# Preferential occurrence of attacks during night sleep and/or upon awakening negatively affects migraine clinical presentation

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**Summary**

**It is well known that migraine attacks can preferentially occur during night sleep and/or upon awakening, however the possible implications of this timing on migraine clinical presentation remain unclear. The aim of this study was to assess the possible consequences of sleep-related migraine (defined as ≥75% of migraine attacks occurring during night sleep and/or upon awakening) on the migraine clinical picture (i.e. migraine-related disability, attack severity, use of symptomatic drugs), subjective sleep quality, excessive daytime sleepiness and fatigue.**
**Two hundred consecutive migraine without aura patients were enrolled; patients with comorbid disorders or chronic medication use were excluded. 39% of the migraineurs included in the study received a diagnosis of sleep-related migraine. The mean frequency of migraine attacks (days per month) did not significantly differ between the patients with and those without sleep-related migraine, whereas migraine-related disability ($p<0.0001$), mean attack severity ($p<0.0001$), and monthly intake of symptomatic drugs ($p<0.0001$) were significantly higher in patients with migraine preferentially occurring at night-time and/or upon awakening. Subjective sleep quality and excessive daytime sleepiness did not differ significantly between the two groups, whereas fatigue was significantly more present in the patients with sleep-related migraine ($p=0.0001$).**
**These data seem to support the hypothesis that patients with sleep-related migraine represent a subset of individuals with a more severe and disabling clinical presentation of migraine and greater impairment of daily functioning, as suggested by the higher degree of fatigue. Migraineurs with night-time attacks also showed a greater use of symptomatic drugs, possibly related to delayed use of symptomatic treatment. The identification of subtypes of patients with a higher disability risk profile could have crucial implications for individually tailored management of migraine patients.**

*KEY WORDS: daytime sleepiness, fatigue, migraine-related disability, sleep-related migraine, subjective sleep quality.*

## Introduction

Migraine is a primary headache disorder, characterized by recurrent attacks, lasting 4-72 hours, of pain, typically described as unilateral, pulsating, moderate or severe, aggravated by routine physical activity, and associated with nausea and/or photophobia and phonophobia (Headache Classification Subcommittee of the International Headache Society, 2004; Headache Classification Committee of the International Headache Society (IHS), 2013). Migraine is a highly disabling condition, ranked by the World Health Organization as the seventh highest cause of disability globally; it has a significant impact on the quality of life of affected subjects and is associated with a high socio-economic burden (Vos et al., 2012; Steiner et al., 2013). Migraine attacks can affect several aspects of a patient's life, including work and social/leisure activities, therefore the identification of subtypes of patients at a higher risk of disability could have crucial implications for the management of migraine patients.
A preferential occurrence of attacks at night-time or in the early morning has been widely ascertained in migraine without aura patients. In particular, Galego et al. (2002) documented that both episodic (55%) and chronic (62.5%) migraineurs reported waking up in the morning or being woken up during the night by headache, and subsequently Kelman and Rains (2005), in a study carried out in a larger sample of migraineurs (n=1283), found that 71% of patients exhibited morning headache on awakening (in 35% of the whole sample this was a very frequent or frequent occurrence, whereas in 36% it was occasional). Furthermore, a chronobiological study by Solomon (1992) found the occurrence of migraine attacks to be greatest between 6 a.m. and 10 a.m. and subsequent research by Fox and Davis (1998), looking for a circa-

dian periodicity in the time of onset of 3,582 migraine headache attacks experienced by 1,698 patients, documented that onset of migraine without aura was most likely to occur between 4 a.m. and 9 a.m., the likelihood of its occurrence during this interval of time being far greater than at any other time of the day. Similar results were subsequently obtained in a selected sample of migraineurs with a low monthly frequency of attacks; in particular, according to clinical diaries referring to the previous three months, 42% of migraineurs presented more than 75% of their attacks at night and in the early morning, especially between 3 a.m. and 7 a.m. (Gori et al., 2005); in addition, a more recent study, carried out in a population of 734 patients affected by migraine without aura, documented that nocturnal and/or upon-awakening migraine progressively increases with aging (Gori et al., 2012a).

