INTRODUCTION

Cataplexy is a symptom that occurs when the muscle tension in various areas of the body is suddenly decreased involuntarily and lasts from few seconds to several minutes. It is a pathognomonic symptom of narcolepsy, generally induced in response to laugh, excitement, anger, and other emotional changes (1, 2). In addition, among excessive daytime sleepiness, cataplexy, hypnagogic hallucination, sleep paralysis and nocturnal sleep disorder, which are known to be a symptom of narcolepsy, cataplexy has been known to be a pathognomonic symptom in narcolepsy. This study was designed to investigate the frequency of the HLA-DQB1 allele and cerebrospinal fluid (CSF) hypocretin levels in Korean narcolepsy with cataplexy as compared with those who do not have cataplexy. Seventy-two narcoleptics were selected based on polysomnography and multiple sleep latency test as well as their history and clinical symptoms at Sleep Disorders Clinic. The patients were divided into a narcolepsy with cataplexy group (n=56) and a narcolepsy without cataplexy group (n=16). All patients were subjected to HLA typing to determine the frequency of DQB1 allele and to spinal tapping to measure the level of CSF hypocretin. In cataplexy-positive patients, as compared with cataplexy-negative patients, the frequency of HLA-DQB1*0602 was found to be significantly high (89.3% vs. 50.0%) (p=0.003). On the other hand, the frequency of HLA-DQB1*0601 was found to be significantly low (0% vs. 43.8%) (p<0.001). The high frequency of HLA-DQB1*0602, low frequency of HLA-DQB1*0601 and low hypocretin levels in cataplexy-positive groups suggest that cataplexy-positive narcolepsy might be an etiologically different disease entity from the cataplexy-negative.

Key Words : Narcolepsy; Cataplexy; HLA-DQBbeta antigen; Hypocretin; Orexins

Cataplexy is one of the most pathognomonic symptoms in narcolepsy. This study was designed to investigate the frequency of the HLA-DQB1 allele and cerebrospinal fluid (CSF) hypocretin levels in Korean narcolepsy with cataplexy as compared with those who do not have cataplexy. Seventy-two narcoleptics were selected based on polysomnography and multiple sleep latency test as well as their history and clinical symptoms at Sleep Disorders Clinic. The patients were divided into a narcolepsy with cataplexy group (n=56) and a narcolepsy without cataplexy group (n=16). All patients were subjected to HLA typing to determine the frequency of DQB1 allele and to spinal tapping to measure the level of CSF hypocretin. In cataplexy-positive patients, as compared with cataplexy-negative patients, the frequency of HLA-DQB1*0602 was found to be significantly high (89.3% vs. 50.0%) (p=0.003). On the other hand, the frequency of HLA-DQB1*0601 was found to be significantly low (0% vs. 43.8%) (p<0.001). The high frequency of HLA-DQB1*0602, low frequency of HLA-DQB1*0601 and low hypocretin levels in cataplexy-positive groups suggest that cataplexy-positive narcolepsy might be an etiologically different disease entity from the cataplexy-negative.
prohypocretin mRNA was significantly decreased in the brain of narcolepsy patients (14). Along with these findings, the report showing the concentration of hypocretin in the cerebrospinal fluid (CSF) was measured below the detection limit in over 80% narcoleptics (16, 17) suggests that hypocretin deficiency may be one of the most important pathophysiologic mechanisms of narcolepsy.

In this regard, this study was performed on narcoleptics diagnosed by polysomnography and multiple sleep latency test (MSLT) to understand the pathophysiology of narcolepsy in Korean narcolepsy patients by examining the frequency of HLA-DQB1 allele and the concentration of CSF hypocretin. In addition, this study was designed to investigate the frequency of the HLA-DQB1 allele and the concentration of CSF hypocretin levels in Korean narcoleptics with cataplexy as compared with those who have not cataplexy.

MATERIALS AND METHODS

Subjects

From August 2003 to July 2005, among the patients reporting excessive daytime sleepiness, those who were suspicious of having narcolepsy were selected, based on diagnostic criteria for the International Classification of Sleep Disorders (3), and polysomnography and MSLT were performed at Sleep Disorders Clinic of St. Vincent’s Hospital, The Catholic University of Korea. All patients with a chief complaint of excessive daytime sleepiness not obviously from sleep disordered breathing (SDB), delayed sleep-phase syndrome or behaviorally-induced insufficient sleep syndrome were included. Seventy-five subjects were selected, who had at least 2 sleep onset REM periods (SOREMPS) on MSLT, and the mean sleep latency shorter than 5 min. And in polysomnography, they did not have any evidence of sleep disorders that can cause excessive daytime sleepiness such as sleep apnea syndrome, periodic limb movement disorder, etc. Seventy-two of the seventy-five subjects (96%) accepted further evaluation, including blood and CSF tests.

