Clinical Predictors for Migraine in Patients Presenting With Nausea and/or Vomiting

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Background/Aims
Many migraine patients develop nausea and/or vomiting (N/V) and are referred to gastroenterologists. This can lead to an inappropriate treatment and a delay of the correct diagnosis. We therefore aimed to identify predictors for migraine in patients presenting with N/V as well as headache.

Methods
A total of 407 patients who were first diagnosed with migraine at Samsung Medical Center, Seoul, Korea, in 2009 were analyzed. Among them, 261 patients had N/V (migraine with N/V group) and 146 did not (migraine without N/V group). Each patient was evaluated using a structured questionnaire.

Results
Migraine with N/V group was younger, comprised of more females, had more abnormal body mass index, less alcohol intake, more family history of migraine, higher attack severity, more stress association, more aggravation by physical activity, more abdominal pain, and more photophobia/phonophobia than migraine without N/V group. Multivariate analysis revealed that young age (age < 40 years vs. ≥ 40 years, odds ratio (OR), 2.128; 95% confidence interval (CI), 1.206-3.756; \( P = 0.009 \)), female (OR, 2.703; 95% CI, 1.492-4.896; \( P = 0.001 \)), family history of migraine (OR, 2.080; 95% CI, 1.169-3.700; \( P = 0.013 \)), abdominal pain (OR, 4.452; 95% CI, 1.263-15.693; \( P = 0.020 \)), and photophobia/phonophobia (OR, 2.296; 95% CI, 1.308-4.030; \( P = 0.004 \)) were independent predictive factors associated with migraine in patients with N/V.

Conclusions
Because young age, female, family history of migraine, abdominal pain, and photophobia/phonophobia are associated with migraine in patients presenting with N/V as well as headache, physicians should have a high index of suspicion for migraine in N/V patients who belong to these categories.

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Key Words
Headache; Migraine disorders; Nausea; Vomiting
Introduction

Migraine is an episodic severe headache generally associated with nausea, and/or photophobia and phonophobia. Its discriminative features include pulsating, duration of 4-72 hours, unilateral, nausea, and disabling. Migraine is a common disease occurring in up to 15% of the population in Western countries. In South Korea, the 1-year prevalence rate varied from 6.1% to 22.3%. However, it is frequently underdiagnosed in the general population. This is because many patients do not fully report symptoms, which is a mainstay of diagnosis, and many physicians misinterpret them.

Migraine and headache are frequently reported by patients with gastrointestinal (GI) symptoms such as nausea, vomiting, retching, abdominal pain, and food intolerance. Among these symptoms, nausea and vomiting are the most common GI symptoms associated with migraine. Nausea occurs in more than 90% of all migraineurs and vomiting in almost 70% of all migraineurs. The most important features of migraine medications are rapid and effective relief of headache pain, decreasing the likelihood of headache recurrence, and not causing nausea. Nevertheless, many migraine patients suffer needlessly from their nausea and vomiting, because some migraine patients with GI symptoms are referred to a gastroenterologist and this leads to an inappropriate treatment and a delay of correct diagnosis.

We therefore aimed to investigate the characteristics of migraine patients with nausea and/or vomiting (N/V) and to identify predictive factors associated with migraine in patients presenting with N/V as well as headache.

Materials and Methods

Patients

The present study included data from a total of 407 patients who were first diagnosed with migraine at Samsung Medical Center, Seoul, Korea, between January 2009 and December 2009. Among them, 261 patients had N/V (migraine with N/V group) and 146 did not (migraine without N/V group). We included migraine patients with either nausea or vomiting into the migraine with N/V group. The diagnosis of migraine was based on the reporting of headache characteristics and associated symptoms, as detailed in the International Classification of Headache Disorders. The patients underwent radiologic evaluations on the brain with computed tomography (CT), magnetic resonance imaging (MRI), and/or transcranial doppler (TCD) by indication. To rule out organic GI problems, an endoscopy was performed in some patients with upper GI symptoms. The study protocol was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board at Samsung Medical Center, Seoul, Korea.

Headache Questionnaire

Each patient was evaluated using a structured questionnaire at the first visit. The questionnaire assessed age, gender, body mass index (BMI), alcohol intake, current smoking, caffeine intake (e.g., coffee, tea and carbonated drink), family history of migraine, and characteristics of migraine. Characteristics of migraine included onset of headache, frequency of headache (per month), location and nature of headache, severity score of headache (according to a numeric score system: 0-10), presence of photophobia and/or phonophobia, concurrent symptom (e.g., nausea, vomiting, abdominal pain and eye pain) and triggers (insomnia, menstruation, physical or psychological problem). BMI was calculated as weight (kg) divided by height (m) squared (kg/m²). Abnormal BMI was defined as BMI < 18.5 kg/m² (underweight) or ≥ 23.0 kg/m² (overweight and obese). These categories were created with the consideration of BMI cut-off points recommended by the World Health Organization Working Group for Asian populations.

Patients diagnosed with migraine previously or treated with medications for migraine were excluded from this study.

