中 國 醫 藥 大 學
臨床醫學研究所
博士學位論文

偏頭痛與睡眠:
睡眠疾患於偏頭痛病患之相關性、臨床睡眠影響與影像學研究

Migraine and Sleep:
The Association、Sleep Impact and Neuroimaging Finding in Migraine Patients Comorbid with Sleep Disorder

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本論文係　陳炳錕　於中國醫藥大學臨床醫學研究所完成之博士論文，經考試委員審查及口試合格，特此證明。

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中文摘要

頭痛是全世界最常見的疾患。依據國際頭痛疾病分類第二版(ICHD-2)，頭痛疾病可分為原發性與次發性頭痛兩大類。偏頭痛，是原發性頭痛中的主要疾患，全世界成人中的 9-15%受其影響，並造成全球疾病負擔中的 30%。偏頭痛有許多不同的共病症。其中，不寧腿症候群與偏頭痛的相關性也在近年受到注意。但是，不寧腿症候群對偏頭痛病患的臨床影響仍未清楚。

我們於一個頭痛門診連續收錄偏頭痛病患，以了解偏頭痛病患中合併有不寧腿症候群的比例，並與其他原發性頭痛病患比較。結果顯示偏頭痛病患合併不寧腿症候群的比例遠高於叢發性頭痛與張力性頭痛病患。此外，合併有不寧腿症候群的若偏頭痛病患，也較容易合併有頭暈、耳鳴，頸部疼痛、怕光、怕吵等症狀。而合併有不寧腿症候群的偏頭痛病患的睡眠品質較一般偏頭痛病患更差。

偏頭痛與不寧腿症候群均曾被報導與中樞鐵的代謝有關，但在研究中顯示，偏頭痛病患在腦中鐵的沉積增加，而不寧腿症候群卻是減少，在我們的研究中發現，偏頭痛病患會造成紅核鐵的沉積增加而不寧腿症候群會使鐵在紅核與黑質的鐵濃度減少。在偏頭痛合併不寧腿症候群的病患，因為兩者均為陣發性發作，兩者之間發作是否有其時間相關性仍未清楚，本研究中收錄偏頭痛合併不寧腿症候群的病患，並依其日記記錄研究其相關性，發現偏頭痛發作與不寧腿之發作有正相關性，且偏頭痛可能為不寧腿發作的誘發因子。

在基因研究中，不寧腿有 19 個已知的基因變異，而在偏頭痛合併不寧腿症候群的病患卻仍未知，我們經由檢測這些已知的基因變異位置，在 1024 位病患中發現 MEIS1 基因與偏頭痛合併不寧腿症候群相關。

偏頭痛與不寧腿症候群之間的相關性，經由一系列的研究，逐漸了解其可能的共病原因，基因的變異合併偏頭痛發作時造成的神經傳導物質改變，可能進一步加強不寧腿發作的機會。

此外，我們也試著了解晨間頭痛這個與睡眠呼吸中止症與偏頭痛相關的臨床常見疾患。在偏頭痛病患中，晨間頭痛相當常見且常以偏頭痛的形式發生，而且其他失眠等問題也是造成晨間頭痛的重要因素。因此，晨間頭痛並非專屬於呼吸中止症的特異症狀，臨床上應了解病患是否有偏頭痛與其他相關睡眠疾患，才能給予適當的治療。

English Abstract

Headache is the most prevalent disorder in the world.(1) On the basis of The International Classification of Headache Disorder, 2nd edition (ICHD-2), the headache disorders were separated into primary and secondary headache groups.(2) Migraine, the major primary headache disease, affects approximately 9-15% of the adult population in the world and accounts 30% global burden.(1) Migraine have many different comorbidities. An association between restless legs syndrome and migraine has been reported recently. However, the clinical correlates and impact of comorbidity of restless legs syndrome (RLS) are not fully described in patients with migraine.

Our research investigated the frequency of RLS in patients with migraine in a headache clinic, and the clinical impact on sleep in migraine patients comorbid with RLS, Our results demonstrated that the frequencies of RLS in patients with migraine (11.4%) was higher than in those with TTH (4.6%) or CH (2.0%) ($p=0.002$). In migraine patients, comorbidity with RLS was associated with higher frequencies of photophobia, phonophobia, exacerbation due to physical activities, vertigo, dizziness, tinnitus and neck pain. Migraine patients with RLS had a poorer sleep quality.

Magnetic resonance imaging studies ever showed decreased levels of brain iron in RLS but increased iron deposition in migraine. This study assessed regional brain iron levels in migraine with RLS by magnetic resonance relaxometry. Four groups patients: migraine with RLS. Migraine without RLS, idiopathic RLS and normal control were included. All of them received a multislice T2*-weighted gradient echo sequence for T2* relaxometry and serum ferritin level measurement. T2* relaxation time (T2*-RT) was measured in the substantia nigra, red nucleus, periaqueductal gray matter, putamen, caudate and globus pallidus. Longer T2*-RTs denote lower iron levels. Among these four groups, T2*-RT was significantly different in the red nucleus (migraine without RLS<migraine with RLS≒control< primary RLS: 79.0±8.6, 86.4±10.0, 84.0±7.5, 92.1±11.2ms, $p<0.0001$) and substantia nigra (migraine without RLS≒control<migraine with RLS< primary RLS: 75.9±8.2, 77.6±7.0, 84.3±10.2, 88.7±11.9ms $p=0.0001$). Migraine was associated with higher iron levels in the red nucleus; whereas, RLS was associated with lower iron levels in both the red nucleus and substantia nigra.

We also tried to clarify the temporal association between migraine and RLS attacks based on the daily diary records of migraine patients comorbid with RLS. 30 migraine patients with RLS were recruited from a headache clinic. Based on the 420 days diary without any medication use, we noted a positive temporal and severity correlation between migraine and RLS attacks in migraine patients with RLS. It is

postulated that migraine and RLS may share some common mechanisms or migraine attacks might trigger the RLS symptoms.

Genetic studies have identified the 19 variants in 7 genomic region associated with idiopathic RLS. However, the genetic importance in migraine patients comorbid with RLS remains to be explored. The current study was performed to assess the role of these genetic variants in migraine patients. Migraine patients were investigated from a headache clinic. RLS was diagnosed based on essential criteria of International RLS Study Group (IRLSSG). Night-teen single nucleotide polymorphisms (SNPs) within the 7 genomic regions were selected for analysis according to the results of previous genetic reports in idiopathic RLS. All genotypes were determined blinded to the clinical characteristics. We investigated 188 migraine patients with RLS and 1024 migraine patients without RLS (262M/950F, mean age 39.4±12.6). Two SNPs encompassing the genes MEIS1 were identified associated with the RLS in migraine patients. (rs2300478, p=0.037, OR:1.31; rs12469063, p=0.024, OR:1.34)

In addition, obstructive sleep apnea syndrome related morning headache and stroke related headache were common secondary headaches encountered by neurologists in day to day practice. The morning headache was suspected to be one of the symptoms of obstructive sleep apnea syndrome (OSAS). Our study showed that morning headache was common in habitual snorers and associated with a pervasive impairment of health related quality of life. Migrainous features were not uncommon. Not only OSAS, but migraine, insomnia and psychological distress were also important predictors for morning headache, even in snoring patients.

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1. Migraine and Restless Legs Syndrome

1.1 Introduction and background

1.1.1 Introduction of Migraine

Migraine is of the most common complaints encountered by neurologists in day to day practice. The onset age of migraine is commonly in the second and third decades of life (3,4,5,6), potentially the most productive period of life. The life time prevalence of migraine is up to 15% in the population.(6) It accounts for 30% of the global burden and more than 50% of the disability burden attributable to all neurological disease worldwide.(1) Migraine is also the 7th ranking cause of disease-associated disability worldwide.(1) Generally, migraine patients suffer severe headache associated with nausea and light/sound sensitivity.

The diagnosis of migraine is based on a compatible history, physical examination, and fulfillment of the diagnostic criteria. It is a clinical task and no diagnostic test is specific for migraine.

Based on ICHD-2 proposed by The International Headache Society (IHS), diagnostic criteria for migraine are as follows (2):

Migraine with aura: Patients have transient appearance of focal neurologic symptoms developing gradually over 5 to 20 minutes and last for less than 60 minutes. The symptoms preceded or accompany by migraine attack.

IHS diagnostic criteria for migraine with aura are as follows (2):

- At least two attacks of aura with migraine headache
- The migraine aura fulfills criteria for one of the subforms of aura with migraine headache
- The symptoms are not attributed to another disorder

Migraine without aura: Migraine without aura is a recurrent headache disorder that fulfills the following criteria (2):

- Headache attacks last 4 to 72 hours
- Headache has at least two of the following characteristics: unilateral location; pulsating quality; moderate or severe intensity; aggravation by routine physical activity
- During headache at least one of the following occurs: nausea and/or vomiting; photophobia and phonophobia
- At least five attacks occur fulfilling the above criteria
- History, physical examination, and neurologic examination do not suggest any underlying organic disease

1.1.2 Migraine and Sleep Comorbidity

The term comorbidity is used to refer to the statistical association of two distinct diseases in the same individual at a rate higher than expected by chance (7). Many illnesses are reported to be comorbid with migraine (8), which stresses the clinical complexity of this headache disorder. Comorbidity in migraine is important from several perspectives: (a) co-occurrence of diseases can complicate the diagnosis, e.g., focal sign of migraine and stroke; (b) one disease can remind the clinicians of the other diseases, e.g., migraine and restless legs syndrome (RLS); (c) one treatment for two diseases, e.g., tricyclic antidepressants for migraine patients with depressive disorders; and (d) comorbidity of illnesses can provide clues to the pathophysiology of migraine.

Both headache and sleep disorders are common in general population. The relationship between migraine and sleep has been known for a long time.(9) Migraine can emerge during nocturnal sleep or following a brief period of daytime sleep. Sleep disturbance was noted to be one of the principal headache causes (9) and often migraine can be predicted by the length of sleep from the night before (10). Sleep has also been reported to relieve migraine.(11) In one large sample size observation study, Kelman reports more than one-third of 1283 migraineurs having difficulty initiating and maintaining a healthy sleep pattern.(12) Additionally, a large majority of migraineurs reported sleep being an effective acute treatment. Furthermore, short sleepers exhibited significantly more frequent headaches than long sleepers and were also more likely to experience morning headaches at awakening. (12) It is important to understand the association between specific sleep disorders and migraine and the possible underlying mechanism and impact.

Restless legs syndrome is a common sensorimotor disorder, which is characterized by uncomfortable sensations in the legs especially at rest or at bed time and relieved by voluntary movement.(13) The prevalence of RLS is 5% to 10% in Western countries (14-16) but only 0.6-3.9% in Asians.(17-19) Women and older aged populations have a higher prevalence. RLS has been found to be associated with a variety of medical and psychiatric conditions and is diagnosed in conjunction with other sleep disorders.(20) It has substantial impacts on sleep as well as on health-related quality of life.(21,22) RLS has also been found to be a risk factor for cardiovascular diseases (23).

1.1.3 Association between migraine and restless legs syndrome

Several studies identified a higher prevalence of RLS in patients with migraine.(24-26) Whether RLS is also associated with other primary headache disorders is uncertain. Migraine has been reported to have an association with poor sleep quality, especially in those with chronic migraine.(12,27)

Restless legs syndromes was one of the sleep comorbidity of migraine, but the inter-relationship among comorbid RLS, sleep disturbance and headache clinical profiles in patients with migraine has not been fully investigated.(26)

In this part of study, we aim to examine the frequency of RLS in Taiwanese patients with three major primary headache disorders: Migraine, tension-type headache (TTH), and cluster headache (CH); and to explore the clinical correlates of comorbid RLS and its impact on sleep in patients with migraine.

1.1.4 Regional brain iron levels in migraine with comorbid restless legs syndrome: a magnetic resonance relaxometry study

In addition to the clinical association between migraine and RLS(24-26), the change of iron deposition in the brain was reported in both migraine and RLS.(27-31) Iron is important co-factor of dopamine synthesis. However, magnetic resonance imaging studies showed decreased levels of brain iron in RLS (29) but increased iron deposition in migraine.(27-28) The animal and human studies showed iron deficiency related to increase of dopamine synthesis. (31-33) Dopaminergic dysfunction is both important in migraine and RLS patients.(34-36) In migraine patients, the hypersensitivity to dopamine was long term suspected to be the cause of some migraine accompanied symptoms, like nausea, vomiting and yawing.(37) In RLS patients, the diurnal change of dopamine level and over-compensation of D2 receptor in putamen was suspected responsible to RLS symptoms.(33) The change of brain iron deposition in migraine patients comorbid with RLS could offer the chance to understand the possible mechanism in the relation between migraine and RLS. In this part, we will assess regional brain iron levels in migraine with RLS by magnetic resonance relaxometry and compare the difference between 4 different group participants, including migraine patients with RLS, migraine patients without RLS, idiopathic RLS patients and normal control.