Morning headache is a frequent complaint in the general population and it requires an extensive and complex differential diagnosis. Ohayon (2004), in a study carried out in a sample of 18,980 subjects, documented a 7.6% prevalence of morning headache in the general population and found that rates were higher in women and in subjects aged between 45 and 64 years. Various conditions and disorders were found to be positively associated with morning headaches, the most significant associated factors being: anxiety and depressive disorders, major depressive disorder alone, dyssomnias not otherwise specified, insomnia disorder, circadian rhythm disorder, sleep-related breathing disorder, hypertension, musculoskeletal diseases, use of anxiolytic medications, and heavy alcohol consumption.

Therefore, it is well known that nocturnal migraine attacks need a complex diagnostic approach in order to achieve an adequate differential diagnosis; conversely, it still remains to be established whether the preferential emergence of migraine at night-time and/or in the early morning might significantly affect its clinical presentation and subsequently its management and outcome.

This study was carried out in order to evaluate the possible implications of night-time and/or early morning migraine occurrence, formally defined as sleep-related migraine (i.e. ≥75% of migraine attacks occurring during night sleep and/or upon awakening), on both migraine clinical presentation (i.e. migraine-related disability, severity of migraine attacks and use of symptomatic drugs) and subjective sleep quality and parameters of daily living, such as excessive daytime sleepiness and fatigue.

## Materials and methods

Two hundred consecutive migraine patients (178 females, 22 males) were enrolled at the Headache Center of the Institute of Neurology, University of Pisa, between July 2012 and June 2013; all the patients fulfilled the International Headache Society (IHS) diagnostic criteria for migraine without aura (Headache Classification Subcommittee of the International Headache Society, 2004; Headache Classification Committee of the International Headache Society (IHS), 2013). The patients had a mean age of 40.1±11.2 years (range 19-65) and a mean migraine duration of 8.5 years (range 2-30).

The inclusion criteria were: i) four or fewer migraine attacks per month, as ascertained from headache diaries referring to the previous three months; ii) a migraine duration of more than 12 months; iii) no prophylactic migraine treatment in the previous three months; iv) no comorbid/coexisting medical conditions, in particular, no fulfilment of clinical criteria for a diagnosis of hypertension or pre-hypertension, absence of comorbid sleep disorders (an aspect clinically evaluated by means of condition-specific diagnostic questionnaires), no present or past history of psychiatric disorders; v) no chronic use of any medication; and vi) normal neurological examination and neuroimaging (cranial CT with contrast and/or brain MRI). With regard to psychiatric comorbidity, patients with a current or past history of psychiatric disorders were excluded. Indeed, in order to evaluate subclinical mood or anxiety disorders, the Beck Depression Inventory (Beck et al., 1996) and the State-Trait Anxiety Inventory (Spielberg, 1983) were administered and patients with pathological scores were excluded.

The International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2005) defines sleep-related migraine as migraine attacks occurring during sleep and/or upon awakening; in order to have a more clearly defined and unequivocal criterion, sleep-related migraine was arbitrarily defined as migraine in which at least 75% of attacks occur during nocturnal sleep and/or upon awakening.

Migraine-associated disability was assessed using the Migraine Disability Assessment (MIDAS), a five-item questionnaire measuring headache-related disability over a three-month period (Stewart et al., 1999).

The mean frequency of attacks per month (i.e. migraine days per month), the mean severity of attacks (based on a ten-point verbal numerical scale or VNS), and the mean use of symptomatic drugs per month were ascertained from the headache diaries referring to the previous three months.

Subjective sleep quality was assessed by means of the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire which determines sleep quality and disturbances over a period of one month; the score range is 0-21 (a score greater than 5 is indicative of poor sleep quality) (Buysse et al., 1989).