Data Collection and Definitions

The following clinical and laboratory information was collected from each patient: age, gender, white blood count (WBC), aspartate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time, fasting glucose, estimated glomerular filtration rate and serum low-density lipoprotein cholesterol (LDL-C). Radiologic and endoscopic data were collected from the final reports.

Abnormal WBC was defined when WBC count was < 4,000 or > 9,000/μL. Abnormal liver function was defined as serum total bilirubin > 2.0 mg/dL, aspartate aminotransferase and/or alanine aminotransferase > 40 U/L, or prothrombin time > 120%. Abnormal kidney function was defined as an estimated glomerular filtration rate < 60 mL/minutes. Dyslipidemia was defined as serum LDL-C > 130 mg/dL.
### Statistical Methods

Statistical analyses were conducted using PASW Statistics 18 for Windows (SPSS, Chicago, IL, USA). The statistical results are presented as mean ± SD or number (percentages). Continuous variables were compared parametrically using Student’s *t*-test or non-parametrically using the Mann–Whitney *U* test. Categorical variables were compared using the χ²-test or Fisher’s exact test as appropriate. Multiple logistic regression analysis was performed on variables that showed a distinct difference with statistical significance between the 2 groups, in order to identify variables independently associated with migraine in patients with N/V. A two-sided *P*-value < 0.05 was taken as statistically significant.

### Results

#### Patients

Baseline characteristics of the two groups are shown in Table 1. Migraine with N/V group was younger (44.7 ± 15.0 years vs. 50.5 ± 13.5 years, *P* < 0.001) and had more females (70.8% vs. 63.0%, *P* < 0.001), more abnormal BMI (45.7% vs. 31.7%, *P* = 0.006), less alcohol intake (23.4% vs. 34.9%, *P* = 0.012), and more family history of migraine (32.2% vs. 17.8%, *P* = 0.002) than migraine without N/V group. However, there were no significant differences between the 2 groups regarding current smoking and caffeine intake.

#### Headache Characteristics

Headache characteristics of the 2 groups are shown in Table 2.

|                | Migraine with N/V (n = 261) | Migraine without N/V (n = 146) | *P*-value |
|----------------|-----------------------------|---------------------------------|-----------|
| Age (yr)       | 44.7 ± 15.0                 | 50.5 ± 13.5                     | < 0.001   |
| Gender (female [%]) | 223 (85.4)                 | 92 (63.0)                       | < 0.001   |
| Abnormal BMI   | 118 (45.7)                  | 45 (31.7)                       | 0.006     |
| Alcohol intake | 61 (23.4)                   | 51 (34.9)                       | 0.012     |
| Current smoking| 25 (9.6)                    | 17 (11.6)                       | 0.753     |
| Caffeine intake| 184 (70.5)                  | 112 (76.7)                      | 0.202     |
| Family history of migraine | 83 (32.2)              | 26 (17.8)                       | 0.002     |

N/V, nausea and/or vomiting; BMI, body mass index.

Data are presented as mean ± SD or number (%).

Migraine with N/V group had higher attack severity (score, 7.9 ± 2.0 vs. 7.2 ± 2.2; *P* = 0.004), more stress association (67.8% vs. 53.2%, *P* = 0.005), more aggravation by physical activity (45.6% vs. 26.4%, *P* < 0.001), more abdominal pain (10.8% vs. 2.1%, *P* = 0.001), and more photophobia and/or phonophobia (41.9% vs. 17.8%, *P* < 0.001).

#### Laboratory, Brain Imaging and Endoscopic Results

Laboratory and brain imaging results of the 2 groups are shown in Table 3. There were no significant differences between the 2 groups in laboratory results including WBC, liver function, kidney function, fasting glucose level, and LDL-C.

Many migraine patients showed abnormal TCD findings such as mild to moderate narrowing or decreased blood flow in the intracranial vessels. In addition, several organic lesions were found on brain CT and MRI (ischemia in 20, small unruptured aneurysm in 7, intracranial vessel stenosis in 7, Arnold-Chiari malformation in 4, small intracranial hemorrhage in 5, Rathke’s cleft cyst in 3, maxillary sinusitis in 3, vertebral artery occlusion in 2, suprasellar mass in 1, vestibular schwannoma in 1 and arachnoid cyst in 1). However, there were no significant differences between the 2 groups in TCD and brain imaging.

A total of 71 (27.2%) migraine patients with N/V underwent upper GI endoscopy. Among them, 1 patient (1.4%) had peptic ulcer, 2 (2.8%) had reflux esophagitis and the remaining 68 (95.8%) had no remarkable findings.