1.1.5 The temporal relationship between migraine and restless legs syndrome

Migraine and restless legs syndrome (RLS) are both chronic neurological diseases with episodic attacks (6,38). Some biogenic amines (i.e. dopamine and serotonin) are postulated as crucial factors in the pathophysiology of these two disorders (35,38). Nevertheless, the temporal relationship between migraine and RLS has not been well documented. However, the episodic characteristics of migraine and RLS provide an excellent opportunity to evaluate their temporal relationship. Thus, in this part, our study will investigate whether migraine attacks can trigger RLS or whether RLS can trigger migraine attacks.

1.1.6 Genetic association in Migraine patients with RLS

Genetic studies have identified association with variants in MEIS1, BTBD9, PTPRD and MAP2K5/LBXCOR1 genes in patients with idiopathic RLS. In recent years, a higher prevalence of RLS in migraine patients was reported. However, the genetics of comorbid RLS remains undetermined. (40-49) Three of them (BTBD9, MEIS1, and PTPRD) were related to iron homeostasis.(45, 50,51) Higher frequency of RLS in migraine patients was reported in both clinical- and population- based studies. The iron deposition change on the brain region was also suspected to be important in both migraine and RLS. In this part, our study was performed to assess the role of these genetic variants in migraine patients.

1.2 Methods

1.2.1 Association between migraine and restless legs syndrome: methods and statistical analysis

We prospectively enrolled consecutive patients aged≧18 years with three primary headache disorders, i.e. migraine, TTH or CH, who visited the headache clinic of Taipei Veterans General Hospital (VGH) from January 2008 to May 2009.

Diagnoses of headache disorders were based on the International Classification of Headache Disorders, 2nd edition (ICHD-2).(2) For study inclusion, patients had to fulfill the diagnostic criteria for migraine (coded 1.1, 1.2, 1.5.1, 1.6), TTH (coded 2.2, 2.3), or CH (code 3.1). The patients with headaches fulfilled both migraine and TTH diagnostic criteria were classified as migraine patients. We excluded patients with secondary headache disorders except for medication overuse headache. If patients with migraine, chronic migraine was defined if headache, of either tension-type and/or migraine quality, occurs on ≥15 days per month and migraine frequency≧8 days per month lasting for 3 months; other patients were diagnosed as episodic migraine.(52)

Study assessment

We recorded demographic data including body weight and height, and headache profiles such as headache intensity, frequency, locations, characteristics, analgesics use, accompanying symptoms in a headache intake form. Patients were asked to self-report their medications used for headache prophylaxis especially tricyclic antidepressants, dopamine antagonists, mirtazapine, selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), all of which have been reported to be related to RLS (53). Body mass index (BMI) was calculated as body weight divided by body height squared (kg/m2). Each patient also completed the Migraine Disability Assessment (MIDAS).(54) Hospital Anxiety and Depression scale (HADS),(55) and the Pittsburgh Sleep Quality Index (PSQI).(56) Symptoms of RLS were screened by using a screening questionnaire including four essential diagnostic criteria proposed by the International RLS Study Group (IRLSSG)(13) and the ratings of RLS severity were assessed according to the 10-item International RLS Study Group Rating Scale (IRLS).(57) In this study, periodic leg movements in sleep (PLMS) and family history of RLS were also queried. The PLMS diagnosis was based on self-reported nocturnal leg jerks during sleep. Patients with RLS were queried if similar symptoms of legs discomfort and an urge to move occurred in their family.

Migraine Disability Assessment (MIDAS)

The 5-item MIDAS questionnaire measures headache-related disability in a 3-month period by recording time lost due to headache from employment or school, household work, or family and social activities. The total score of the MIDAS lies between 0 and 270. (54)

Hospital Anxiety and Depression Scale (HADS)

HADS is a self-administered instrument developed for detecting states of depression and anxiety in the setting of a hospital medical outpatient clinic.(55) It does not consider the somatic symptoms of anxiety and depression, and thereby excludes the influence of the confounding factors of physical symptoms and signs. The questionnaire includes 14 questions: 7 for depression and 7 for anxiety. Each question rated with a score of 0-3 depending on the severity of the problem with a total score ranging from 0 to 42.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is designed to measure the quality and patterns of sleep in the past month and contains 19 self-rated questions from which 7 component scores are calculated and summed into a global score. Higher scores represent worse sleep quality: component scores range from 0 to 3, and global scores range from 0 to 21. Poor sleep quality was defined with a PSQI score of more than 5(56)

The RLS screening questionnaire

The screening questionnaire for RLS is comprised of four “yes/no” type questions based on the essential criteria proposed by the IRLSSG including (1) if any urge to move legs accompanied with the leg uncomfortable sensation; (2) if the urge to move or uncomfortable sensation partially or totally relieved by legs movement; (3) if the urge to move or uncomfortable sensation worsen during inactivity like sitting or lying; and (4) if the urge to move or uncomfortable sensation worsen in the evening or night compared with the day time or only occur in the evening or night.

International RLS Study Group Rating Scale (IRLS)

The IRLS includes 10 questions related to the severity and frequency of RLS symptoms. Each question is a five-point Likert scale. The IRLS total score ranged from 0 to 40. The severity was mild when the score was 0-10, moderate 11-20, severe 21-30 and very severe 31-40.(57)

Case ascertainment of RLS

We reviewed the RLS screening questionnaires and interviewed the patients via phone if they replied with at least one positive answer to the four screening questions. In addition, another 20 patients who denied any symptoms in the screening questionnaire were randomly sampled for interview as controls. The criteria for

diagnosis of RLS in this study complied with the recommendations of the IRLSSG. (13) i.e. when all four essential criteria were met. “Clinically relevant” RLS patients were defined if patients’ symptoms occurred greater or equivalent 2 days per week during the last 12 months and were reported to have moderate to severe interference on their quality of life.(13)

STATISTICS

SPSS version 17.0 for Windows (SPSS, Chicago, Illinois) was used for statistical analysis. Descriptive data were reported as mean ± SD or percentages. For categorical data, a X^2 test or Fisher exact test was used to test the difference between groups. The Student t test and one-way analysis of variance (ANOVA) with the post-hoc least significant difference (LSD) test were used to compare the means of continuous variables. Logistic regression models were used to determine if there was any difference in the frequencies of RLS among different headache disorders after adjustment for age and gender. The linear-by linear association analysis was used to analyse the trend of the frequencies of RLS among different numbers of migraine symptoms in patients with migraine. General linear models were employed to test if comorbidity of RLS was independently associated with sleep disturbance in patients with migraine after controlling for potential confounders for sleep disturbances. All calculated p values were two-tailed, and statistical significance was defined as $p<0.05$.

1.2.2 Regional brain iron levels in migraine with comorbid restless legs syndrome: methods and statistical analysis

This study assessed regional brain iron levels in migraine with RLS by magnetic resonance relaxometry. Four groups adult patients or controls of similar age and sex were recruited: 26 migraineurs with RLS, 26 migraineurs without RLS, 18 primary RLS patients, and 26 normal controls. All of them received a multislice T2*-weighted gradient echo sequence for T2* relaxometry and serum ferritin level measurement. T2* relaxation time (T2*-RT) was measured in the substantia nigra, red nucleus, periaqueductal gray matter, putamen, caudate and globus pallidus. Longer T2*-RTs denote lower iron levels.

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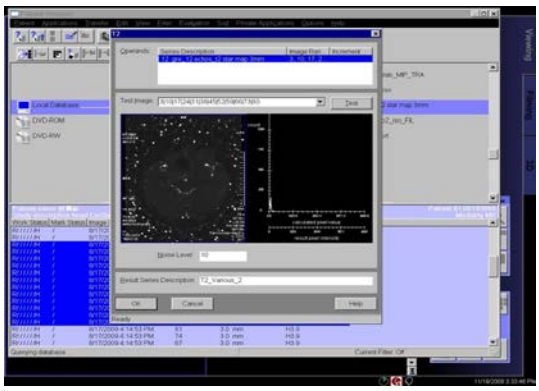
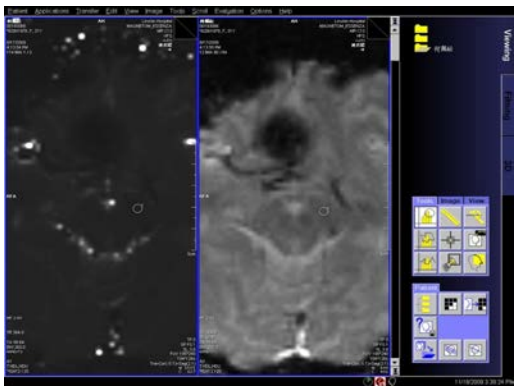




1.2.3 The temporal relationship between migraine and restless legs syndrome: : methods and statistical analysis

All migraine patients were also questioned about the symptoms of RLS in the headache clinic from April 1, 2010 to December 31, 2010 at Lin-Shin Hospital, a 500-bed regional hospital in central Taiwan. One physician (Chen PK) interviewed, examined, and diagnosed all patients. Migraine was diagnosed according to the International Classification of Headache Disorders, 2nd edition (ICHD-2) (2). RLS diagnosis was based upon patient fulfilment of all four essential criteria proposed by the International RLS Study Group (IRLSSG) (13).

Migraine patients comorbid with RLS were invited to join the study. Patients were excluded if they 1. refusing to record the diary during the study period 2. having “daily” headaches or “daily” RLS within the last month because either condition could confound the potential temporal relationship between disorders. All participants were examined by magnetic resonance imaging (MRI), detailed medical history, neurological examination, and blood tests were used to exclude patients with intracranial lesions, symptomatic RLS, or RLS mimics (58).

The demographic data, migraine and RLS clinical profiles, body mass index (BMI) were collected from patients. During the 2-week study period, participants were prohibited from taking any medications except for abortive treatments prescribed for acute headache attacks or medications for chronic medical diseases. Subjects were asked to record both the onset of headache and RLS attacks in a daily diary. Headache and RLS intensity were individually rated on a 4-point Likert scale, ranging from 0−3 (0-none, 1-mild, 2-moderate, and 3-severe intensity). Headache profiles, accompanying symptoms, and painkiller usage were also recorded, including

headache duration, unilateral location, pulsating quality, headache aggravation by or causing avoidance of routine physical activity, nausea, vomiting, photophobia, and phonophobia. Every single headache episode was defined as headache onset and remission before bedtime at the same day. If the headache still persisted at bedtime, the attack was assigned as headache episode at next day. The interval of headache was not limited but all headache attacks at the same day were accounted into 1 attack. Based upon diary entries, we also separated headache attacks into migraine and non-migraine headache attacks according to the ICHD-2 criteria. Since headache characteristics may be altered after the use of abortive medications, we defined those headaches not fulfilling ICHD-2 migraine diagnosis as migraine attacks if patients took abortive treatment (52). Patients were requested to record RLS attack if they felt urge to move the legs during rest or supine position on the bed and at last partially relieved by voluntary movement.

In order to examine the temporal relationship between migraine and RLS, we first tested if migraine attacks could trigger RLS. We defined the "triggering relationship" into three categories of occurrence: within 24, 24−48, and 48−72 hours. The "within 24 hours" criteria defined as the remission of migraine attack before bedtime and the onset of RLS attacks at the same night. The onset of RLS attacks at the next night was assigned into group of "within 24−48 hours" and into "within 48−72 hours" if RLS onset at the third night. The same assessment was used for non-migraine headache attacks. Identical criteria were used to determine whether RLS triggered migraine within 24 hours, 24−48 hours, and 48−72 hours (Figure 1).

Study participants were explained that the diary records were going to be used to understand the real frequency and severity of diseases and not informed were going to be used to investigate the temporal relationship between migraine and RLS. The Institutional Review Board at the Lin-Shin Hospital, Taichung, Taiwan, approved the study protocol. All patients signed informed consents before participating in this study.

Statistical analyses

SAS version 9.2 for Windows was used for statistical analyses. Descriptive data were shown as mean ± SD. We calculated kappa statistics to represent a "triggering" relationship. In consideration of the different degree of severity of migraine or RLS, the weighted linear kappa coefficients were used to measure the strength of agreement between migraine and RLS attacks under the hypotheses of similar importance between the degrees of severity. A kappa coefficient of 0.41¬−0.60 indicated moderate concordance, 0.61−0.80 indicated substantial concordance, and 0.81 and above indicated almost perfect concordance (13). Spearman's rank correlation

coefficient (rs) was used to measure the association between frequencies of migraine and RLS. In this study, statistical significance was determined as two-tailed p-values <0.05.

