

## Discussion

The mean values of alcohol consumption differed significantly among subjects with different genotypes, in both the control and the PD group. The finding that people with the *ALDH2\*2* allele refrain from excessive alcohol consumption due to aversive symptoms (Harada et al., 1981) might explain the observed differences among subjects with these three different genotypes. Previous studies have also shown that PD patients consume less alcohol than healthy control subjects (Jimenez-Jimenez et al., 1992; Pollock et al., 1966; Duvoisin et al., 1981; Koller, 1981), and that genetic polymorphisms of ALDH2 may influence drinking habits among Japanese people (Harada, 1991). Moreover, individuals who are homo- or heterozygous for the *ALDH2\*2* allele were found to consume significantly less alcohol than those who are homozygous for the *ALDH2\*1* allele (Ishibashi et al., 1997). Therefore, in the present study we classified participants into three groups according to their ALDH2 genotypes, and compared the alcohol consumption of PD patients and control subjects with the same genotype. These PD patients consumed significantly less alcohol than control subjects with the same genotype, although the distributions of the ALDH2 genotypes and allele frequencies were not different between PD patients and control subjects.

This study had several limitations. Because all of the PD patients were hospitalized and had abstained from alcohol for a long time at the time we obtained information on their alcohol consumption, we estimated the mean values of alcohol consumption in their premorbid years (40~50 years old) by direct interview. On the other hand, the data of alcohol consumption from the control subjects were obtained by questionnaire; the average ages of the control group were  $33.9 \pm 8.0$  years. Thus, there were methodological discrepancies in the way. Data were acquired from the two groups, and

mismatch in the present average age between patients and control subjects. The mean age of PD patients during their premorbid years was higher than that of the control subjects at the time of this study. However, the mean alcohol consumption of the male control group of this study was approximately the same as that of the previously reported 40 to 50 years old male workers (Morimoto et al., 1996; Takeshita, 1999), indicating that the age difference between patients and controls in alcohol consumption may not be misleading. Moreover, alcohol consumption ( $808.3 \pm 441.0$  g/year/person) in the 1980's was not significantly lower than that in the 1990's ( $847.0 \pm 164.0$  g/year/person) ( $p=0.22$ ), when calculated from the data in Health and Welfare statistics in Japan (Health and Welfare Statistics Association, Tokyo 1998).

Although we used different methods to obtain information from the two groups, we have no data to indicate that information obtained by direct interview is less or more problematic than that obtained by questionnaire. We employed direct interviews for the PD patients because their clinical condition and hospitalization made questionnaires difficult to administer. On the other hand, the large number of control subjects made direct interviews too time-consuming.

It is unclear whether patients with PD refrain from alcohol intake because of changes in personality caused by the disease, or because of their premorbid personality. Previous studies have revealed the possible existence of certain premorbid features in the personalities of patients with PD (Jimenez-Jimenez et al., 1992; Poewe et al., 1983; Todes et al., 1985), although another study found conflicting results (Glosser et al., 1995).

Recently, Menza et al. (1993) used the TPQ (Cloninger, 1987; Takeuchi et al., 1993) to classify the personalities of PD patients and control subjects, and found that PD patients had significantly lower total scores than healthy

control subjects in NS. The preliminary data suggest that these PD patients had significantly higher total HA scores and lower NS scores than the control subjects. Alcohol consumption was compared between PD patient groups with higher and lower scores of HA, but there was no significant difference between both groups. However, further studies on the relationship between the premorbid personality of PD patients and alcohol consumption are necessary to reach a final conclusion.

The data of TPQ test for Japanese patients with PD suggested that the high HA scores, and the low NS scores observed in PD patients is a cross cultural phenomenon. In the original report published by Menza et al. (1993), the total score for the HA dimension was higher for the PD patients than for the control group, however this difference did not reach statistical significance. In the present study, the total score for the HA dimension was significantly higher in the PD patient group than in the control group, and higher scores in the subcategories of "Anticipatory worry and pessimism", and "Fatigability and asthenia" were also observed in the PD patient group. The lack of significant differences in the RD scores was also consistent with the previous report by Menza et al. (1993).

It is possible that these particular personality differences might arise from motor dysfunction caused by the disease itself, or from the concomitant depression. HA is thought to be highly correlated with measures of depression (Menza et al., 1993), and almost one-half of the patients with PD are depressed (Mayeux et al., 1984). Indeed, the PD patients treated with anti-depressant drug were 31.1% of all patients in our study. Although the mean scores on HA for the anti-depressant drug-treated patients was significantly higher than in the non-treated patients, the HA scores of the latter group was also significantly higher, compared with the control group (Non-treated patients:  $18.8 \pm 5.0$ , Control:  $15.7 \pm 6.5$ ,  $t=2.9$ ,

P=0.005 ).