### Table 1. The Baseline Characteristics of Migraine Patients According to the Presence of Nausea and/or Vomiting

|                | Migraine with N/V (n = 261) | Migraine without N/V (n = 146) | *P*-value |
|----------------|-----------------------------|---------------------------------|-----------|
| Headache duration (yr) | 8.8 ± 8.6                   | 6.3 ± 9.1                       | < 0.001   |
| Number of attack (/mo) | 12.0 ± 11.5                 | 13.2 ± 11.8                     | 0.418     |
| Attack duration (days) | 2.5 ± 4.3                   | 1.9 ± 3.4                       | 0.211     |
| Attack severity (score) | 7.9 ± 2.0                   | 7.2 ± 2.2                       | 0.004     |
| Stress association | 175 (67.8%)                 | 75 (53.2%)                      | 0.005     |
| Sleep disturbance | 120 (47.1%)                 | 52 (37.1%)                      | 0.073     |
| Aggravation by physical activity | 114 (45.6%)     | 37 (26.4%)                      | < 0.001   |
| Abdominal pain | 28 (10.8%)                  | 3 (2.1%)                        | 0.001     |
| Photophobia and/or phonophobia | 109 (41.9%)       | 26 (17.8%)                      | < 0.001   |

N/V, nausea and/or vomiting.

Data are presented as mean ± SD or number (%).
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Multivariate analysis revealed that young age (age < 40 years vs. ≥ 40 years), odds ratio [OR], 2.128; 95% confidence interval [CI], 1.206-3.756; P = 0.009), female (OR, 2.703; 95% CI, 1.492-4.896; P = 0.001), family history of migraine (OR, 2.080; 95% CI, 1.169-3.700; P = 0.013), abdominal pain (OR, 4.452; 95% CI, 1.263-15.693; P = 0.020), and photophobia and/or phonophobia (OR, 2.296; 95% CI, 1.308-4.030; P = 0.004) were the independent factors associated with migraine in patients with N/V (Table 4).

Discussion

In the present study, we sought to identify predictive factors associated with migraine in patients presenting with N/V as well as headache. Many migraine patients present with a variety of GI symptoms. Therefore, some migraine patients are referred to gastroenterologist resulting in inappropriate treatment and delay of correct diagnosis. If physicians are well aware of characteristics of migraine patients with N/V, timely diagnosis and appropriate treatment can be provided to migraine patients.

Migraine is a disorder characterized by broad sensory processing dysfunction. It can alter the perception of sensory stimuli, somatosensory, visual, auditory and olfactory sensations, which can lead to various combinations of headache, photophobia, phonophobia, and N/V. Autonomic dysfunction in the periaqueductal gray area of the fourth ventricle has been suggested as the cause of nausea and vomiting in patients with migraine.

However, it is not known specifically which factors trigger N/V in patients with migraine.

In the present study, migraine patients with N/V had more abnormal BMI than migraine patients without N/V. This result is consistent with the findings of other studies that reported that both underweight and obese patients were more likely to experience severe headaches or migraines than patients with normal BMI ranges.

Our results show that migraine patients with N/V have more family history of migraine than migraine patients without N/V. Migraine is well known to have a strong genetic association. Recent studies suggest multifactorial patterns of inheritance including environmental factors in addition to family history. The cyclic vomiting syndrome (CVS) is an episodic disorder characterized by nausea and vomiting in children, which is considered as migraine variant. CVS and migraine with abdominal symptoms appear to present with similar clinical features. In both CVS and migraine with abdominal symptoms, frequency of headache experienced by patient’s mother was noted to be twice that of patient’s father, suggesting the possibility of mitochondrial inheritance.

Migraine patients with N/V had longer headache duration prior to diagnosis than migraine without N/V. It is common that patients with unexplained GI symptoms and headaches are consulted to gastroenterologist; this frequently delays a correct diagnosis and often results in an inappropriate treatment. The symptoms discussed might not include headache; they can be incomplete and misinterpreted. Therefore, physicians should include migraine in a differential diagnosis of patients presenting with N/V as well as headache and should inquire specifically about headache.

In the present study population, 47.7% (n = 197) had abnor-
nal TCD and/or brain imaging findings. However, migraine symptoms of enrolled patients were not considered attributable to these abnormal findings. Therefore, they continued to receive migraine treatment even after detection of TCD and/or brain imaging abnormality. Nevertheless we performed additional analysis in subgroup population excluding patients with either abnormal TCD or brain imaging findings (data not shown). The results of subgroup analysis were similar to that of total study population. Young age, female, family history of migraine and photophobia and/or phonophobia were also independent predictive factors associated with migraine in patients with N/V as well as. However, abdominal pain did not show statistical significance in the subgroup analysis ($P = 0.087$).

In the present study, the incidence rate of N/V among migraine patients was 64.1%, which is lower than that (85.0-87.9%) of the latest report. This discrepancy might be due to the possible heterogeneity of the present study population. This retrospective study recruited patients who were diagnosed with migraine. Although the diagnosis of migraine was made according to the criteria of the International Classification of Headache Disorders, there might be some patients who had practically suspicious, but not definite migraine including probable migraine in the present study population. Hence, our results should be interpreted in the context of this limitation and require prospective validation studies.

In conclusion, when encountering N/V patients with headache, careful questioning about family history of migraine, abdominal pain, and photophobia and/or phonophobia is necessary. Because young age, female gender, family history of migraine, abdominal pain, and photophobia and/or phonophobia are associated with migraine, physicians should have a high index of suspicion for migraine in patients who belong to these categories, which might lead to timely diagnosis and appropriate treatment in migraine patients.

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