2, ALDH2, 5-HTTLPR, and COMT polymorphisms between alcoholics with and without ADHD (Table 3).

DISCUSSION

In this study, 32.9% of the patients with alcohol dependence were identified as having comorbid ADHD, and this percentage was higher than the results of the previous studies (15–25%) (Wilens, 1998). However, our result is comparable with the results of one study, which reported that 32% of the substance use disorder patients met the criteria for ADHD (Clure et al., 1999).

The results of this study show that pathological drinking developed ~4 years earlier and alcohol withdrawal hallucinations occurred ~7 years earlier in alcoholics with ADHD as compared with those without ADHD. These results agree with the findings of a couple of previous studies (Wilens et al., 1997; Hahesy et al., 2002) that ADHD is associated with an increased risk for early onset substance use disorders. In Wilens et al.’s (1997) study, alcohol and substance use disorders appeared at earlier ages in subjects with ADHD than in those without ADHD (mean age of onset: 19 versus 22 years, respectively). Hahesy et al. (2002) suggested that ADHD may represent antecedent risk factors for and is also associated with earlier onset of substance use disorders, including alcohol dependence.

According to Cloninger’s (1987) typology of the alcoholic subtypes, Type 1 alcoholics have a disorder that is more responsive to environment and less related to genetic factors, and the onset of alcohol problems for this subtype occurs after...
the age of 25. Type 2 alcoholics, on the other hand, have a disorder that is thought to be highly influenced by hereditary factors, with an early onset (<25 years) of alcohol problems, and they have an antisocial personality configuration of high novelty seeking, low harm avoidance, and low reward dependence. In this study, there was no significant difference between alcoholics with and without ADHD in the percentage of subjects who experienced pathological drinking before the age of 25. However, significant difference was found (81.5 versus 60.8%) when we stratified the onset age as either early-onset (<30 years) or late-onset (≥30 years). In light of the fact that the ALDH2*2 allele may contribute to protecting against the development of alcohol dependence and that this allele commonly occurs in Asian populations, but is not seen in most other ethnic groups (Muramatsu et al., 1995; Lee et al., 1997; Chen et al., 1999; Ramchandani et al., 2001), there is a possibility that the onset age of alcohol dependence in Koreans, regardless of the preceding or comorbid psychopathology, might be later than the onset age seen in Western populations.

With regard to psychiatric conditions, the alcoholics with ADHD in this study exhibited an increased severity of alcohol-dependence symptoms according to the ADS results, and these subjects were found to be more depressive, anxious, and aggressive according to the BDI, BAI, and OAS results when compared with those without ADHD. In addition, the alcoholics with ADHD showed more interpersonal problems, lower self-esteem, and more anxiety/fear symptoms according to the codependence test results. The above-mentioned behavioural/emotional problems have been described in previous studies as the comorbid psychiatric symptoms associated with ADHD (August et al., 1996; Biederman et al., 1996; Jensen et al., 1997). In light of the fact that alcoholics with ADHD in this study exhibited a higher frequency of having a history of antisocial behaviour than those without ADHD (25.0 versus 7.4%), there is a possibility that the antisocial spectrum of behaviour problems, which include oppositional defiant disorder (ODD) or conduct disorder (CD) in childhood, and antisocial personality disorder in adulthood, might have preceded or combined with a particular subgroup of alcoholics with ADHD. Several studies have suggested that children who have a combination of ADHD and CD are at an elevated risk for developing antisocial behaviours, delinquency, and committing criminal offences (August et al., 1996; Nolan et al., 2001), and children who have both ADHD and ODD are at a higher risk of exhibiting depressive symptoms, interpersonal problems, and impairment in psychosocial functions when compared with the ADHD subjects without ODD (Biederman, 1998; Wilens et al., 2002). The higher incidence of behavioural and emotional problems in alcoholics with ADHD in this study may, in part, be explained by the results of the above-mentioned studies.

With respect to the genetic data in this study, there were no significant differences in the genotype frequencies of the DRD2, ALDH2, 5-HTTLPR, and COMT polymorphisms between alcoholics with and without ADHD. Our results are comparable with the results of one recent study (Johann et al., 2003), which reported that no significant difference was found in the 5-HTTLPR genotype distribution between alcohol-dependent patients with and without ADHD. Genetic variants of the dopaminergic and serotonergic systems have been suggested as reasonable candidate genes that are associated with ADHD or alcohol dependence, and the DRD2 and 5-HTTLPR genes have been proposed as the candidate genes for both of these entities. The frequency of the DRD2 A1 allele has been reported to be significantly higher in the ADHD probands when compared with the normal control group (Blum et al., 1995), and a significantly increased risk of alcohol dependence in the subjects carrying this allele has been confirmed in several studies (Arinami et al., 1993; Lawford et al., 1997). The frequency of the ‘S’ allele of the 5-HTTLPR gene has also been reported to be significantly higher in the ADHD subjects (Cadoret et al., 2003), and this allele has been suggested to be associated with alcoholism, particularly with the alcoholic subtype having antisocial personality traits or aggressive behaviour (Sander et al., 1998; Hammoumi et al., 1999).

There are several limitations to this study. First, the clinical data reported in this study were derived from the self-reports of the subjects and thus, were prone to reporter biases. Second, we only examined male alcoholics and, therefore, the results might not be representative of all of the subjects with alcohol dependence in Korea. Finally, the sample size of the study was relatively small and, therefore, might lack statistical power.

However, despite these limitations, the results of this study suggest that the comorbidity of alcohol dependence and ADHD in a sample of the Korean population forms a distinct clinical phenotype that shows an increased severity of alcohol-related symptoms and behavioural/emotional problems, and that ADHD is associated with an increased risk for early onset alcohol dependence in Korean male alcoholics. To the best of our knowledge, this is the first study to evaluate the genotype distributions of the DRD2, ALDH2, and COMT polymorphisms in alcoholics with and without ADHD. Further work is required to confirm the findings of this study and to investigate the putative common genetic predisposition of ADHD and alcohol dependence.

REFERENCES