The Epworth Sleepiness Scale (ESS) provided a measurement of each patient's subjective habitual level of daytime sleepiness, and excessive daytime sleepiness was defined as an ESS score of more than 10 (Johns, 1991). Finally, the degree of fatigue was evaluated using the validated Fatigue Severity Scale (FSS) questionnaire (cut-off >27) (Krupp et al., 1989).

Written informed consent was obtained from each patient before his/her inclusion in the study.

Data are presented as percentages or as arithmetic means with standard deviations. The statistical analysis was performed using the unpaired Student's t test with Bonferroni correction for multiple comparisons, and the chi-square test with Yates' correction or Fisher's exact test when appropriate. The level of significance for all the tests was $p<0.01$. All tests were two tailed.

## Results

Sleep-related migraine was diagnosed in 78 migraine patients (39% of the whole sample of migraineurs), without gender predilection (sleep-related migraine was diagnosed in 39.9% of the 70 females and 36.3% of the eight males, p=0.9704, ns).

The patients with and those without sleep-related migraine did not significantly differ in mean migraine frequency (2.7±1.5 vs 2.5±0.5 days per month, ns), whereas the mean MIDAS score, assessing migraine-related disability, was significantly higher in the patients with sleep-related migraine compared to those not showing preferential occurrence of migraine attacks during night sleep and/or upon awakening (13.0±2.0 vs 10.5±2.0, respectively, p<0.0001).

Furthermore, the patients with sleep-related migraine showed a significantly higher use of symptomatic drugs (intakes per month: 9.0±3.5 vs 6.0±2.0, p<0.0001), as well as a greater mean severity of migraine attacks (VNS score: 9.0±1.0 vs 7.0±0.5, p<0.0001).

As regards subjective sleep quality, the mean PSQI score was 7.9±4.1 in the patients with sleep-related migraine and 6.9±3.9 in the migraineurs without a preferential occurrence of attacks during night sleep and/or upon awakening (ns); in addition, the mean ESS score did not significantly differ between the patients with and those without sleep-related migraine (5.0±3.8 vs 4.8±2.9, ns).

On the contrary, fatigue was significantly more severe in the patients with sleep-related migraine (mean FSS score in patients with vs those without sleep-related migraine: 33.1±11.4 vs 27.5±8.5, p=0.0001). The data are summarized in table I.

## Discussion

These data showed a high occurrence of sleep-related migraine in a selected sample of migraineurs with low attack frequency (39% of the total sample of migraineurs), supporting previous literature data documenting that migraine attacks can preferentially occur during night sleep and/or upon awakening (Fox and Davis, 1998; Galego et al., 2002; Gori et al., 2012a; Kelman and Rains, 2005; Solomon, 1992).

The relationship between migraine and sleep is complex and pluridirectional (i.e. excessive sleep causes headache, sleep deprivation causes headache, sleeping relieves headache, and so on), however the main reason for the link between migraine and sleep might be that the two phenomena are intrinsically related, anatomically and physiologically (Evers, 1989). Different hypotheses have been advanced to explain the occurrence of migraine attacks during night sleep and/or upon awakening, one suggesting a role for REM sleep mechanisms and another the existence of a chronobiological disorder. These hypotheses are not mutually exclusive. The two explanations might simply coexist or they could even be linked, as suggested by the role of the hypothalamus in controlling not only circadian rhythms but also sleep (Mistlberger, 2005), especially the REM phase (Suntsova et al., 2000). The limited number of polysomnographic studies to date performed in patients with migraine without aura suggested a relationship between the REM sleep phase, and to a lesser extent the NREM 3 and 4 stages, and nocturnal migraine without aura attacks (Dexter and Weitzman, 1970; Dexter, 1979; Sahota and Dexter, 1990). The anatomical structures involved both in the regulation of sleep – especially REM sleep – and in migraine generation seem to be located mainly in the brainstem, specifically in the locus coeruleus and the dorsal raphe nucleus; since these aminergic nuclei represent an important part of the antinociceptive pain processing network, it can be speculated that their strongly reduced firing rates during the REM sleep phase may help to trigger migraine attacks. Moreover, the onset of migraine without aura attacks at a consistent time each night seems to sug-