Seventy-two narcoleptic patients underwent HLA typing to determine the DQB1 allele and spinal tapping to determine the level of CSF hypocretin. The study subjects were divided into a narcolepsy with cataplexy group (n=56) and a narcolepsy without cataplexy group (n=16) according to the presence or absence of cataplexy. Narcoleptics were excluded if they had a personal history of medical illness that may affect sleep, substance or alcohol abuse, seizure disorder, definite neurological deficit, and mental disorder that may cause sleep abnormalities. This study was approved by the institutional review board of the St. Vincent’s Hospital, The Catholic University of Korea. Informed consent was obtained according to the Declaration of Helsinki.

Methods

All clinical symptoms of narcolepsy were collected through a structured interview in each patient by psychiatrists who had completed the sleep medicine course and through a sleep questionnaire. The structured interview revealed the frequency of excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucination, and the characteristic of cataplexy. In the questionnaire, triggering factors, duration, frequency of cataplexy were included, and the Stanford Center for Narcolepsy Sleep Inventory (18) consisting of total 146 questions was used.

Lymphocytes were isolated from the blood (2 × 10^6 cells/mL), and 0.5 mL PCR-K buffer (10 × PCR buffer 1 mL, NP-40 40 μL, Tween-20 45 μL, proteinase K (20 mg/mL) 30 μL, D/W 8.8 mL) was added, and dissolved by treating at 58°C for 60 min, and treated at 95°C for 10 min, to inactivate proteinase K, and DNA was extracted. To determine the HLA-DQB1 allele, allele-specific probes were labeled with Dig-11-dUTP using terminal transferase, each sample was dropped on a Nylon membrane, Dig-11-dUTP labeled allele-specific probe was hybridized with the membrane dropped a sample, the expression was assessed using anti-DIG antibody, and finally the genotypes were determined.

Between 11 a.m. and 4 p.m., CSF was collected by lumbar puncture, and immediately stored frozen at -70°C until the measurement of hypocretin. Hypocretin-1 was measured by 125I radioimmunoassay (RIA) kit (hypocretin-1: Phoenix Pharmaceuticals, Mountain View, CA, U.S.A.). CSF was acidified with the same volume of 0.1% trifluoroacetic acid (TFA), purified using equilibrated C-18 Sep-Columns (Phoenix Pharmaceuticals), and the columns were washed with 0.1% TFA twice and eluted with 0.1% TFA and 60% acetonitrile (HPLC grade). The eluted solution was dried by applying negative pressure, and the pellets produced were dissolved with 300 μL RIA buffer. The detection limit was 40 pg/mL, and all samples were measured in duplicate.

Statistical analyses

Statistical analysis was performed using SPSS for Windows (Version 10.0). Demographic data, the frequency of clinical symptoms, and the HLA-DQB1 allele frequencies were presented as the mean ± standard deviation, as well as in percentage. These variables and the CSF hypocretin levels were analyzed by independent t-test and chi-square test. A p-value less than 5% was considered statistically significant.

RESULTS

Demographical characteristics

Of the total 72 patients, 47 were male patients (65.3%), and 25 were female patients (34.7%). The age distribution
was 7-68 yrs (mean age 26.4±11.6 yrs). The mean body mass index was 24.2±3.7 kg/m², and the mean duration of illness was 9.5±8.3 yr.

The narcolepsy with cataplexy group consisted of 34 male patients (60.7%) and 22 female patients (39.3%). The age distribution was 7 to 59 yrs (mean age: 25.4±10.4 yrs). The mean body mass index was 24.5±3.7 kg/m², and the mean duration of illness was 9.9±8.8 yr.

The narcolepsy without cataplexy group consisted of 13 male patients (81.3%) and 3 female patients (18.8%). The age distribution was 8-68 yrs (mean age 29.8±14.8 yrs). The mean body mass index was 23.1±3.8 kg/m². The mean duration of illness was 8.3±6.2 yr. No significant differences were observed in demographic variables between two groups (Table 1).