1.2.4 Genetic association in Migraine patients with RLS: methods and statistical analysis

Migraine patients were enrolled from a headache clinic. RLS was diagnosed based on the four essential criteria of International RLS Study Group (IRLSSG).(13) The mean headache days and Beck Depression Inventory (BDI)(59) were recorded. Eleven single nucleotide polymorphisms (SNPs) within the four genomic regions were selected for analysis. All genotypes were determined blinded to the clinical characteristics.Quality control criteria leading to exclusion of an SNP from further analysis were a call rate <95%, a minor allele frequency (MAF) <5%, and value of $p<0.001$ for deviation from Hardye Weinberge Equilibrium (HWE) in controls. Furthermore, DNA samples with a call rate <95% over all SNPs were excluded from the analysis.

Statistical analysis

Statistical analysis was performed using PLINK v1.0721 for the SNP association tests and R 2.10.1 (http://www.r-project.org) for all other analyses. Statistical significance was defined at the 95% level ($p<0.05$). Descriptive data were reported as mean ± SD or percentages. For categorical data, a X2 test or Fisher exact test was used to test the difference between groups. The Student t test and one-way analysis of variance (ANOVA) were used to compare the means of continuous variables.

1.3 Results

1.3.1 Association between migraine and restless legs syndrome: Results

During the study period, 1360 patients with headache visited our headache clinic. After excluding patients with secondary headache disorders, unclassified headaches and other primary headache disorders, 1046 patients entered the study. Five patients were excluded because of incomplete data records (n=3) and loss to follow-up (n=2). A total of 1041 patients (801F/240M, mean age 43.7±14.4 years, range 18-93) completed the study, and 772 patients were diagnosed as migraine, 218 TTH and 51 CH. The demographics of the three headache groups are shown in table 1. Age, gender ratio and BMI values differed among the three headache groups.

Table 1 Demographics and the clinical data of restless legs syndrome (RLS) among patients with different headache disorders

	Total (N=1041)	Migraine (N=772)	Tension-type headache (N=218)	Cluster headache (N=51)	p Value
Total subjects					
Mean age (years)	43.7±14.4	42.1±13.3	50.6±16.2	38.4±12.6	<0.001
Female patients, n (%)	801 (76.9%)	644 (83.4%)	146 (67.0%)	11 (21.6%)	<0.001
Mean BMI, kg/m^2	23.1±3.6	22.9±3.7	23.5±2.9	24.7±3.6	<0.001
RLS, n (%)	99 (9.5%)	88 (11.4%)	10 (4.6%)	1 (2.0%)	0.002
Clinically relevant RLS, n (%)	37 (3.6%)	33 (4.3%)	3 (1.4%)	1 (2.0%)	0.39
RLS subjects only					
Mean International RLS Study Group Rating Scale	12.1±7.6	12.3±7.5	10.0±8.7	14	0.64
Mean Hospital Anxiety and Depression Scale score	16.5±7.5	16.7±7.9	15.1±3.2	13	0.75
Pittsburgh Sleep Quality Index mean global sore	11.1±4.0	11.1±4.1	11.3±3.6	9	0.86
RLS with nocturnal leg jerks during sleep, n (%)	42 (42.4%)	38 (43.2%)	4 (40.0%)	0 (0%)	0.68
Clinically relevant RLS, n (%)	37 (37.4%)	33 (37.5%)	3 (30%)	1 (100%)	0.39
Family history of RLS, n (%)	17 (17.2%)	15 (17.0%)	2 (20.0%)	0 (0%)	0.88
Willingness to treat; n (%)	56 (57.1%)	49 (56.3%)	6 (60.0%)	1 (100%)	0.67

RLS screening and diagmosis

Of 1041 patients, 206 patients (19.8%) reported≧1 positive question on the RLS screening questionnaire. After physician telephone interviews, 42 of 47 (89.4%) patients with four positive questions were diagnosed as having RLS, 33 of 47 (70.2%) with three positive questions, 15 of 48 (31.3%) with two, and nine of 64 (14.1%) with one. None of the randomly selected 20 patients with negative answers to the four screening questions were diagnosed as having RLS. In total, 99 patients (9.5%) were diagnosed as having RLS with a higher frequency in women than men (85 women (10.6%) vs 14 men (5.8%), p=0.027).

Thirty-nine patients (3.7%) fulfilled the definition of ‘clinically relevant RLS,’ and 17 (17.2%) reported a positive family history of RLS symptoms. The mean IRLS score of RLS patients was 12.167.8, with one patient (1.2%) having a very severe degree, 13 (13.1%) severe, 40 (40.4%) moderate and 45 (45.5%) mild. Fifty-six patients (57.1%) expressed a willingness to treat their comorbid RLS.

In our study, only 159 patients (15.3%) had a history of having taken headache prophylactic agents before visiting our clinic. Sixty-four patients (6.1%) reported current usage of at least one of the following medications: tricyclic antidepressants, dopamine antagonists, mirtazapine, SSRIs or SNRIs. Three of them used two or more types of medications. The frequency did not differ between patients with RLS and without (10.1% vs 5.7%, p=0.09). As for the individual medication category, there were no differences in the frequencies between patients with RLS and without including tricyclic antidepressants (2.0% vs 1.2%, p=0.47), dopamine antagonist (1.0% vs 2.1%, p=0.45), mirtazapine (1.0% vs 0.2%, p=0.26), SSRIs (4.0% vs 2.2%, p=0.26) and SNRIs (2.0% vs 0.3%, p=0.08).

RLS in Patients with Different Headache Disorders

The frequency of RLS among patients with migraine was 11.4% (n=88), and that of clinically relevant RLS was 4.3% (n=33). The frequencies of RLS did not differ between genders (F/M: 11.8% vs 9.4%; p=0.43) among migraineurs. Patients with migraine had higher frequencies of RLS than those with TTH (4.6%) and CH (2.0%) groups (p=0.002). After controlling for gender and age by logistic regression analyses, migraine patients still had a higher frequency of RLS than those with TTH (p=0.017), but the difference did not reach significance between migraine and CH patients (p=0.106) (table 1). Of note, the frequencies of RLS among different headache subtypes did not reach statistical significance in both migraine (migraine with aura 8.3%, migraine without aura 10.9%, chronic migraine 11.8%, probable migraine 14.0%, p=0.85) and TTH (frequent TTH 3.5%, chronic TTH 5.0%, p=0.65) patients. The comparison was not made in the CH group because all our patients with CH had an episodic form. The low incidence of chronic CH is typical of this headache disorder in Asians.24 Among RLS patients, the mean IRLS, HADS, PSQI scores, frequencies of nocturnal jerks during sleep or clinically relevant RLS did not differ between patients with migraine and those with tension-type or cluster headaches (table 1).

Comparisons of Migraine patients with RLS and those without RLS

The comparisons of demographic data, headache profiles, MIDAS scores, past medical history, usage of analgesics and HADS scores between migrainous patients with RLS and those without RLS are shown in table 2. The frequencies of chronic illnesses did not differ between migraine patients with RLS and those without (table 2). Patients with RLS had higher MIDAS and HADS scores than those without. Regarding headache profiles, migraine patients with RLS had higher frequencies of

exacerbation due to physical activities, photophobia, phonophobia, vertigo, dizziness, tinnitus and neck pain than those without RLS (table 2). We grouped patients with migraine according to the six migrainous symptoms (unilateral, throbbing, aggravation by physical activities, moderate to severe intensity, nausea/ vomiting, photophobia and phonophobia). Figure 1 shows that the frequencies of RLS increased with an increasing number of migrainous symptoms (linear-by-linear association, $p<0.001$).

Table 2 Comparisons of demographic data, headache profiles and Hospital Anxiety and Depression Scale scores between migraine patients with restless legs syndrome (RLS) and those without

	RLS (N = 88)	No RLS (N = 684)	p Value
Mean age (years)	40.1±12.7	42.4±13.4	0.14
Female patients, n (%)	76 (86.4%)	568 (83.0%)	0.43
Mean BMI	23.5±4.2	22.8±3.7	0.09
Migraine subgroups, n (%)			0.75
Migraine with aura	4 (4.5%)	44 (6.4%)	
Migraine without aura	29 (33%)	238 (34.8%)	
Probable migraine	6 (6.8%)	37 (5.4%)	
Chronic migraine	49 (55.7%)	365 (53.4%)	
Past history, n (%)			
Hypertension	12 (13.6%)	90 (13.2%)	0.90
Diabetes mellitus	4 (4.5%)	23 (3.4%)	0.54
Asthma	8 (9.1%)	28 (4.1%)	0.054
Thyroid disease	6 (6.8%)	41 (6.0%)	0.76
Mitral valve prolapse	3 (3.4%)	18 (2.6%)	0.72
Depressive disorder	12 (13.6%)	68 (9.9%)	0.28
Epilepsy	0	3 (0.4%)	1.0
Self-report nocturnal leg jerks during sleep	38 (43.2%)	48 (7.0%)	<0.001
Headache characteristics			
Mean headache frequency, times/week	4.5±2.3	4.1±2.4	0.11
Mean headache intensity, 0–10 scale	6.4±2.1	6.3±2.0	0.64
Unilateral, n (%)	69 (78.4%)	495 (72.4%)	0.23
Pulsatile quality, n (%)	65 (73.9%)	458 (67.0%)	0.19
Exacerbation due to physical activities, n (%)	62 (70.5%)	369 (54.0%)	0.003
Accompanying symptoms			
Nausea, n (%)	66 (75.0%)	494 (72.2%)	0.58
Vomiting, n (%)	33 (37.5%)	233 (34.1%)	0.52
Photophobia, n (%)	66 (75.0%)	406 (59.4%)	0.005
Phonophobia, n (%)	50 (56.8%)	310 (45.3%)	0.04
Other features			
Vertigo, n (%)	36 (40.9%)	141 (20.6%)	<0.001
Dizziness, n (%)	70 (79.5%)	441 (64.5%)	0.005
Tinnitus, n (%)	52 (59.1%)	230 (33.7%)	<0.001
Neck pain, n (%)	53 (60.2%)	335 (49.0%)	0.047
Mean Migraine Disability Assessment score	42.9±52.2	30.8±39.6	0.04
Medication overuse, n (%)	28 (31.8%)	249 (36.4%)	0.40
Mean Hospital Anxiety and Depression Scale score	16.7±7.9	14.4±7.8	0.01

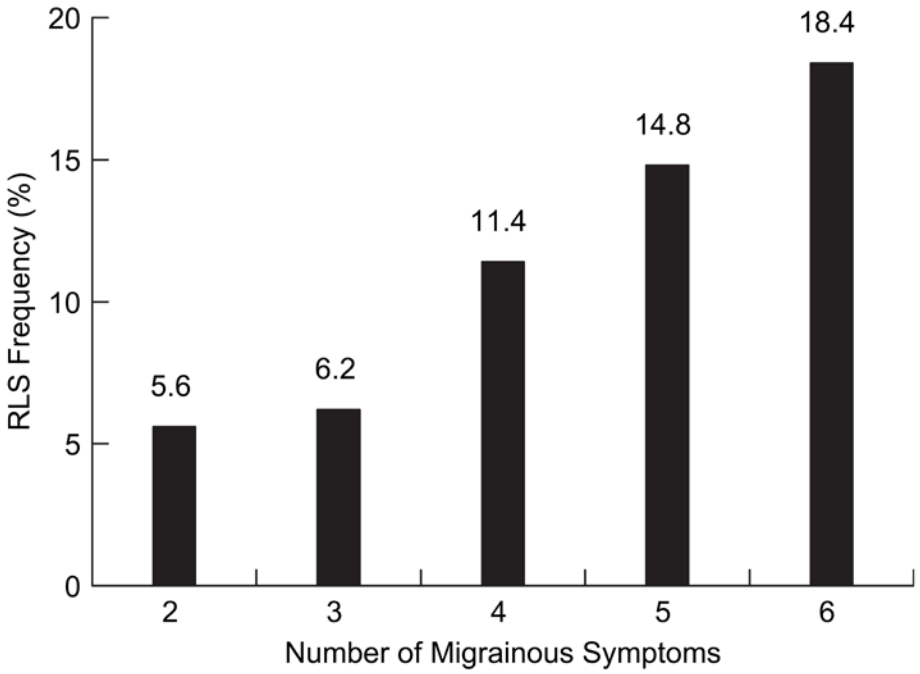


Figure 1 Relationship between the frequencies of restless legs syndrome (RLS) and the number of migrainous symptoms (unilateral, throbbing, aggravation by physical activities, moderate or severe intensity, nausea/vomiting, photophobia and phonophobia) in patients with migraine ($p<0.001$, linear-by-linear association).