Table I - Comparison of clinical parameters, subjective sleep quality, excessive daytime sleepiness and fatigue in migraine patients with and without sleep-related attacks.

| | Sleep-related migraine (n=78) | Not sleep-related migraine (n=122) | Significance (p value) |
|---|---|---|---|
| Mean MIDAS score | 13.0±2.0 | 10.5±2.0 | <0.0001 |
| Mean n. attacks/month | 2.7±1.5 | 2.5±0.5 | 0.1751 (ns) |
| Mean severity of attacks (VNS score) | 9.0±1.0 | 7.0±0.5 | <0.0001 |
| Mean symptomatic drug use (intakes per month) | 9.0±3.5 | 6.0±2.0 | <0.0001 |
| Mean PSQI score | 7.9±4.1 | 6.9±3.9 | 0.0846 (ns) |
| Mean ESS score | 5.0±3.8 | 4.8±2.9 | 0.6745 (ns) |
| Mean FSS score | 33.1±11.4 | 27.5±8.5 | 0.0001 |

Abbreviations: MIDAS=Migraine Disability Assessment; VNS=verbal numerical scale; PSQI=Pittsburgh Sleep Quality Index; ESS=Epworth Sleepiness Scale; FSS=Fatigue Severity Scale.

gest that pain onset may be further controlled by a timing mechanism, possibly located in the suprachiasmatic nucleus of the hypothalamus, the area considered to be the human biological clock (Mistlberger, 2005; Ralph et al., 1990). Involvement of the hypothalamus in the pathogenesis of migraine without aura has been suggested by analysis of prodromal symptoms: indeed, almost 60% of a series of patients questioned by Blau (1980) reported elation, irritability, depression, hunger, thirst or drowsiness during the 24 hours preceding migraine headache, which may indicate a hypothalamic site of origin; moreover, a positron emission tomography study in patients with spontaneous migraine without aura attacks confirmed the previously reported activation of midbrain and pontine nuclei and also provided the first demonstration of hypothalamic activation during migraine attacks (Denuelle et al., 2007). It is still not clear whether this hypothalamic activation simply reflects the general processing of painful stimuli, or instead, whether its involvement in the pathogenesis of migraine is more specific, since hypothalamic orexigenic mechanisms could play a key role in the initiation of migraine attacks (Bartsh et al., 2004).

As regards the migraine clinical parameters, the monthly frequency of migraine, expressed as days/month with migraine headache, did not significantly differ between the patients with and those without sleep-related migraine, whereas migraine-related disability, mean attack severity, and mean monthly use of symptomatic drugs were significantly higher in the patients with sleep-related migraine. These data suggest that the temporal distribution of migraine attacks might significantly affect the clinical disease presentation, which seems to be more severe and more disabling in patients with preferential occurrence of attacks during night sleep and/or upon awakening.

The present data suggest that subjective sleep quality was affected in both groups of migraineurs, without significant differences emerging between the patients with and those without sleep-related migraine (mean PSQI score 7.9±4.1 vs 6.9±3.9); our findings support previous data reporting that sleep quality is impaired in migraine patients as a consequence of migraine itself, independently of comorbidities such as depression, anxiety or sleep disorders (Seidel et al., 2009; Gori et al., 2012b).