**Clinical symptoms**

Excessive daytime sleepiness was shown in all 72 patients (100%), and it was found that cataplexy was experienced in 56 patients (77.8%), hypnagogic hallucination in 40 patients (55.6%), and sleep paralysis was experienced in 40 patients (55.6%). In addition, sleep paralysis was found to be experienced more frequently in the narcolepsy without cataplexy group (6/16, 25.0%) with a statistical significance (p=0.005). In comparison, only 6 of 16 cataplexy-negative patients (37.5%) had a decreased hypocretin level (<40 pg/mL) (19) or below the detection limit of assay (<40 pg/mL) in 48 out of 56 cataplexy-positive patients (85.7%). In comparison, only 6 of 16 cataplexy-negative patients (37.5%) had a decreased hypocretin level (p<0.001) (Table 3).

**CSF hypocretin level**

The CSF hypocretin concentration was lower than 110 pg/mL in 54 of the total 72 patients (75.0%). The hypocretin levels were decreased (≤110 pg/mL) in 48 out of 56 cataplexy-positive patients (85.7%). In comparison, only 6 of 16 cataplexy-negative patients (37.5%) had a decreased hypocretin level (p<0.001) (Table 3).

**HLA-DQB1 Allele**

Of 72 narcoleptic patients, 58 patients (80.6%) had HLA-DQB1*0602. HLA-DQB1*0602 was significantly more frequent in the narcolepsy with cataplexy group, but the difference was not significant (34 patients among 56 patients [60.7%] vs. 6 patients among 16 patients [37.5%]) (Table 2).

### Table 1. Demographic data of narcoleptic patients with and without cataplexy

|                  | Total (N=72) | With cataplexy (N=56) | Without cataplexy (N=16) | p-value |
|------------------|--------------|-----------------------|--------------------------|---------|
| Sex, male       | 47 (65.3%)   | 34 (60.7%)            | 13 (81.3%)               | NS      |
| female           | 25 (34.7%)   | 22 (39.3%)            | 3 (18.8%)                |         |
| Age (yr)         | 26.4±11.6    | 25.3±10.4             | 29.8±14.8                | NS      |
| Mean BMI (kg/m²) | 24.2±3.7     | 24.5±3.7              | 23.1±3.8                 |         |
| Illness duration (yr) | 9.5±8.3   | 9.9±8.8               | 8.3±6.2                  | NS      |

N. Number of subjects; NS, Not significant; BMI, body mass index. Statistical analysis was done by independent t test or chi square test.

### Table 2. Clinical symptoms of narcoleptic patients with and without cataplexy

|                  | Total (N=72) | With cataplexy (N=56) | Without cataplexy (N=16) |
|------------------|--------------|-----------------------|--------------------------|
| EDS              | 72 (100%)    | 56 (100%)             | 16 (100%)                |
| Hypnagogic      | 40 (55.6%)   | 36 (64.3%)            | 4 (25.0%)                |
| hallucination    |              |                       |                          |
| Sleep paralysis  | 40 (55.6%)   | 34 (60.7%)            | 6 (37.5%)                |

N. Number of subjects; EDS, Excessive daytime sleepiness; NS, Not significant. *p<0.005 by Pearson Chi Square Test.

### Table 3. Comparison of CSF hypocretin level in narcoleptic patients with and without cataplexy

|                  | Total (N=72) | With cataplexy (N=56) | Without cataplexy (N=16) |
|------------------|--------------|-----------------------|--------------------------|
| No. of subjects  |              |                       |                          |
| ≤110 pg/mL       | 54 (75.0%)   | 48 (85.7%)*           | 6 (37.5%)*               |
| >110 pg/mL       | 18 (25.5%)   | 8 (15.4%)*            | 10 (62.5%)*              |