Impact of RLS in sleep quality

Migraine patients reported higher mean scores on the PSQI (9.2± 4.1 vs 8.6± 4.4, p=0.045) than those with TTH or CH. Among migraine patients, comorbidity with RLS was associated with a higher mean PSQI global score (11.1±4.1 vs 8.9±4.0, p<0.001) and higher frequencies of poor sleep quality (PSQI>5) (92.0% vs 78.1%, p=0.002). Except for the sleep latency, the other six components of the PSQI were significantly higher in migraine patients with RLS than in those without (table 3). General linear model analyses showed that comorbidity with RLS was independently associated with PSQI scores after controlling for age, gender, BMI, HADS and MIDAS scores

Table 3 Comparison of Pittsburgh Sleep Quality Index (PSQI) component and global scores between migraine patients with restless legs syndrome (RLS) and those without

	RLS (N=88)	No RLS (N=684)	p Value
PSQI mean component score			
Subjective sleep quality	2.1±0.7	1.8±0.8	0.002
Sleep latency	1.6±1.0	1.4±1.0	0.067
Sleep duration	1.9±0.9	1.7±0.9	0.023
Habitual sleep efficiency	1.3±1.2	0.9±1.1	0.007
Sleep disturbance	1.6±0.6	1.3±0.5	<0.001
Sleep medications	1.0±1.3	0.7±1.1	0.035
Daytime dysfunction	1.6±0.9	1.1±0.9	<0.001
PSQI mean global sore	11.1±4.1	8.9±4.0	<0.001
Poor sleeper (PSQI>5) (n, %)	81 (92%)	534 (78.1%)	0.002

Our study demonstrated an association between migraine and RLS among different primary headache disorders. Comorbid RLS in migraine patients worsened sleep quality. A shared underlying mechanism may account for the correlates between migraine features and comorbid RLS.

1.3.2 Regional brain iron levels in migraine with comorbid restless legs syndrome: : Results

The demographic data did not differ between four groups. (Table 4) Among these four groups, T2*-RT was significantly different in the red nucleus (migraine without RLS<migraine with RLS≒control< primary RLS: 79.0±8.6, 86.4±10.0, 84.0±7.5, 92.1±11.2ms, p<0.0001) and substantia nigra (migraine without RLS≒ control<migraine with RLS< primary RLS: 75.9±8.2, 77.6±7.0, 84.3±10.2, 88.7±11.9ms p=0.0001) (one-way ANOVA, post-hoc LSD test). The ferritin levels did not differ among these four groups.

Table 4 The demographic data of four study groups

	Primary RLS N=18	Migraine with RLS N=26	Migraine without RLS N=26	Control N=26	P Value
Age	35.8±6.3	34.3±5.7	35.2±6.0	34.7±5.3	0.84
Female(%)	83.3%	88.5%	80.8%	85.2%	0.89
Ferritin	74.9±48.4	64.7±59.9	89.7±77.9	71.6±43.3	0.50
HgB	13.3±1.8	13.0±1.6	13.7±1.2	13.4±2.2	0.49
IRLSS	19.7±8.6	17.3±7.2	ND	ND	0.32
MIDAS	ND	32.1±24.7	33.2±40.1	ND	0.9

Migraine duration (year)	ND	14.7±6.9	14.3±8.6	ND	0.87

HgB: hemoglobin; IRLS: International RLS Study Group Rating Scale; MIDAS: Migraine Disability Assessment; ND: No data

Table 5. Comparison of the T2* relaxation time between groups (milliseconds)

	Primary RLS N=13	Migraine with RLS N=22	Migraine without RLS N=22	Control N=22	P Value
Ant. Pu	117.4±6.1	118.4±10.6	118.3±8.2	119.3±8.1	0.91
Post. Pu	99.4±7.7	103.6±8.4	101.3±8.3	102.6±10.1	0.44
CN	127.1±9.9	129.1±11.9	126.0±13.1	129.4±10.4	0.68
GP	84.7±12.8	79.8±14.5	76.0±11.25	81.4±12.2	0.15
Red Nu	92.1±11.2	86.4±10.0	79.0±8.6	84.0±7.5	<0.0001
PAG	123.3±12.4	118.9±8.0	115.1±6.2	117.3±6.2	0.014
SN	88.7±11.9	84.3±10.2	75.9±8.2	77.6±7.0	<0.0001

Ant. Pu: anterior putamen; Post. Pu: posterior putamen; CN: caudate nucleus; GP: globus pallidus; Red BU: red nucleus; PAG: periaqueductal gray matter; SN: substantia nigra

1.3.3 The temporal relationship between migraine and restless legs syndrome: : Results

During the study period, 40 out of 403 migraine patients (9.3%) presented at our headache clinic diagnosed migraine comorbid with RLS. Seven patients excluded from the study because of difficulty in diary record and 33 patients were enrolled in this study. Three of these patients were excluded from analyses due to incomplete diary records, which resulted in 30 patients completing the study. Table 6 presents patient demographics, headache profiles, and RLS characteristics. Most subjects (n = 22) had episodic migraine, and 8 patients experienced chronic migraine. Only one patient took amlodipine for blood pressure control.

Table 6. Patient demographics, headache profiles, and RLS symptoms

Characteristic	Value
Number of patients	30
Gender	28F/2M
Mean age (range), years old	35.5±9.0, (20-54)

Migraine diagnoses	
Episodic migraine with aura and without aura	2 (6.7%)
Episodic migraine without aura	20 (66.7%)
Chronic migraine	8 (26.7%)
Baseline of headache profiles	
Mean migraine days per month (range)	8.8±4.2 (2-18)
Unilateral location	22 (73.3%)
Pulsating quality	24 (80.0%)
Headache aggravation by physical activities	28 (93.3%)
Nausea	22 (73.3%)
Vomiting	10 (33.3%)
Photophobia	12 (40.0%)
Phonophobia	24 (80.0%)
RLS attack days per month (range)	11.2±5.6 (2-20)
Mean BMI (range)	23.7±3.6 (18.4-26.1)

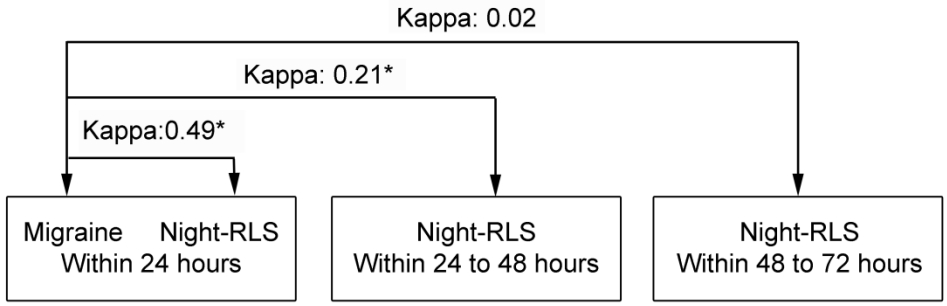
We collected 420 daily diary entries from the 2-week patient diary records. Diary results showed that patients reported 182 headache days (43.3%), including 133 migraine (31.7%) and 171 RLS days (40.7%). According to Spearman rank correlational analyses, the frequencies of migraine and RLS attacks were positively correlated (rs=0.56, p=0.001).

After combining diary entries, we first treated migraine attacks as a trigger for RLS and evaluated the observed agreement by calculating weighted linear kappa statistics (Figure 1a). Within the 24 hours category, the results showed a moderate overall agreement for the occurrence of migraine and the following RLS (weighted linear kappa=0.49, 95% CI:0.40-0.57, p<0.0001; Figure 2a). On the days with migraine attacks, the frequencies of RLS did not differ between those with and without usage of abortive medications (69.5% vs. 76.3%, p=0.53).

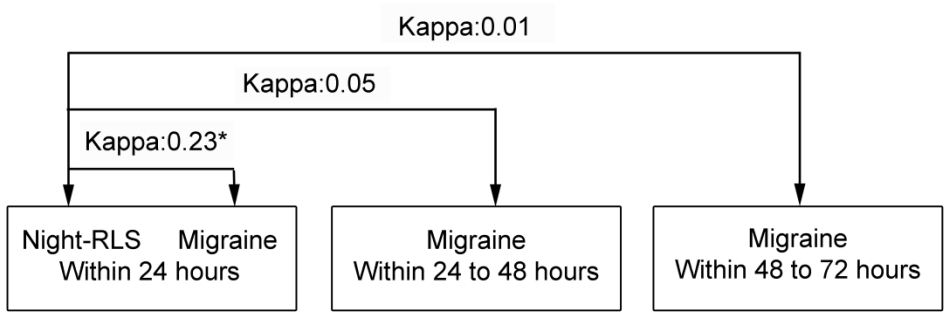
Regarding migraine and followed RLS attacks within the 24−48 hour category, the weighted linear kappa value was low (0.21, 95% CI:0.13-0.29) but significant (p<0.001; Figure 1a). The agreement between migraine and RLS occurrence in the 48−72 hour assessment was not significant (weighted linear kappa: 0.02, 95% CI:-0.05-0.1, p=0.6; Figure 2a).

Fig 2. The Temporal Relationship between migraine and RLS attack

a. Weighted Linear kappa coefficients between migraine and the following RLS attacks



b. Weighted Linear kappa coefficients between RLS and the following migraine attacks



* p<0.001

Results for the agreement between non-migraine headache and RLS were calculated from the weighted linear kappa coefficients in 17 patients (migraine attack days were excluded from the analysis). The data revealed agreement between non-migraine headache and RLS within 24 hours was low but significant (weighted linear kappa: 0.23, 95% CI: 0.16-0.30, p<0.001). In contrast, the agreement was not statistically significant between non-migraine attacks and subsequent RLS attacks within 24−48 hours (weighted linear kappa: 0.05, 95% CI:-0.02-0.12 p=0.72) or within 48−72 hours (weighted linear kappa: 0.01, 95% CI:-0.03-0.16, p=0.75).

If RLS attacks were considered as a trigger for the subsequent migraine, the weighted agreement between RLS and migraine within 24 hours was low but significant (weighted linear kappa: 0.16, 95% CI:0.07-0.24, p<0.001) but did not reach significance between the RLS attacks and the following migraine attacks within 24-48 hours (weighted linear kappa: 0.03, 95% CI:-0.05-0.11, p=0.44) or within 48-72 hours (weighted linear kappa: 0.07, 95% CI:-0.02-0.16, p=0.1). (Figure2b)

1.3.4 Genetic association in Migraine patients with RLS: Results

A total of 188 migraine patients with RLS and 1024 migraine patients without RLS (262M/950F, mean age 39.4±12.6) were investigated. Migraine patient comorbid with RLS reported higher mean headache days (15.1±10.4 vs. 12.2±9.7, p=0.001) and higher BDI scores (14.8±9.6 vs. 10.0±8.8, p<0.001) than those without RLS. The gender and age did not differ between groups. (Table 7)

Table 7. The Comparison of Demographic data between migraine patients with or without RLS

	Migraine without RLS (n=1026)	Migraine with RLS (n=188)	P Value
Female(n, %)	797(77.7%)	154(81.9%)	0.20
Age (mean±SD)	39.3± 12.4	40.2±13.7	0.34
Ferritin (mean±SD)	90.6±93.2	127.4±212.7	0.21
BDI	10.0±8.8	14.8±9.6	<0.001
Mean headache days (months, mean±SD)	12.2±9.7	15.1±10.4	0.001

Two SNPs encompassing the genes MEIS1 were identified associated with the RLS in migraine patients. (rs2300478, p=0.037, OR:1.31; rs12469063, p=0.024, OR:1.34) The SNPs on BTBD9, PTRD and MAP2K5/LBXCOR1/SKOR1did not revealed the association with RLS in migraine patients. (Table 8)

Table 8. Analysis of allelic association of SNPs in MEIS1, BTBD9, PTPRD and MAP2K5/LBXCOR1 genes

SNP	Gene	Risk allele	OR (95% CI)	MAF		p value
				Migraine with RLS (n=188)	Migraine without RLS (n=1024)	
rs12469063	MEIS1	A	1.34 (1.04-1.73)	0.08	0.12	0.03
rs2300478		T	1.32 (1.02-1.70)	0.08	0.11	0.02
rs9349077	BTBD9	A	1.04 (0.85-1.28)	0.29	0.31	0.68
rs3923809		A	1.03 (0.84-1.27)	0.44	0.46	0.75
rs7740763		C	1.01 (0.82-1.23)	0.43	0.44	0.96

rs1975197	PTPRD	T	1.19 (0.95-1.48)	0.43	0.36	0.13
rs4626664		A	1.01 (0.83-1.25)	0.48	0.47	0.89
rs11635424		A	1.04 (0.84-1.28)	0.47	0.48	0.72
rs3784709	MAP2K5/ LBXCOR1/ SKOR1	C	1.00 (0.81-1.24)	0.39	0.39	0.99
rs1026732		A	1.09 (0.87-1.36)	0.36	0.39	0.47
rs6494696		C	1.07 (0.86-1.33)	0.37	0.39	0.57

1.4 Discussion

In the association between migraine and RLS, our study showed that patients with migraine reported a higher frequency (11.4%) of RLS than those with TTH or CH. The frequency of RLS in our migraine patients is much higher than the result from a recent community-based Taiwanese study (1.5%).(60) Our findings imply that RLS is a comorbidity of migraine. Our patients with migraine had a more severe sleep disturbance than those with TTH or CH. Moreover, migraine patients with RLS were associated with higher PSQI global and in six of the seven component scores. Therefore, the impact of RLS on sleep in patients with migraine was pervasive. Our study further confirmed more psychological symptoms in migraine patients with RLS by means of the HADS questionnaire, an instrument measuring only the aspect of emotional status.

