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Clinical commentary

Significance of fatigue in patients with migraine

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ABSTRACT

Fatigue is often stated as a headache trigger or migraine-specific symptom. We investigated predictors of fatigue and its impact on quality of life (QOL) in patients with migraine. Patients with migraine were recruited from a headache clinic and completed psychosomatic instruments, including the 12-item Allodynia Symptom Checklist (ASC-12), the Migraine Disability Assessment Scale (MIDAS), the Patients Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder-7 (GAD-7), the Epworth Sleepiness Scale (ESS), the Insomnia Severity Index (ISI), the Fatigue Severity Scale (FSS), and Migraine-Specific Quality of Life Questionnaire (MSQ). Two hundreds twenty-six patients with migraine were eligible for the study. Pathologic fatigue was manifested in 133 patients (58.8%). The FSS score was significantly associated with age, age of onset, the Visual Analog Scale (VAS) depicting headache intensity, photophobia, phonophobia, and the scores of the ASC-12, the MIDAS, the ESS, the ISI, the PHQ-9 and the GAD-7. The strongest predictor for the FSS was the PHQ-9 ($\beta = 0.432$, $p < .001$), followed by age ($\beta = -0.169$, $p = .002$), the ISI ($\beta = 0.151$, $p = .016$), and the VAS ($\beta = 0.139$, $p = .018$). There was an inverse correlation between the FSS score and three dimensional scores of the MSQ ($p < .001$). Appropriate interventions for depression, insomnia, and headache intensity are likely to lessen fatigue and improve QOL.

1. Introduction

Fatigue has been defined as a difficulty initiating or sustaining voluntary activities [1]. It is one of the commonest presenting symptoms in clinical practice that can severely interfere with daily activities impairing the quality of life (QOL) of affected people [2]. Fatigue can be produced by several factors. In a review of the literatures, various medical, neurological, and psychiatric diseases were included as primary causes of pathologic fatigue, and drugs, irradiation, chronic pain, depression, and sleep disorder were indicated as secondary causes of pathologic fatigue [3]. Multiple sclerosis and Parkinson's disease were well known neurological disorders having fatigue. In a review of the literatures, estimated prevalence of fatigue was 38–83% for multiple sclerosis, and 28–58% for Parkinson's disease [4].

Migraine represents a primary headache disorder characterized by recurrent attacks lasting 4–72 h of pain typically described as unilateral, pulsating, moderate, or severe, aggravated by routine physical activity [5]. It is a highly disabling condition and associated with impaired QOL [6]. Data focusing the prevalence of fatigue in patients with migraine are few and reveal conflicting results due to heterogeneous samples of headache patients. In a hospital-based study in Austria, authors investigated fatigue severity between migraine patients and migraine-free controls, and found fatigue was more prominent in migraine patients than controls, but the difference did not reach the level of statistical significance [7]. On the other hand, the frequency of fatigue was significantly higher in episodic migraine (EM) without aura patients (62%) than healthy controls (5%) in an Italian, hospital-based study [8]. Because the study excluded patients who had high frequency of attacks, chronic medication, and comorbid medical or psychiatric disorders, authors concluded fatigue is likely to be a migraine-specific symptom.

Fatigue has several clinical implications in patients with migraine. Fatigue is one of commonly reported headache triggers. In a Korean, hospital based study, fatigue was the third most common trigger for EM following stress and sleep deprivation, and 48.5% of patients indicated fatigue as a headache trigger [9]. Fatigue was higher in women, and comorbid depression or anxiety in a hospital-based study for chronic migraine (CM) [10]. Fatigue was associated with CM and higher attack frequency in a comparative study between EM and CM [11].

Although some factors were associated with fatigue in patients with migraine, their differential effects on fatigue have not been reported yet. If we identify a high priority factors for fatigue in

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migraine, we can suggest a guideline for clinicians to manage fatigue adequately. So the first purpose of our study is to identify predictors for fatigue in patients with migraine. In addition, although harmful effects of migraine have been known to affect on QOL, the role of fatigue on QOL was not emphasized. So the second purpose of our study is to delineate the impact of fatigue on QOL and give information about its significance for clinicians.

2. Methods

2.1. Subjects

We invited new patients with migraine who had consecutively visited an outpatient clinic in the Department of Neurology at Kyungpook National University Hospital between September 2015 to August 2016. Patients aged between 18 and 70 years were included. A diagnosis of migraine was based on the International Classification of Headache Disorders, 3rd edition, beta version.[6] Patients were excluded if they refused to participate or could not cooperate the study because of illiteracy, mental retardation, serious medical, neurological, or psychiatric disorders, and alcohol or drug abuse. Patients with probable migraine were also excluded.

