Neurological Sciences (2019) 40:1841–1848
https://doi.org/10.1007/s10072-019-03886-4

ORIGINAL ARTICLE

Influence of chronotype on migraine characteristics

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Received: 29 November 2018 / Accepted: 5 April 2019 / Published online: 2 May 2019

Abstract

Background The aim of this study was to investigate chronotype in migraine patients and possible influences on the clinical expression of the disease.

Methods During a one-year period, all consecutive patients admitted to two third-level headache centres with a new diagnosis of migraine were enrolled in a cross-sectional study. All subjects were submitted to the Morningness–Eveningness Questionnaire (MEQ-SA) and then classified in five different categories, from late to early-rising chronotype. Differences and trends among MEQ-SA categories and years from migraine onset, attacks' intensity and frequency were analysed first with analysis of variance, then with a multivariate/generalized linear model.

Results One hundred seventy one migraine patients were included. Early-rising patients showed a lower migraine attacks frequency and longer disease duration with respect to late-rising patients. The categorical variable containing the five circadian types was able to identify a significantly different trend both for the monthly attacks frequency and for the disease duration ($p < 0.0001$ and $p < 0.0001$, respectively, analysis of variance). The results were also confirmed after correction for main influencing variables (multivariate/generalized linear model). The intensity of migraine attacks was not influenced by chronotype.

Conclusions According to the results of the present study, chronotype seems to influence number and duration of migraine attacks. Although sleep–wake cycle is a well-recognized factor able to influence thalamic–cortical synchronization, it usually does not receive appropriate consideration during migraine patients' assessment.

Keywords Headache · Sleep–wake cycle · Circadian rhythm · Sleep

Introduction

Circadian rhythm (CR) is one of the major determinants of sleep–wake cycle [1, 2], regulated by a "biological clock" localized in the suprachiasmatic nucleus (SCN) [2, 3]. Several physiological and behavioural aspects, including body temperature, hormonal profile and blood pressure are regulated by this biological rhythm. The genetically determined endogenous rhythm is longer than 24 h, but it is synchronized to the daily 24-h by different social and environmental "zeitgebers". A zeitgeber is an ethologic term used to define any external cue that synchronizes biological rhythms to environmental conditions [4]. Light is the most relevant zeitgeber. In addition to the SCN, retinal photoreceptors and the melatonin secretion by the pineal gland play a prominent role in the circadian rhythm regulation. SCN activation by bright retinal inputs inhibits melatonin production by the pineal gland which, on the contrary, is stimulated by the dark. One of the most relevant expressions of CR deregulation is the sleep–wake cycle alteration that may manifest with sustained levels of vigilance or propensity to inappropriately falling asleep.

Three main typologies of the circadian asset can be recognized: the "morning type" (the so-called "lark"), characterized by an early awakening and bedtime and better performance in the morning, an "evening type" (also defined "owl"), with late wake and bedtime and satisfactory activities in the evening, and an "intermediate typology". Most subjects are characterized by the intermediate phenotype.

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Sleep is able to influence the expression of different clinical conditions, including migraine. A good sleep quality, together with a keep sleep–wake cycle, exerts a protective factor; on the other hand, migraine subjects with severe and frequent attacks often suffer from primary or secondary sleep disturbances [5]. Several studies investigated the relationship between sleep and migraine, but data explaining the influence of circadian typology on migraine characteristics are not exhaustive [6].

The aim of this study was to explore the circadian phenotype in a group of migraine patients and to evaluate the possible influences on different diseases' characteristics.

Materials and methods

This cross-sectional study was performed in two third-level centres: the Headache centre of the Neurological Clinic, Polytechnic University of Ancona and of the Neurology Unit at Campus Bio-Medico University, Rome. In both centres, expert neurologists in headache diagnosis and management evaluated and enrolled migraine subjects undergoing outpatients' assessment.

Inclusion criteria were the following: (a) a diagnosis of migraine without aura (MWoA), according of the International Classification of Headache Disorders criteria, 3rd edition (beta version) (ICHD-III beta) [7]; and (b) Italian nationality or good Italian language comprehension and practice. In each patient, a collection of clinical history, comprehensive of drug utilization, was performed in addition to a general and neurological examination. We investigated the presence of other relevant pathologies, especially psychiatric illnesses and related drug assumption. Exclusion criteria were the following: (a) headache determined by brain tumours or other neurological diseases; (b) relevant pathologies as diabetes, renal or hepatic failure or other metabolic chronic disease; (c) night-shift work; (d) long-distance transmeridian flights in the previous month; (e) history of sleep alterations (obstructive sleep apnoea, restless legs syndrome, narcolepsy, etc.); (f) mood or affective disorders, especially seasonal ones; (g) use of melatonin or drugs able to influence endogenous melatonin secretion; (h) chronic use of antidepressants or sleep-inducing drugs; (i) substance and alcohol abuse; (l) relevant neurological or visual deficits; and (m) presence, in the clinical history, of previous preventive therapy for migraine. Mood disorders were evaluated by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM V) criteria employing clinical history, Structured Clinical Interview for DSM V (SCID) and 20-item Beck Inventory II (patients with a score > 13 at Beck Inventory II were excluded) [8].