In our MRI study, the finding revealed that the iron deficiency was still important in migraine patients comorbid with RLS. However, in migraine patients, the level of iron deficiency was milder than that in the patients with idiopathic RLS. Iron deficiency related dopamine level increase and fluctuation were suspected to be the most important pathophysiology of RLS attack. The result provided the possibility that the threshold of RLS attack seemed to be lower in migraine patients. The dopaminergic dysfunction was both important in migraine and RLS.

In our diary study for the temporal relationship between migraine and RLS, our findings show that migraine attacks likely triggered RLS, but not vice versa. The finding that migraine triggered RLS was supported by a strong dose-response relationship, which may describe the " biological gradients" between migraine and RLS (62). The first supporting evidence comes from the fact that the more severe the migraine attack, the more severe the following RLS symptoms. Second, the temporal effects declined as the time interval increased following migraine attacks. Third, non-migraine headache attacks also had a weak but significant association between RLS attacks triggered within 24 hours. Migraine has been considered as a spectrum disorder; (63) therefore, the "weaker" correlation supports the notion that non-migraine headaches might represent aborted migraine or mild migraine attacks in migraine patients.

In addition, a positive correlation was also found between migraine and RLS attack frequencies (rs=0.56). This finding supports the results of a population-based study that found RLS comorbidity was present with active migraine but not past migraine (64). It should be noted that our previous study demonstrated similar RLS occurrence among patients with chronic and episodic migraine (65). Therefore,

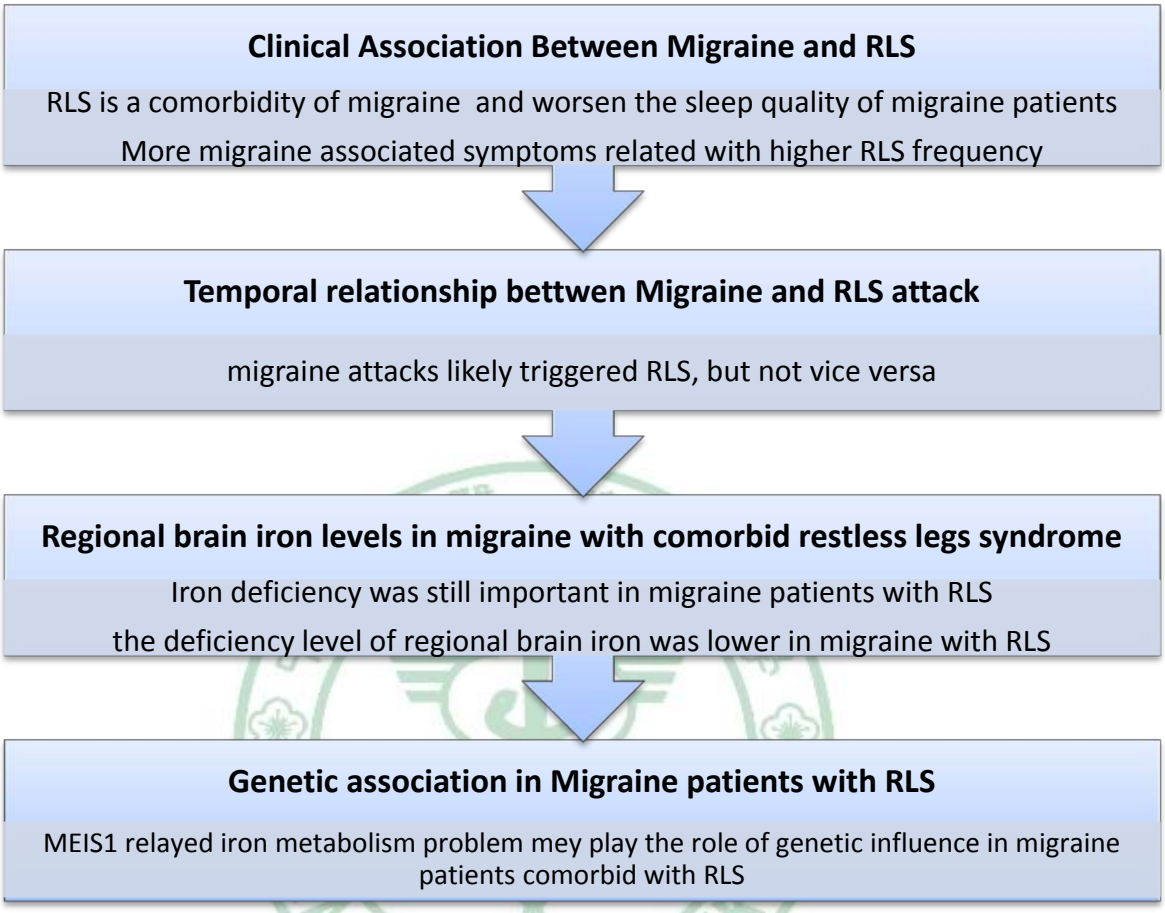
chronicity of migraine may determine the frequency, but not the presence or absence, of RLS.

The underlying mechanisms responsible for the migraine triggering RLS attacks remain unknown; however, our results suggest a possible neurochemical explanation. A PET study showed that the synthesis of serotonin increased during migraine attacks, (66) and it is known that serotonin and dopamine have some opponent interactions (67). Subsequently, we postulate that the extracellular increase in serotonin may be taken up into dopamine terminals, which would hamper dopamine secretion (68). These actions of serotonin may partially account for the imbalance of dopamine, and thus explain the occurrence of RLS following migraine attacks.

In our genetic study, we investigated the SNPs reported associated with indiopathic RLS in previous studies. Our finding revealed the influence of MEIS1 gene related to RLS attack in migraine patients. The result suggests iron metabolism may play a role in the pathophysiology of comorbid RLS.

1.5 Conclusion

Figure 3. Summary of our findings of Migraine and RLS



The figure 3 summarized our finding of study series on th association between migraine and RLS. A clinical association between migraine and RLS among different primary headache disorders is demonstrated. Comorbid RLS in migraine patients worsened sleep quality. In migraine patients with comorbid RLS, the correlation was stronger between migraine attacks and the following RLS attacks within 24hours than RLS attacks and the following migraine attacks. Migraine was associated with higher iron levels in the red nucleus; whereas, RLS was associated with lower iron levels in both the red nucleus and substantia nigra. Compared to primary RLS, the deficiency level of regional brain iron was lower in migraine with RLS. MEIS1 play the role of genetic influence in migraine patients comorbid with RLS. This finding of MRI and genetic studies suggests iron metabolism may play a role in the pathophysiology of comorbid RLS.

2 Morning headache in habitual snorers: Frequency, characteristics, predictors and impacts

2.1 Introduction and background

Headache present upon awaking, commonly referred to as morning headache, has been considered as a secondary headache resulting from obstructive sleep apnea syndrome (OSAS). (69,70) Based on the International Classification of Headache Disorders, 2nd edition (ICHD-2), (2) sleep apnea headache (code 10.1.3) is specified as morning headache with tension-type headache features, of a short duration (<30 minutes) or with frequent attacks (Table 9). However, evidence on the relationship between morning headache and OSAS is conflicting. (70,71-76) It is estimated that 7.6% of the general population has morning headache (71), and a high frequency of morning headache has also been reported in patients with depression, migraine, periodic leg movement disorder (PLMD), insomnia or snoring. (71,72,75-77) The criteria for morning headache vary among studies, which makes comparisons difficult. The criteria have included: 3 or more morning headaches in the past year (69), the presence of any morning headache, (70,71) morning headache equal or more than one time every week, (74) “always,” “often,” or “sometimes" headaches when waking up in the morning, (75) and “often,” or “very often" headaches when waking up in the morning. (73,76)

Habitual snoring is a common health problem (78) and also a sensitive symptom of OSAS (79), but the predictors for morning headache in patients with snoring are not known. In addition, the impact of morning headache on the health-related quality of life (HRQoL) in habitual snorers is not well defined.

This study investigate the frequency of morning headache, its impact on HRQoL and relevant predictors in habitually snoring patients. All these patients underwent a study of overnight polysomnography (PSG).

2.2 Methods and statistical analysis

We prospectively enrolled consecutive patients aged ≥ 18 years referred to our sleep laboratory between January 1, 2009 and March 31, 2010 with the complaint of habitual snoring, which was defined as self-reported frequent snoring in this study. One physician (Chen PK) interviewed all patients to determine whether they had morning headache, migraine, and insomnia. Diagnoses of migraine and other headache disorders were based on the ICHD-2.(2) Diagnosis of insomnia was based on the International Classification of Sleep Disorders, 2nd edition (ICSD-2). (80)

Since there were no globally accepted diagnostic criteria for morning headache, we defined “morning headache” as headache on awakening ≥1 day/week for ≥6 months in this study. Patients with persistent headache were excluded because it was difficult to separate persistent headache from morning headache.

All patients filled out a structured questionnaire designed for morning headache. Information included demographics, body mass index (BMI), headache frequency, duration, location, quality, intensity, and accompanying symptoms, such as nausea, vomiting, photophobia and phonophobia. The study also investigated if the patient’s morning headache fulfilled the criteria for migraine attacks based on the ICHD-2 (2), that is, duration equal or more than four hours with two or more of the headache symptoms, including pulsatile quality, unilateral location, moderate or severe intensity and exacerbation due to physical activities; and one or more accompanying symptoms, including either “nausea or vomiting” or “photophobia and phonophobia”. Each patient also completed the Hospital Anxiety and Depression scale (HADS), (55) and the Short Form-36 health survey (SF-36).(81,82) All patients underwent an overnight PSG study after the questionnaire survey. This study protocol was approved by the Institutional Review Board at the Lin-Shin Hospital, Taichung, Taiwan. Patients signed an informed consent form before entering the study.

Polysomnography (PSG)

The PSG was performed on Embla S4500 (Flaga, Reyjavick, Iceland) and Alice 4 (Healthdyne, Atlanta, GA, USA) sleep systems. The EEG (C3/A2-C4/A1, and O1/A2 according to the 10–20 international electrode placement system), the two-channel electro-oculogram, chin electromyogram and electrocardiogram were recorded with surface electrodes. Airflow was assessed with nasal-oral thermistors, and respiratory movements with thoracic and abdominal inductive plethysmography.

Oxygen saturation during sleep was measured continuously using pulse oxymetry with a finger probe. Snoring was evaluated with a neck microphone. Leg movements were recorded by bilateral tibial electromyograms. Apnea, hypopnea and periodic leg movements in sleep (PLMS) were defined based on the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events. (57) The apnea is a period of breathing cessation. The hypopnea is defined as a ≥ 30% reduction in breathing with a ≥ 4% oxygen desaturation or arousal. The minimum duration of an event was 10 seconds. The apnea–hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of total sleep time. PLMS was scored if there were at least four consecutive leg movements of 0.5–10 seconds’ duration, and between 5 and 90 seconds apart. The minimum amplitude of a leg movement event was an 8 μV-increase in EMG. The PLMS index was calculated as

the number of PLMS per hour. OSAS was defined as AHI ≥ 5. (80) PLMD was defined as a periodic leg movement index of >15 per hour of sleep with disturbed sleep or daytime fatigue. (80)

Statistical analyses

Descriptive data were presented as mean ± standard deviation (SD) or percentages. For categorical data, a chi-square test or Fisher's exact test was used to test the difference between groups. The Student's *t*-test was used to compare the means of continuous variables. The potential predicting variables for the presence of morning headache included age, gender, smoking habits, migraine, HADS score (≧8 or <8), insomnia, OSAS and PLMD. The predictors for morning headache were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Logistic regression was used to calculate adjusted ORs (AORs) after controlling for potential confounders. An estimated difference of each domain of the SF-36 due to morning headache was calculated after controlling for potential confounders by general linear models. All calculated p-values were two-tailed and statistical significance was defined as a p-value of <0.05.

Statistical analyses. Descriptive data were presented as mean± standard deviation (SD) or percentages. For categorical data, a chi-square test or Fisher's exact test was used to test the difference between groups. The Student's t-test was used to compare the means of continuous variables. The potential predicting variables for the presence of morning headache included age, gender, smoking habits, migraine, HADS score (≥8 or <8), insomnia, OSAS and PLMD. The predictors for morning headache were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Logistic regression was used to calculate adjusted ORs (AORs) after controlling for potential confounders. An estimated difference of each domain of the SF-36 due to morning headache was calculated after controlling for potential confounders by general linear models. All calculated p-values were two-tailed and statistical significance was defined as a p-value of <0.05.