2.2. Study design

This study was conducted as part of a hospital-based study that examined the impact of psychiatric and psychosocial problems on migraine. The Institutional Review Board of Kyungpook National University Hospital approved the study. All participants obtained written informed consent. We collected demographic, socioeconomic, and clinical information of the participants at initial visit. Demographic data included age, gender, and education. Socioeconomic data included employment and household income (earning at least three million KRW per month, equivalent to 2800 USD per month or not). Clinical data included body mass index, concurrent medical disease, fatigue inducing drug, type of migraine, migraine chronicity, family history of migraine, medication overuse headache, age of onset, duration of migraine, headache intensity, accompanying symptoms including nausea and/or vomiting, photophobia, phonophobia, osmophobia, and allodynia). Fatigue inducing drug included psychotropics, antispastics, antiepileptic drugs, antihistamines, and narcotics [3] which were taken in the preceding month. Headache intensity was measured by the Visual Analog Scale (VAS). We applied the VAS when patients were conducting psychosomatic tools. Photophobia, phonophobia, and osmophobia were defined as hypersensitivity to light, sound, and certain odors during migraine attacks, which could cause avoidance of those stimuli or aggravation of migraine symptoms. Allodynia was measured using the 12-item Allodynia Symptom Checklist (ASC-12) with a cut-off score of >2 defining allodynic patients [12].

Eligible subjects conducted several self-reported questionnaires, including the Migraine Disability Assessment Scale (MIDAS) [13], the Patient Health Questionnaire-9 (PHQ-9) [14], and the Generalized Anxiety Disorder-7 (GAD-7) [15], the Epworth Sleepiness Scale (ESS) [16], the Insomnia Severity Index (ISI) [17], the Fatigue Severity Scale (FSS) [18], and the Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ) [19].

2.3. Questionnaires

2.3.1. Migraine Disability Assessment Scale (MIDAS)

The Korean version of the MIDAS, a five-item questionnaire designed to evaluate disability during the previous three months, was used in this study [13]. Patients were asked to report the number of days with decreased performance in the domains of work/school, household work, and family/social activities. Scores measure the overall level of disability: Grade I (0–5), Grade II (6–10), Grade III (11–20), and Grade IV (above 21). Its Cronbach's α coefficient was 0.75.

2.3.2. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 was designed for detecting depression in primary care patients [20]. The PHQ-9 includes nine items pertaining to the DSM-IV criteria for major depressive disorder (MDD) [21]. Each item asking depressive symptom is rated on a 4-point scale from 0 to 3 in the preceding two weeks. The overall score can range from 0 to 27 and the higher score means higher degree of depressive symptoms. The Korean version of the PHQ-9 has been validated in patients with migraine, and a cutoff score of 7 was suggested as a score differentiating MDD. Its Cronbach's α coefficient was 0.894 [14].

2.3.3. Generalized anxiety disorder-7 (GAD-7)

The GAD-7 was designed for detecting anxiety in primary care patients [22]. The GAD-7 consists of seven items pertaining to the DSM-IV criteria for GAD [21]. Each item asking anxiety symptom is rated on a 4-point scale from 0 to 3 in the preceding two weeks. The overall score can range from 0 to 21 and the higher score means higher degree of anxiety symptoms. The Korean version of the GAD-7 has been validated in patients with migraine, and a cutoff score of 5 was suggested as a score differentiating GAD. Its Cronbach's α coefficient was 0.915 [15].

2.3.4. Epworth Sleepiness Scale (ESS)

The ESS is comprised of eight questions, each asking about the subject's likelihood of dozing off or falling asleep in a particular situation that is commonly met in daily life. Thus, each ESS item score measures a particular "situational sleep propensity", and the sum of those item scores, i.e., the total ESS score, measures the subject's average sleep propensity across those different situations in daily life. Respondents use a four-point scale for each of the eight questions [23]. Higher scores indicate higher subjective sleepiness. The Korean version of the ESS has been validated in patients with obstructive sleep apnea. Its Cronbach's α coefficient was 0.9 [16].

2.3.5. Insomnia Severity Index (ISI)

The Insomnia Severity Index (ISI) is a seven-item questionnaire that measures the patient's perception of insomnia severity [24]. Each of the ISI items is rated on a scale of 0–4; the total score ranges from 0 to 28, with a higher score indicating greater insomnia severity. The Korean version of the ISI has been validated in patients with sleep disorders and a cutoff score of 15.5 was suggested for discriminating patients with insomnia. Its Cronbach's α coefficient was 0.92 [17].

2.3.6. Fatigue Severity Scale (FSS)

The FSS consists of nine items that assess fatigue on a scale from 0 to 7 [25]. After summing the scores of the nine items, the total score is divided by 9, yielding values from 0 to 7. The FSS is useful in clinical practice because it has fewer items than other questionnaires that evaluate fatigue and it is easy to score. The Cronbach's α coefficient of the Korean version of the FSS is 0.935, and a total score of 3.22 or more is suggestive of pathologic fatigue [18].

2.3.7. Migraine-Specific Quality of life Questionnaire version 2.1 (MSQ)

The MSQ measures the impact of migraine on QOL over the previous four weeks across three dimensions; Role Function-Restrictive (RR), Role Function-Preventive (RP), and Emotional Function (EF) [26]. The MSQ Version 2.1 consists of 14 questions, seven questions in the RR dimension, three questions in the PR dimension and four questions in the EF dimension. Analysis of

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