Literature data on indicators of daily functioning (e.g. excessive daytime sleepiness and fatigue) in migraineurs, and on their possible relationship with the preferential occurrence of migraine attacks during night sleep and/or upon awakening, are limited and conflicting. As regards the level of daytime drowsiness, Barbanti et al. (2007), in a case-control study on 100 episodic migraine patients compared to 100 healthy controls, found that excessive daytime sleepiness was more frequent in migraineurs than in controls (14% vs 5%) and correlated with migraine disability, sleep problems and anxiety, whereas Seidel et al. (2009), comparing 489 migraine patients with 119 migraine-free controls, found that daytime sleepiness was not increased in migraineurs; furthermore, a more recent study (Gori et al., 2012b) suggested that habitual excessive daytime sleepiness, evaluated by means of the ESS, was not significantly more frequent in patients with episodic migraine than in controls (12% migraineurs versus 8% controls). As regards fatigue in migraine patients, Peres et al. (2002) initially reported an 84.1% prevalence of fatigue (defined as an FSS score greater than 27), in chronic migraine patients; in addition, a more recent study (Lucchesi et al., 2013) found that the level of fatigue was significantly higher in episodic migraine without aura patients compared to a control group of healthy, headache-free subjects. Furthermore, in a study by Stronks et al. (2004) analyzing interictal daily activities and heart rate in migraine patients compared with healthy subjects, the migraine patients reported significantly lower levels of daily functioning (during the morning and the afternoon) and of vigor (throughout the day); during much of the interictal day, the migraineurs were significantly less physically active than the controls, with lower realizable levels of activity and vigor. In the present study, the patients with and those without sleep-related migraine recorded ESS mean scores of 5.0±3.8 vs 4.8±2.9 respectively, a finding which suggests that migraineurs, irrespective of whether or not they have a diagnosis of sleep-related migraine, do not present a condition of habitual excessive daytime sleepiness; the lack of daytime vigilance level impairment in migraineurs with poor sleep quality could be related to a condition of psycho-physiological hyperarousal similar to that found in chronic insomnia. Moreover, these data showed that fatigue, at least as evaluated using the FSS, is significantly more severe in patients with sleep-related migraine than in those not showing preferential occurrence of attacks at night-time and/or upon awakening (mean FSS score 33.1±11.4 vs 27.5±8.5, respectively, p=0.0001); therefore patients with sleep-related migraine seem to represent a subgroup of migraineurs with greater impairment of daily functioning, as shown by their higher level of fatigue.

The present data, showing a 39% prevalence of sleep-related migraine in a selected sample of migraineurs with low monthly attack frequency, document, for the first time, a higher level of disability, higher consumption of symptomatic drugs, greater severity of attacks, and a higher degree of fatigue in patients with sleep-related migraine compared with patients whose migraine is not sleep related. A possible factor that should certainly be considered when analyzing the results of the present study is treatment response; it is well known that early treatment significantly affects clinical outcome in migraine symptomatic therapy (Dodick et al., 2008; Rapoport 2012; Viana et al., 2013), and treatment is almost invariably delayed in migraine attacks arising during nocturnal sleep. Delayed symptomatic treatment in sleep-related attacks might account for a greater use of symptomatic drugs and also play a role in determining higher disability and severity of migraine attacks that occur during sleep, and may also impact on daily functioning parameters, like daytime fatigue.

In conclusion, these data seem to support the hypothesis that patients with sleep-related migraine represent a subset of individuals with a more disabling and more severe migraine clinical presentation, with greater impairment of daily functioning, and a higher degree of fatigue. The identification of subtypes of patients with a higher disability risk profile might have crucial implications for individually tailored management of migraine patients.

## References


American Academy of Sleep Medicine (2005). International Classification of Sleep Disorders. Diagnostic and Coding Manual (2nd ed.). Westchester, American Academy of Sleep Medicine.

Barbanti P, Fabbrini G, Aurilia C, et al (2007). A case-control study on excessive daytime sleepiness in episodic migraine. Cephalalgia 27:1115-1119.

Bartsch T, Levy MJ, Knight YE, et al (2004). Differential modulation of nociceptive dural input to [hypocretin] orexin A and B receptor activation in the posterior hypothalamic area. Pain 109:367-378.

Beck AT, Steer RA, Brown GK (1996). Manual for the Beck Depression Inventory-II. San Antonio TX, Psychological Corporation.

Blau JN (1980). Migraine prodromes separated from the aura: complete migraine. Br Med J 281: 658-660.

Buysse DJ, Reynolds CF 3rd, Monk TH, et al (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193-213.

Denuelle M, Fabre N, Payoux P, et al (2007). Hypothalamic activation in spontaneous migraine attacks. Headache 47:1418-1426.