2.3 Results

During the study period, 284 patients with habitual snoring who were referred to our sleep laboratory were recruited. After excluding 2 patients due to refusal and 12 patients with persistent headache, 270 patients signed informed consent forms to enter the study. Two patients were excluded due to incomplete data. A total of 268 patients (178M/90F, mean age 44.4±12.2, range 18-76 years) completed the study. Of them, 184 (68.7%) (135M/49F) were diagnosed with OSAS and 33 (12.3%) (21M/12F)

were diagnosed with PLMD, according to the PSG results. Based on the physician interview, 116 patients (43.3%) (73M/43F) had insomnia and 58 (21.6%) (35M/23F) had migraine, including 8 with and without aura and 50 without aura. Based on the HADS, 193 (72.0%) (123M/70F) had psychological distress (HADS ≥8 points).

Table 9 Diagnostic criteria of sleep apnea headache proposed by the International Classification of Headache Disorders, 2nd edition. (ICHD-2, code 10.1.3) and the frequencies of each criterion in our snoring patients with OSAS and morning headache

Diagnostic criteria:	Morning headache in habitual snorers with OSAS (N=50)
A. Recurrent headache with at least one of the following characteristics, and fulfilling criteria C and D:	
A1. occurs on >15 days per month	9 (18%)
A2. bilateral, pressing quality and not accompanied by nausea, photophobia or phonophobia	20 (40%)
A3. each headache resolves within 30 minutes	16 (32%)
At least one of the A1-A3 criteria	31 (62%)
B. Sleep apnea (Respiratory Disturbance Index ≥5) demonstrated by overnight polysomnography	50 (100%)
C. Headache is present upon awakening	50 (100%)
D. Headache ceases within 72 hours, and does not recur after effective treatment of sleep apnea	Not available

Headache profile of morning headache

Overall, 63 patients (23.5%) (37M/26F) had morning headache based on the physician interview. The characteristics of morning headache are shown in Table 2. The locations of the morning headache were not specific, and a side-locked unilateral location was unusual (4.8%). Dull pain was more common (n=33, 52.4%) than pulsatile headache (n=29, 46.0%). The headache intensity was most commonly moderate (n=29, 46.0%). The headache profile did not differ between morning headache patients with and without OSAS. In contrast, compared with those without migraine (n=28), the headache profile of morning headache patients with migraine (n=35) was more likely to be pulsatile, of severe intensity and longer duration, and associated with nausea. The morning headache profile fulfilled ICHD-2 migraine attacks in 19% (12/63) of all morning headache patients, especially in those with migraine, compared with those without (31.4% (11/35) vs.3.6 % (1/ 28), p=0.005).

Table 10. Clinical profiles of morning headaches (N=63) in habitual snorers and comparisons in relation to obstructive sleep apnea syndrome (OSAS) and migraine --the number and the parentheses below should be separated

		In relation to OSAS			In relation to migraine		
	All patients (N=63)	OSAS (n=50)	No OSAS (n=13)	P value	Migraine (N=35)	No migraine (N=28)	P value
Locations							
frontal	12 (19.0%)	9 (18.0%)	3(23.1%)	0.70	7 (20.0%)	5 (17.9%)	0.83
occipital	18(28.6%)	14(28.0%)	4(30.8%)	1.0	12(34.3%)	6(21.4%)	0.26
temporal	25(39.7%)	18(36.0%)	7(53.8%)	0.24	13(37.1%)	12(42.9%)	0.65
vertex	11(17.5%)	8(16.0%)	3(23.1%)	0.55	6(17.1%)	5(17.9%)	0.94
side-locked	3(4.8%)	2(4.0%)	1(7.7%)	0.58	2(5.7%)	1(3.6%)	0.69
Characteristics							
Pulsatile	29(46.0%)	23(46.0%)	6(46.2%)	0.99	22(62.9%)	7(25.0%)	0.003
Dull	33(52.4%)	26(52.0%)	7(53.8%)	0.91	12(34.3%)	21(75.0%)	0.001
Intensity							
Mild	17(27.0%)	14(28.0%)	5(38.5%)		5(14.3%)	14(50.0%)	
Moderate	29(46.0%)	25(50.0%)	7(53.8%)		20(57.1%)	12(42.9%)	
Severe	17(27.0%)	11(22.0%)	1(7.7%)	0.47	10(28.6%)	2(7.1%)	0.004
Frequency (days/m)	11.7±6.2	11.7±6.3	11.8±6.3	0.93	11.3±4.8	12.3±7.7	0.52
Duration							0.03
<0.5 hour	21(33.3%)	16(32.0%)	5(38.5%)		9(25.7%)	12(42.9%)	
0.5-4 hours	25(39.7%)	20(40.0%)	5(38.5%)		12(34.3%)	13(46.4%)	
≥ 4 hours	17(27.0%)	14(28.0%)	3(23.1%)	0.89	14(40.0%)	3(10.7%)	
Accompanied Symptoms							
Nausea	20(31.7%)	18(36.0%)	2(15.4%)	0.14	15(42.9%)	5(17.9%)	0.03
Vomiting	4(6.3%)	4(8.0%)	0	0.39	4(11.4%)	0	0.09
Photophobia	4(6.3%)	4(8.0%)	0	0.39	3(8.6%)	1(3.6%)	0.40
Phonophobia	11(17.5%)	9(18.0%)	2(15.4%)	0.60	9(25.7%)	2(7.1%)	0.05
Physical activity exacerbations	23(36.5%)	17(34%)	6(46.2%)	0.42	18(51.4%)	5(17.9%)	0.006
Fulfilling migraine attack criteria	12(19%)	10(20%)	2(15.4%)	0.71	11(31.4%)	5(17.9%)	0.005

Sleep apnea headache

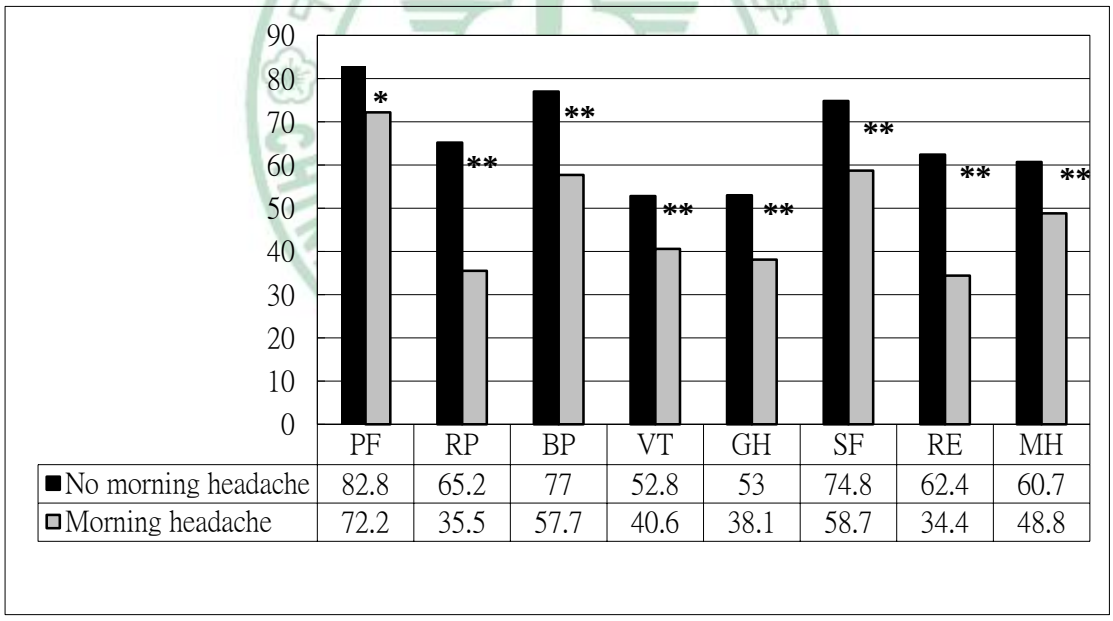
Habitual snorers with OSAS were more likely to have morning headache than those without (27.2% (50/184) vs. 15.5% (13/84), p<0.001). The frequencies of the three proposed headache symptoms (A1 to A3) of ICHD-2 sleep apnea syndrome in our morning headache patients are shown in Table 1. Forty percent of patients with

morning headache could fulfill the criteria for headache symptoms (A2), 32% experienced a short duration of <30 minutes (A3) and 18% had morning headache more than 15 days per month (A1). Overall, 62% (n=31) of OSAS patients fulfilled criterion A, i.e., at least one of three proposed headache symptoms. In this study, we did not test criterion D, i.e., disappearance of morning headache after treatment of OSAS.

The impact of morning headache on the SF-36

Patients with morning headache had significantly lower scores in all eight domains of the SF-36. (Fig.4) The general linear model showed that the presence of morning headache independently accounted for more than 5 points of estimated difference in the domains of RP (-19.1 points, p=0.006), BP (-11.5 points, p=0.002), SF (-8.4, p=0.02) and RE (-22.5, p=0.02), after controlling for age, gender, BMI, smoking, insomnia, OSAS, migraine, psychological distress (HADS≥8), and PLMD.

Figure 4. The SF-36 domain scores between snoring patients with and without morning headache



	PF	RP	BP	VT	GH	SF	RE	MH
■No morning headache	82.8	65.2	77	52.8	53	74.8	62.4	60.7
□Morning headache	72.2	35.5	57.7	40.6	38.1	58.7	34.4	48.8

PF: Physical functioning; RP: Role limitations due to physical problems; BP: Bodily pain; VT: Vitality; GH: General health; SF: Social functioning; RE: Role limitations due to emotional problems; MH: Mental health. * p=0.005, **p<0.001

Predictors for morning headache in habitual snorers

The frequencies of morning headache were higher in subjects with migraine, insomnia, HADS≥8, and OSAS than those without (Table 10). In contrast, the frequencies were not associated with gender, smoking habits, body mass index

(BMI≥27), or PLMD. Except for the frequency of OSAS (AHI≥5), the other sleep parameters of the PSG, including percentages of stage 1, stage 2, stage 3 and 4, and REM sleep, mean AHI, mean SaO_2, lowest SaO_2, desaturation index, snoring index and arousal index, did not differ between habitual snorers with and without morning headache.(data not shown). The logistic regression model showed the presence of migraine, insomnia, HADS≥8, and OSAS were independent predictors for morning headache in habitual snorers after adjustment of age, gender, smoking habits, and BMI (Table 11). Migraine had the highest AOR (6.3), whereas OSAS, the lowest (2.6).

Table 11. The frequencies, odds ratios (OR), and adjusted odds ratios of predictors for morning headache in habitual snorers

	Morning Headache, n (%)	OR (95% CI)	Adjusted OR (95% CI)
Migraine			
Yes (n=58)	35 (60.3%)	9.9 (5.1-19.1)**	6.5 (3.1-13.7)**
No (n=210)	28 (13.3%)		
Insomnia			
Yes (n=116)	47(40.5%)	5.8 (3.1-10.9)**	4.2 (2.0-8.7)**
No (n=152)	16(10.5%)		
Psychological distress (HADS≥8)			
Yes (n=193)	58(30.1%)	6.0 (2.3-15.7)**	3.9 (1.5-10.1)*
No (n=75)	5(6.7%)		
Obstructive sleep apnea syndrome			
Yes (n=184)	50(27.2%)	2.0 (1.0-4.0)*	2.6 (1.0-6.7)*
No (n=84)	13(15.5%)		
Periodic leg movement disorders			
Yes (n=33)	7 (21.1%)	0.9 (0.4-2.1)	0.7 (0.2-2.0)
No (n=235)	56 (23.8%)		
Gender			
Male (n=178)	37(20.8%)	0.6 (0.4-1.2)	0.6 (0.3-1.2)
Female (n=90)	26(28.9%)		
Smoking habit			
Yes (n=82)	22(26.8%)	1.3 (0.7-2.4)	1.6 (0.5-5.2)
No (n=186)	41(22.0%)		
Body mass index≥27kg/m^2			
Yes (n=88)	27(30.7%)	1.77 (0.9-3.2)	1.6 (0.8-3.5)
No (n=180)	36(20.0%)		

HADS: Hospital Anxiety and Depression Scale; OR: odds ratios by univariate analysis

Adjusted OR by multivariate logistic regression after controlling for the other variables

**p<0.001, *p<0.05

2.4 Discussion

The study found that 23.5% of habitual snorers had morning headache, with those with OSAS having a higher frequency than those without (27.2% vs. 15.5%). These findings were similar to those of prior studies, in which 7.4% to 33.6% of OSAS subjects (69-76) and 16.2% of snorers without OSAS had morning headache (2), even though different diagnostic criteria for morning headache were used. Of 63 habitual snorers with morning headache, 12 (19%) suffered from morning headaches with characteristics fulfilling the criteria of migraine attacks. Eleven of them had a history of migraine, accounting for 31.4% (11/35) of migraine patients with morning headache. Based on the ICHD-2 criteria for sleep apnoea headache, 62% of the morning headaches in our OSAS patients had at least one of three proposed headache symptoms (A1 to A3, Table 9). This is because only 40% of the patients with morning headaches had tension-type features (A2), and only one-third had a short duration (A3). We do not know if comorbidity with migraine in our snoring patients complicated the headache pattern, or the subjects fulfilling these ICHD-2 criteria were more compatible with OSAS-induced headache, because our study did not test these criteria by treating these morning headache patients with OSAS.