The data suggest that the comparatively high HA scores, and the low scores in the NS trait observed in PD patients is a cross cultural phenomenon, although both traits might be influenced by many factors such as depression, long-term treatment, and gene/environment interactions. Further association studies using genetic polymorphism for neurotransmitters and receptors related to HA trait may also lead to a better understanding of the high HA scores of patients with PD.

There have been no reports prior to the present study associating polymorphism of the CCK gene with PD. A total of four polymorphic loci of the CCK gene in PD patients and controls subjects were found. The polymorphisms at the -45C/T site, the 1270C/G site, and the 6662C/T site have been described in a previous studies (Harada et al., 1998; Wang et al., 1998; Bowen et al., 1998), and the -45C/T and the 1270C/G polymorphisms each demonstrate complete linkage disequilibrium (Bowen et al., 1998). The complete linkage disequilibrium for both loci were confirmed in PD patients and controls. A novel polymorphism corresponding to the transversion at the -196G→A site in the promoter region of the CCK gene was found in the present study. In addition, we found that both the -196 and the -45 loci were likely in linkage disequilibrium.

Significant association was found between PD and polymorphism for the -45 locus, including the 1270 locus. However this difference was not significant after Bonferroni correction. Significant deviation from Hardy-Weinberg equilibrium was observed in the genotype distribution of the controls. Further investigation is necessary to explore this finding by using larger member of age-matched controls.

Moreover, an important result was found when the frequencies of the three genotypes for the -45C locus were compared with respect to the

occurrence of hallucination in the PD patients treated with dopaminergic drugs. Hallucination is a common side effect of dopaminergic drug-treatment in PD, and is observed in more than 30% of PD patients (Moskowitz et al., 1970; Inzelberg et al., 1998). More recently, De la Fuente-Fernandez et al. (1999) suggested that apolipoprotein E epsilon 4 allele increases the risk of drug-induced hallucinations in PD. Aging and dementia appear to be possible risk factors for the occurrence of treatment-related hallucinations (Celesia et al., 1970; Fischer et al., 1990). Note however, that individual differences are observed in the occurrence of hallucinations in PD patients treated with anti-Parkinsonian drugs. The data suggest that the *CT* and *TT* genotypes at locus -45 of the CCK gene may represent a vulnerability for hallucination amongst drug-treated PD patients.

Several cis-elements are found binding with trans-acting factors in the promoter region of the CCK gene. They include bHLH-ZIP, CRE/TRE, Sp1, and TFIID (Nielsen et al. 1996). As the C→T transition is found to occur in the Sp1 binding cis-element, it is postulated that mutations to the Sp1 binding cis-element disrupts the binding capacity of the relevant transcription factor, impairing promoter activity. The mutation site (G G/A G A G G G) of the -196 locus corresponded to the putative consensus sequence of the myc-associated zinc finger protein (MAZ) binding cis-element (G G G A G G G) (Kennedy et al., 1992; Pyre, et al., 1992). However, there are at the present time no data suggesting that there might be an interaction between mutation of the CCK gene and the gene's promoter activity. The analysis concerning hallucination is limited by the small size, and future investigations, involving a larger number of patients demonstrating hallucinations, will be necessary to explore this finding further.

PD is characterized by major alterations of neurotransmitter activity

due to damage of the substantia nigra. Changes in neuropeptide concentration within the basal ganglia may play an important role in the putative dopaminergic-peptide interactions associated with the disease. CCK modulates the release of dopamine in the mesolimbic pathway and effects dopamine-related behavior.

### **Conclusion**

- 1) The lower values of alcohol consumption in patients with PD for every ALDH2 genotypes may caused by other factors such as premorbid personality rather than ALDH2 variant.
- 2) The high harm avoidance dimensions, and the low novelty seeking dimensions in the TPQ test observed in patients with PD is a cross-cultural phenomenon, although the influence of depression, long-term treatment and premorbid gene/environmental interactions may also effect these personality traits.
- 3) Mutations at the -45 locus in the promoter region of the CCK gene may influence PD itself, or vulnerability to hallucination in PD patients treated with L-dopa.
- 4) However, the analysis concerning hallucination is limited by the small sample size. Future investigations, involving larger number of patients demonstrating hallucinations, will be necessary to explore this finding further.