Dexter JD, Weitzman ED (1970). The relationship of nocturnal headaches to sleep stage patterns. Neurology 20:513-518.

Dexter JD (1979). Relationship between stage III + IV + REM sleep and arousals with migraine. Headache 19:364-369.

Dodick DW (2008). Applying the benefits of the AwM study in the clinic. Cephalalgia 28 (Suppl 2):42-49.

Evers S (2010). Sleep and headache: the biological basis. Headache 50:1246-1251.

Fox AW, Davis RL (1998). Migraine chronobiology. Headache 38:436-441.

Galego JC, Cipullo JP, Cordeiro JA, et al (2002). Clinical features of episodic migraine and transformed migraine: a comparative study. Arch Neuropsiquiatr 60:912-916.

Gori S, Lucchesi C, Morelli N, et al (2012a). Sleep-related migraine occurrence increases with aging. Acta Neurol Belg 112: 183-187.

Gori S, Lucchesi C, Maluccio MR, et al (2012b). Inter-critical and critical excessive daily sleepiness in episodic migraine patients. Neurol Sci 33: 1133-1136.

Gori S, Morelli N, Maestri M, et al (2005). Sleep quality, chronotypes and preferential timing of attacks in migraine without aura. J Headache Pain 6:258-260.

Headache Classification Committee of the International Headache Society (IHS) (2013). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 33:629-808.

Headache Classification Subcommittee of the International Headache Society (2004). The International Classification of Headache Disorders: 2nd edition. Cephalalgia 24 (Suppl 1):9-160.

Johns MW (1991). A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14:540-545.

Kelman L, Rains JC (2005). Headache and sleep: examination of sleep pattern and complaints in a large clinical sample of migraineurs. Headache 45:904-910.

Krupp LB, LaRocca NG, Muir-Nash J, et al (1989). The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 46:1121-1123.

Lucchesi C, Sassi AN, Siciliano G, et al (2013). Fatigue is increased in episodic migraine without aura patients. Headache 53:1163-1165.

Mistlberger RE (2005). Circadian regulation of sleep in mammals: role of the suprachiasmatic nucleus. Brain Res Brain Res Rev 49:429-454.

Ohayon MM (2004). Prevalence and risk factors of morning headaches in the general population. Arch Intern Med 164:97-102.

Peres MF, Zukerman E, Young WB, et al (2002). Fatigue in chronic migraine patients. Cephalalgia 22:720-724.

Ralph MR, Foster RG, Davis FC, et al (1990). Transplanted suprachiasmatic nucleus determines circadian period. Science 247:975-978.

Rapoport AM (2012). Acute treatment of migraine: established and emerging therapies. Headache 52 (Suppl 2):60-64.

Sahota RK, Dexter JD (1990). Sleep and headache syndromes: a clinical review. Headache 30: 80-84.

Seidel S, Hartl T, Weber M, et al (2009). Quality of sleep, fatigue and daytime sleepiness in migraine - a controlled study. Cephalalgia 29:662-669.

Solomon GD (1992). Circadian rhythms and migraine. Cleve Clin J Med 59: 326-329.

Spielberg CD (1983). Manual for State-Trait Anxiety Inventory (Revised). Palo Alto CA, Consulting Psychologist Press.

Steiner TJ, Stovner LJ, Birbeck GL (2013). Migraine: the seventh disabler. Headache 53:227-229.

Stewart WF, Lipton RB, Whyte J, et al (1999). An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 53:988-994.

Stronks DI, Tulen JH, Bussmann JB, et al (2004). Interictal daily functioning in migraine. Cephalalgia 24:271-279.

Suntsova NV, Dergacheva OY, Burikov AA (2000). The role of the posterior hypothalamus in controlling the paradoxical phase of sleep. Neurosci Behav Physiol 30:161-167.

Viana M, Genazzani AA, Terrazzino S, et al (2013). Triptan non-responders: do they exist and who are they? Cephalalgia 33:891-896.

Vos T, Flaxman AD, Naghavi M, et al (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2163-2196.