Our study found morning headache had a pervasive impact on all domains of the HRQoL as assessed by the SF-36. The differences in scores ranged from 10.6 to 29.7 points, much higher than the suggested scores of clinical significance (>5 points). Moreover, morning headache independently accounted for role limitation due to physical and emotional status, impairment of social functioning, and pain. This suggested that snoring patients comorbid with morning headache were more disabled in their daily activities. In fact, these involved domains and the magnitude of difference were consistent with previous studies of migraine patients (83-85).

Snoring is a sensitive symptom for OSAS (79), and was previously considered an important predictor for morning headache. In contrast to our prior belief, migraine was the most important predictor for morning headache in snoring patients, whereas OSAS was the least. The reasons for the differential impact of these factors were not clear. It is reported that more than 71% of migraine patients had experienced headache on awakening (78). Insomnia and psychological distress are well-known triggers or comorbidities of migraine (65,86), and insomnia-related migraine attacks were more predominant in the morning (87). In contrast, the frequencies of morning headache

were similar among patients with different sleep disorders, not only for OSAS (71,72). In our study, more than half of habitual snorers with migraine had morning headache, and 31.4% of their morning headaches fulfilled the criteria for migraine features. The high frequency of OSAS in snorers both with and without morning headache (79.4% vs. 65.4%) downplayed the relationship between OSAS and morning headache. Because we did not have a control group of non-snorers, we do not know if there is a discrepancy in the degree of association between migraine and morning headache in non-snorers.

The pathophysiology of morning headache is still unknown. Hypoxia, hypercapnia (88) and the transient increase of intracranial pressure (89) in OSAS patients were suspected causes. Our study results showed that except for OSAS, the other PSG sleep parameters were not associated with morning headache. Therefore, morning headache in habitual snorers can be, in part, considered as morning attacks of their prior headaches. In addition, we postulated that the four predictors relative to morning headache raised the possibility of hypothalamic involvement. Migraine was related to hypothalamic activation in both neuroimaging and hormonal studies (90,91). The hypothalamus also accounts for sleep regulation and depression (92,93). Recently, abnormal hypothalamic activation was also noted in OSAS patients (94). Further studies are suggested to investigate the role of the hypothalamus in the morning headache of habitual snorers.

Our study has clinical implications. The presence of morning headache can be used as an indicator for poor quality of life and possible associations with migraine, insomnia and psychological distress in habitual snorers. Management of migraine, insomnia or psychological distress might be more helpful for morning headache than management of OSAS. The disruptive effect of CPAP on sleep should be taken into consideration in the treatment of morning headache in snorers, because the potential adverse event of sleep disturbance (95,96) may in turn worsen morning headache.

2.5 Conclusion

Morning headache was common in habitual snorers and associated with a pervasive impairment of healthrelated quality of life. Migrainous features were not uncommon. Not only OSAS, but migraine, insomnia and psychological distress were also important predictors for morning headache, even in snoring patients.

3. Side Paper: Onset Headache Predicts Good Outcome in Patients with First-Ever Ischemic Stroke

3.1 Introduction and background

Headache that accompanies ischemic stroke is a common symptom that is considered an ominous sign by healthcare professionals treating acute ischemic stroke.(97,98) Very few small-scale studies have examined the clinical impact of stroke-related headache, and their results are inconsistent, from no specific impact to prediction of poor outcome.(97-100) The clinical significance of stroke-related headache remains uncertain because of the absence of systematic studies on large populations of stroke patients. On the basis of the ICHD-2,(2) headache attributed to ischemic stroke (code 6.1.1) is specified as any new acute headache that develops simultaneously with or in very close temporal relation to signs of ischemic stroke. Stroke-related headache can be grouped into 3 types: sentinel headache (headache before stroke onset), onset headache (headache at stroke onset), and late-onset headache (headache after stroke onset).(101-107) Most previous studies do not specify these differences and as such, the frequencies of stroke-related headache vary from 8% to 34%.(97-100,103–113) In fact, stroke-related headache at different time points may result from different mechanisms and may have varying clinical effects. A large sample of patients with stroke-related headache in a well-defined time frame and a systematic follow-up of clinical features and outcomes are required to delineate the clinical impact of stroke-related headaches. The present study sought to investigate the prevalence of onset headache in patients with first-ever ischemic stroke and assess its clinical significance using a nationwide prospective registration of stroke patients.

3.2 Methods and statistical analysis

Data source

The Taiwan Stroke Registry (TSR) was a government-funded project that identified acute stroke admissions. Formally launched on August 1, 2006, it involved 39 academic and community hospitals diffusely covering the entire country, with four steps of quality control to ensure the reliability of entered data. All data were compiled prospectively by TSR-trained neurologists and study nurses, and all enrolled patients were visited by physiatrists, who started rehabilitation within 72 hours after admission. More than 42,000 stroke patients were registered when the present study was undertaken. Approval of TSR as a human study protocol was obtained from the Institutional Review Board of each participating hospital and all subjects provided signed informed consents and permission for follow-up.

The data collection, quality assurance processes, and preliminary results of the stroke patient population in the TSR were detailed elsewhere.19 Briefly, pre-admission medical and medication histories, stroke risk factors, clinical, laboratory and neuro-radiologic findings, interventions, and hospital course, including deterioration and outcome measures, were recorded in the TSR. Infarct locations were documented based on computed tomography (CT) and magnetic resonance imaging (MRI) findings and separated into anterior and posterior circulation territories. The anterior circulation territory was divided into the anterior cerebral artery (ACA) and the middle cerebral artery (MCA) territories, while the posterior circulation territory was divided into several parts, including the cortex supplied by the posterior cerebral artery (PCA), thalamus, midbrain, pons, medulla, and cerebellum. Ischemic stroke subtypes were classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria: large artery atherosclerosis, small vessel occlusion, cardio-embolism, specific aetiologies, and undetermined aetiologies.20

National Institutes of Health Stroke Scale (NIHSS) score was recorded in all patients on admission and on discharge. Investigators who rated the NIHSS were certified by the Taiwan Stroke Society and trained for data entry through a web-based TSR database system. In addition, the Barthel index score and modified Rankin Scale (mRS) were recorded at one, three, and six months after the stroke at the outpatient clinic or through structured-telephone interview.

A total of 42,883 stroke patients were included in the TSR database when the present study was initiated. Only adults (≥18 years old) with first-ever ischemic stroke and confirmed ischemic lesions by neuro-imaging, regardless of whether or not the clinical symptoms remitted spontaneously, were included. From the preliminary study population of 16,313, patients with difficulty in expressing headache (n=4,790) were excluded. They were defined as patients with scores of >0 (consciousness disturbance) in NIHSS items 1A, 1B, and 1C (level of consciousness) or ≥2 (severe aphasia) in item 9 (best language). The final sample consisted of 11,523 patients, accounting for 70.6% of the preliminary population with first-ever ischemic stroke (Figure 1). Their admission NIHSS scores were significantly lower than the scores of those who were excluded (4.1±3.1 vs. 15.5±8.5; p<0•0001)

Onset headache of ischemic stroke

Onset headache was inquired from each patient via structured questionnaire based on the TSR protocol. Based on ICHD-25, onset headache was defined as a new headache that developed at the onset of other neurologic symptoms related to ischemic stroke.

Outcome measures

Three outcome measures were analyzed: (1) the frequency of deterioration during hospitalization; (2) changes in NIHSS score from admission to discharge; and

(3) Barthel index scores and mRS at one, three, and six months after stroke. An mRS ≤2 was defined as good outcome.

Deterioration during hospitalization was prospectively recorded by the physician if the patient's neurologic symptoms worsened with an increase of at least 4 points in NIHSS compared to that at admission. Based on the examination of neuroimaging and laboratory test, the causes of deterioration were classified into three groups: stroke-in-evolution, medical complications, and others. Stroke-in-evolution was defined as progressive worsening of infarction lesion-related neurologic symptoms after excluding the possibility of medical problems. In these patients, herniation and hemorrhagic infarction were also recorded. Medical complications were defined as infection, electrolyte imbalance, or neurologic worsening related to serious fluctuations in blood glucose level.

The mean change of NIHSS scores on admission and on discharge was used for short-term outcome evaluation. The Barthel index and proportions of mRS scores ≤2 at one, three, and six months after stroke onset were used to evaluate long-term outcome.

Statistical analysis

All statistical analyses were conducted using the SAS (version 9.2 for windows; SAS Institute., Cary, NC, USA). Differences between mean age, body mass index (BMI), and Barthel index at one, three, and six months after stroke in patients with and without headaches at stroke onset were examined by Wilcoxon two-sample test with 95% confidence interval (95% CI). Distributions of demographic data, stroke subtypes, deterioration during hospitalization, and good outcomes measured by mRS at one, three, and six months after stroke between the two groups were compared by chi-square test. Prevalence ratios (PR), rate ratios (RR) with 95% CI were calculated by Poisson regression model; whereas, odds ratios, by logistic regression. In multivariable Poisson regression models, continue measure of age, gender, hypertension, anterior and posterior infarct territory, stroke subtype, and recombinant t-PA (rt-PA) treatment were controlled. The least squares means and standard errors of NIHSS scores were calculated using analysis of covariance (ANCOVA) models to compare the mean change of scores from admission to discharge between groups, after adjusting for the same factors in the multivariable Poisson regression models. The Value/DF of deviance of the Poisson regression was nearly 1.00, representing a high level goodness of fit of the data.

Statistical Analysis

All statistical analyses were conducted using the SAS (version 9.2 for Windows; SAS Institute, Cary, NC). Differences between mean age, body mass index, and Barthel

index at 1, 3, and 6 months after stroke in patients with and without headaches at stroke onset were examined by Wilcoxon 2-sample test with 95% confidence interval (CI). Distributions of demographic data, stroke subtypes, deterioration during hospitalization, and good outcomes measured by mRS at 1, 3, and 6 months after stroke between the 2 groups were compared by $\chi 2$ test. Prevalence ratios (PRs), relative risk (RR) with 95% CI were calculated by Poisson regression model In multivariable Poisson regression models, continued measures of age, sex, hypertension, anterior and posterior infarct territory, stroke subtype, and recombinant tissue-type plasminogen activator treatment were controlled. The least squares means and standard errors of NIHSS scores were calculated using ANCOVA models to compare the mean change of scores from admission to discharge between groups, after adjusting for the same factors in the multivariable Poisson regression models. The value/degrees of freedom of deviance of the Poisson regression was ≈1.00, representing a high-level goodness of fit of the data.

3.3 Results

Demographic data

Of the 11,523 adult patients with first-ever stroke, 848 (7.4%) had headache at stroke onset while 10,675 did not (Fig. 5). Patients with onset headache had a higher female ratio (43.9% vs. 38.7%; prevalence ratio (PR)=1.1, 95% CI:1.02-1.2), younger age (61.0±14.3 vs. 66.3±12.6 years old; $p<0.001$), and lower mean NIHSS scores on admission (3.9±3.2 vs. 4.1±3.1; p=0.02) (Table1). Other stroke risk factors, including hypertension, diabetes, dyslipidemia, BMI, and smoking and drinking habits did not differ between the two groups (Table1). There was no difference in previous medication history except for a more frequent prescription of aspirin/extended-release dipyridamole capsules in the headache group (0.2% vs. 0.03%; p=0.01). The length of hospital stay also did not differ between patients with and those without onset headache (11.0±11.7 vs. 11.3±11.9 days, p=0.47).