N. Number of subjects; No., Number. *p<0.001 by Pearson Chi Square Test.

### Table 4. Comparison of HLA-DQB1 allele in narcoleptic patients with and without cataplexy

|                  | DQB1 allele | Total (N=72) | With cataplexy (N=56) | Without cataplexy (N=16) | Hypocretin levels |
|------------------|-------------|--------------|-----------------------|--------------------------|-------------------|
|                  |             |              |                       |                          | ≤110 pg/mL        |
|                  |             |              |                       |                          | >110 pg/mL        |
| 0200             | 7 (9.7%)    | 7 (12.5%)    | 0 (0%)                | 6 (11.1%)                | 1 (5.6%)          |
| 0301             | 18 (25.0%)  | 13 (23.2%)   | 5 (31.3%)             | 14 (25.9%)               | 4 (22.2%)         |
| 0302             | 7 (9.7%)    | 6 (10.7%)    | 2 (12.5)              | 5 (9.3%)                 | 2 (11.1%)         |
| 0303             | 10 (13.9%)  | 7 (12.5%)    | 3 (18.8%)             | 7 (13.0%)                | 3 (30.0%)         |
| 0401             | 10 (13.9%)  | 9 (16.1%)    | 1 (6.3%)              | 8 (14.8%)                | 2 (20.0%)         |
| 0402             | 3 (4.2%)    | 2 (3.6%)     | 1 (6.3%)              | 1 (1.9%)                 | 2 (11.1%)         |
| 0501             | 6 (8.3%)    | 4 (7.1%)     | 2 (12.5%)             | 3 (6.6%)                 | 3 (16.7%)         |
| 0502             | 2 (2.8%)    | 1 (1.8%)     | 1 (6.3%)              | 1 (1.9%)                 | 1 (5.6%)          |
| 0503             | 8 (11.1%)   | 6 (10.7%)    | 2 (12.5%)             | 5 (9.3%)                 | 3 (16.7%)         |
| 0601             | 7 (9.7%)    | 0 (0.0%)*    | 7 (43.8%)*            | 1 (1.9%)                 | 6 (33.3%)*        |
| 0602             | 58 (80.6%)  | 50 (89.3%)   | 8 (50.0%)*            | 50 (92.6%)               | 8 (44.4%)*        |
| 0603             | 0 (0.0%)    | 0 (0.0%)     | 0 (0.0%)              | 0 (0.0%)                 | 0 (0.0%)          |
| 0604             | 2 (2.8%)    | 2 (3.6%)     | 0 (0.0%)              | 2 (3.7%)                 | 0 (0.0%)          |
| 0605             | 0 (0.0%)    | 0 (0.0%)     | 0 (0.0%)              | 0 (0.0%)                 | 0 (0.0%)          |
| 0609             | 1 (1.4%)    | 1 (1.8%)     | 0 (0.0%)              | 1 (1.9%)                 | 0 (0.0%)          |

N. Number of subjects; No., Number. *p<0.001 by Fisher’s Exact Test, *p<0.001 by Pearson Chi Square Test, *p<0.001 by Fisher’s Exact Test.
frequent in cataplexy-positive patients (50/56, 89.3%) than in cataplexy-negative patients (8/16, 50.0%) \( (p < 0.001) \). On the other hand, the frequency of HLA-DQB1*0601 was found to be significantly lower in the narcoleptics with cataplexy group (0 subjects, 0% vs. 7 subjects, 43.8%) \( (p < 0.001) \) (Table 4).

The patients with a decreased CSF hypocretin level had a higher rate of HLA-DQB1*0602 (50/54, 92.6%) and a lower rate of HLA-DQB1*0601 (1/54, 1.9%) than those with a normal hypocretin level (8/18, 44.4% and 6/18, 33.3%, respectively) with a statistical significance \( (p < 0.001) \) (Table 4). We found to be significantly lower in the narcoleptics with cataplexy-negative patients (8/16, 50.0%) \( (p < 0.001) \). This suggests that the CSF hypocretin concentration might be related with HLA-DQB1 allele, and the concentration decreased only in patients among 16 narcoleptics without cataplexy (37.5%). These results raise the possibility that hypocretin deficiency may be an important pathophysiologic mechanism in the development of narcolepsy and also support the fact that narcolepsy with cataplexy and narcolepsy without cataplexy may be different diseases regarding their causality. Also, in 54 narcolepsy patients with hypocretin deficiency, as compared with narcoleptics with a normal hypocretin level (n=18), the frequency of HLA-DQB1*0602 was found to be significant high (50 subjects, 92.6% vs. 8 subjects, 44.4%) and HLA-DQB1*0601 was found to be low (1 subjects, 1.9% vs. 6 subjects 33.3%). This suggests that the CSF hypocretin concentration might be related with HLA-DQB1 allele, and HLA-DQB1*0602 and HLA-DQB1*0601 might be have an important role in developing narcolepsy.

The limitations of our study are the absence of results from a normal control group was the small number of narcoleptics without cataplexy. In summary, this is the first study in Korea that investigated the association of cataplexy with HLA-DQB1 allele and hypocretin level. The high HLA-DQB1*0602 positivity, DQB1*0601 negativity, and hypocretin deficiency in narcolepsy with cataplexy in our study confirms that narcolepsy with cataplexy and narcolepsy without cataplexy are genetically and pathophysiologically different disease entities.

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