Table 12. Demographic Data in Patients With and Without Onset Headache, n (%)

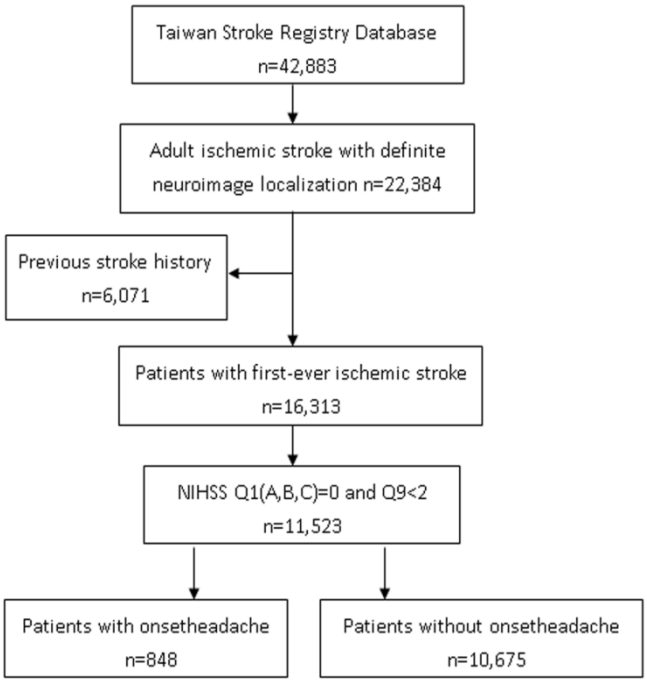
	With Onset Headache (n=848)	Without Onset Headache (n=10675)	Crude PR (95% CI)	*P* Value
Age, y				
Mean±SD	61.0±14.3	66.3±12.6		<0.001
BMI at baseline				
Mean±SD	24.9±3.8	24.8±3.8		0.57
NIHSS on admission				
Mean±SD	3.9±3.2	4.1±3.1		0.02
Sex				
Women	372 (43.9)	4131 (38.7)	1.1 (1.02–1.2)*	
Risk factor				
Diabetes mellitus	321 (37.9)	4221 (39.5)	0.94 (0.85–1.04)	
Hypertension	622 (73.3)	8098 (75.9)	0.96 (0.91–1.01)	
Smoking	359 (42.3)	4512 (42.3)	1.00 (0.91–1.09)	
Alcohol	156 (18.4)	1847 (17.3)	1.07 (0.95–1.22)	
Dyslipidemia	454 (53·6)	5597 (52.5)	1.01 (0.93–1.08)	
Polycythemia	9 (1.1)	94 (0.9)	1.04 (0.86–1.26)	
Depression	43 (5.1)	409 (3.8)	1.02 (0.86–1.20)	
Atrial fibrillation	78 (9.2)	1032 (9.7)	0.95 (0.82–1.11)	

Missing values (all <5%) were considered for all variables except age and sex.

BMI indicates body mass index; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; and PR, prevalence ratios.

*P<0.05.

Figure 5. Patient population from the Taiwan Stroke Registry database enrolled for analysis.



Ischemic stroke subgroups

Based on the TOAST classification, 209 patients were classified as “specific aetiology” Of them, 43 (20.6%) reported onset headache, including 30 (69.8%) diagnosed to have carotid or vertebral artery dissections. There were significantly higher frequencies of onset headache in patients with specific aetiology (PR=3.26, 95% CI: 2.33-4.56) and large-artery atherosclerosis (PR=1.23, 95% CI: 1.1-1.38), but a lower frequency in patients with small vessel occlusion (PR=0.74, 95% CI: 0.66-0.83). After controlling for age, gender, and hypertension in the Poisson regression model, patients with specific aetiology had the highest adjusted PR (PR=1.8, 95% CI: 1.27-2.56) in the presence of onset headache, followed by those with large-artery atherosclerosis (PR=1.28, 95% CI: 1.14-1.44), and cardio-embolism (PR=1.27, 95% CI:1.00-1.61). In contrast, the adjusted PR in onset headache was significantly lower in patients with small vessel occlusion (PR=0.72, 95% CI: 0.64-0.81).

Vascular territory

Patients with onset headache were more likely to have ischemia in the posterior circulation in both models before and after controlling for potential confounding factors (crude PR=1.42, 95% CI:1.30-1.55; adjusted PR=1.39, 95% CI:1.27-1.51) (Table 2). Further comparisons of different infarct localizations in relation to onset headache were shown in Table 3. Patients with cerebellar infarction had the highest adjusted PR (adjusted PR=2.24, 95% CI: 1.97-2.55), followed by PCA cortex (adjusted PR=2.16, 95% CI: 1.86-2.50), medulla (adjusted PR=2.14, 95% CI: 1.86-2.45), and multiple infarct locations in the posterior circulation territory (adjusted PR=1.89, 95% CI: 1.65-2.16). In contrast, the MCA territory had a lower frequency of onset headache (adjusted PR=0.78, 95% CI: 0.72-0.85). The pons, midbrain, thalamus and ACA territory were not associated with onset headache.

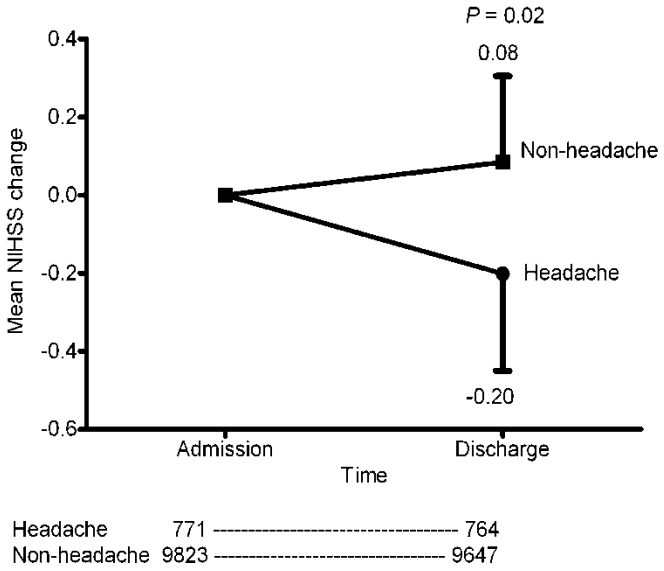
Outcome analysis

Patients with onset headache had lower frequencies of stroke deterioration during hospitalization compared to those without onset headache (5.5% vs. 8.4%, crude relative risk [RR]=0.66, 95% CI: 0.49-0.88; adjusted RR=0.62, 95% CI: 0.52-0.78) with stroke-in-evolution (4.5% vs. 6.7%,crude RR= 0.68, 95% CI:0.57-0.83; adjusted RR=0.64, 95% CI: 0.52-0.79) and medical complications (0.4% vs. 0.9%, crude RR=0.38, 95% CI:0.27-0.53; adjusted RR:0.13, 95% CI:0.08-0.21) accounting for the difference. The frequencies of herniation, hemorrhagic infarction, and in-hospital mortality did not differ between the two groups (Table 4).

Of the study population, 85.9% (9896/11,523) completed the six-month follow-up after stroke onset. After controlling for baseline scores and potential confounding factors for stroke prognosis, including age, sex, infarct location, stroke subtype, length of hospitalization and rt-PA treatment, the improvement in NIHSS scores on discharge

(mean duration 11.3 days of stay) was greater in patients with onset headache than those without (mean NIHSS score change 0.08 vs. -0.2, p=0.02) (Fig.6). Among the groups of different lengths of hospitalization, patients with onset headache had significantly greater NIHSS improvement only in the group of >10 days hospitalization. After controlling potential confounding factors, the difference remained. (Table 4).

Figure 6. Least squares means and standard errors of NIHSS scores after adjusting for age, sex, infarct location, length of hospitalization and rt-PA treatment in all first-ever ischemic stroke patients



The scores of Barthel index were significantly higher in the headache group at one-, three-, and six-month follow-ups. However, after adjusting for potential confounding factors and stroke subtypes, the difference was significant only at one-month follow-up (Table 4). The proportion of patients with mRS ≤2 in the onset headache group was higher than those in the non-onset headache group at one, three, and six months but the difference was significant only at one month follow-up. The difference was still significant after adjusting for potential confounding factors and stroke subtypes (Table 4). The four major sub-groups of ischemic stroke (e.g. large artery, small artery, cardio-embolism, and specific aetiology) showed similar trends in outcome analyses (Supplement).

3.4 Discussion

The present study shows that the frequency of onset headache in patients with first-ever stroke is 7.4%, which is lower than those previously reported (8-18%).(103-106) The cause of this discrepancy may be due to the strict definition used in the present study, i.e. only headache at the “onset” of stroke. In addition, this

study adopts the ICHD-2 criteria and stresses “new” headache but not the “usual” headache. Similar to previous reports, this study suggests that patients with younger age and female sex are more likely to develop onset headache.(99,104-109) Infarctions in the posterior circulation territory are also more likely to be associated with onset headache than infarctions in other territories. Infarctions in the cerebellum, medulla, or PCA cortex are more likely to be associated with onset headache compared to other regions. The cerebellum and PCA cortex have been implicated in prior studies,(110,111) but the medulla is being reported for the first time in the present study. Although the cerebellum is insensitive to pain, the vertebral artery and posterior inferior cerebellar arteries that supply both the medulla and cerebellum are pain-sensitive.(116) Furthermore, the occipital cortex and trigeminal nucleus in the medulla are related to the migraine pain pathophysiology.(117,118) Consistent with prior reports, the present study shows that the midbrain and pons are not associated with onset headache even though these two regions are also important for pain modulation.(117)

Whether or not embolic stroke patients have a higher frequency of onset headache remains to be determined.(103,104,107,110) The data here shows that cardio-embolism and large artery arthrosclerosis have comparable frequencies of onset headache. Since small vessel disease is associated with the lowest probability, the involvement of large vessels may be more important than the underlying causes (i.e., thrombosis vs. embolism).

The clinical impact of onset headache in patients with ischemic stroke is controversial. The results here show that ischemic stroke patients with onset headache have a slightly but significantly lower frequency of stroke-in-evolution during hospitalization (4.5% vs. 6.7%, adjusted RR=0.64, 95% CI: 0.52-0.79). Moreover, ischemic stroke presenting with onset headache has a better outcome based on improvements in NIHSS scores on discharge after an average of 11.3 days of hospitalization, higher Barthel index at one-, three-, and six-month follow-up, and higher proportion of patients with mRS $\leq$2 at one-month follow-up. The finding that onset headache is accompanied by better outlook is consistent across three different outcome measures. Since previous stroke history and baseline NIHSS score at stroke onset are predictors of hospital disposition and long-term outcomes,(115,119-121) the present study has only included first-ever stroke patients and has controlled baseline severity when compared to outcomes.

Although onset headache is suspected to be a dangerous symptom in stroke patients, very few studies, mostly with small sample sizes, have reported outcome evaluations and report either no difference or poorer outcomes in patients with stroke-related headache. Salgado and Ferro report no difference in the functional outcome between

lacunar stroke patients with and those without headache in a six-month follow-up period.4 Similar results have been reported by Jørgensen et al.(99)

In contrast, Arboix et al. have shown that lacunar stroke patients with headache have lower frequencies of symptom-free rate upon discharge compared to those without headache.(98) Leira et al. also note that 83.6% of ischemic stroke patients with headache suffer from stroke progression during hospitalization, much higher than the 19.6% of patients without headache.(97) The study by also noted that patients with headache have higher mean nitric oxide (NO) metabolites in the cerebrospinal fluid (CSF). The apparent discrepancy between this and other studies must be resolved. Nonetheless, the current study has recruited stroke patients from multiple centres using a well-characterized definition for onset headache.

Different stroke patho-physiologies between patients with and those without onset headache may account for the discrepancy in outcomes. The mechanism underlying onset headache must be explored. The disturbance in blood flow or dilation of pain-sensitive collateral vasculature have long been suspected as a cause of onset headache.(102) It is also known that leptomeningeal arteries innervated by the trigeminal nerve are crucial for headache disorders.(118) The presence of leptomeningeal collaterals predicts improvement in clinical outcomes in patients treated with and without thrombolysis.(122,123) The hypothesis of the present study is that the onset headache may be a clinical manifestation of leptomeningeal collaterals and can therefore predict good outcome in patients with ischemic stroke. However, more studies are warranted to confirm this.

The strengths of this study include (1) a very large sample that provides enough power to delineate the clinical correlates and impact of onset headache; (2) a standard and well-recognized stroke classification; and (3) high response rates of follow-up. However, some limitations should also be addressed. First, a history of prior headache, such as migraine or tension-type headache was not routinely queried in the TSR study and whether the headache at stroke onset was “new” was determined by the patients themselves. Coincident headaches or exacerbated primary headache disorders at stroke onset could not be completely excluded. Second, the profiles of onset headache were not recorded in this study so it is not known whether certain headache profiles, such as headache pattern, severity, or locations, are related to stroke or its outcome. Third, late-onset headache was likewise not recorded. Thus, the possibility of differential impacts of headache on outcomes at different time points after stroke cannot be determined. Fourth, since participants had to report whether or not they had onset headache, their stroke severity tended to be mild (mean NIHSS 4.1). As such, even though the stroke patients included in this study accounted for 70.6% of the first-ever ischemic stroke of the total TSR samples, caution must be exercised in

extrapolating the results to the entire stroke population. Lastly, multiple comparisons were used to examine the study outcomes. Although most of the measures showed similar trends, it should be noted that these measurements correlated with each other.

3.5 Conclusion

The present study demonstrates that patients with large artery atherosclerosis and cardio-embolism, especially in the posterior circulation territory, are more likely to have onset headache. Unlike in previous reports, the findings here indicate that in first-ever ischemic stroke patients, onset headache is associated with modest but significantly better outcomes up to six months post-stroke, rather than being a dangerous symptom. It is postulated that the onset headache at stroke may be a “phenotype” of the presence of leptomeningeal collaterals in patients with ischemic stroke and should therefore be documented and assessed when treating stroke patients.

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