Monthly attacks frequency, years from migraine onset, attacks intensity (mild, moderate or severe), and treatments were investigated.

Patients were asked to fill out the Italian validated version of the Morningness–Eveningness Questionnaire (MEQ-SA) [9, 10]. MEQ-SA is a self-assessment, validated questionnaire to evaluate the circadian typology. It is composed by 19 multiple-choice questions regarding sleep characteristics and preference with a final score ranging from 16 to 86. Subjects are defined as late rising, moderately late rising, intermediate, moderately early rising and early rising when their score ranges from 16 to 30, 31 to 41, 42 to 58, 59 to 69 and 70 to 86, respectively.

Pain intensity was evaluated by the Verbal Rating Scale (VRS), a validated 10-point self-reporting score scale. In order to simplify the management of information, pain intensity was also defined by a four-grade scale: 0 for "no pain", 1–3 for "mild pain", 4–6 for "moderate pain", and 7–10 for "severe pain" [11]. All data were collected during the first visit in one of the two enrolling centre after obtaining by each participant his/her informed written consent according to the Declaration of Helsinki. The ethics committees of Marche Polytechnic University and Campus Bio-Medico University of Rome approved the study.

Statistical analysis

Age, MEQ-SA score and number of attacks per month and years from migraine onset were collected as continuous variables. MEQ-SA score was also coded as a categorical variable, including the different typologies of circadian phenotype: early rising, moderately early rising, intermediate, moderately late rising, and late rising. Attacks intensity was synthesized as a categorical variable based on VRS-10 scale score, with attacks defined as mild, moderate and severe.

We coded patients' treatments as categorical variables before the visit. Sex was synthesized as a dichotomous variable.

Continuous variables were compared with *t* test for independent samples, categorical and dichotomous variables were compared with chi-squared test. Differences and trends among MEQ-SA categories of years of migraine, attack intensity and number of attacks per month were analysed first with analysis of variance (ANOVA), then with a multivariate/generalized linear model (GLM/multivariate) considering years of migraine, number of attacks and attacks intensity as outcomes, MEQ-SA categorical variable as the main predictor, age and sex as covariates. Trend among categories was analysed with ANOVA polynomial linear term testing. Statistical analysis was performed with SPSS 13.0 for Windows systems.

Results

During a one-year period, we evaluated 195 migraine subjects. Three subjects refused to participate, and 21 were

excluded for the presence of at least one exclusion criterion. Baseline characteristics of the final sample of 171 consecutive patients are synthesized in Table 1. ANOVA showed that the categorical variable containing the five circadian types was able to identify a significantly different trend both for the monthly attacks frequency ($p < 0.0001$) and for the disease duration ($p < 0.0001$). No influence was detected for the attacks intensity at ANOVA ($p = 0.959$), GLM/multivariate ($p = 0.885$) and chi-squared tests ($p = 0.883$).

The GLM/multivariate test confirmed the previous findings (Figs. 1 and 2), even after correction for age and sex. The GLM/multivariate estimated marginal means are synthesized in Table 2, and pairwise comparisons between the mean number of attacks, mean years from disease onset and mean migraine attacks intensity among each MEQ-SA category are synthesized in Table 3. We observed that the two categories of early-rising subjects had a significantly lower number of migraine attacks but a longer duration of disease if compared to the late-rising subject categories. The chronotype did not seem to affect migraine attacks intensity in this model.

Discussion

The findings of the present study suggest that chronotype may influence some clinical aspects of migraine. In particular, we found that the late-rising chronotype is associated to an increased migraine attacks frequency. The correlation between attacks frequency and serotine chronotype may be, at least in part, explained by the fact that subjects with this chronotype are misaligned to the usual social and working habits. Specifically, in morning-type subjects (the larks), circadian rhythms are not disturbed by daily activities and the number of attacks may depend mostly by individual migraine predisposition and other triggers. On the other hand, in serotine subjects (the owls), the interruption of sleep and the consequent lower sleep quality, due to the necessity to engage in social and work activities scheduled in the morning, can trigger migraine attacks. This is particularly true for school activities or employment duties [12].

In our study, serotine chronotype subjects had a lower number of years from migraine onset when they underwent a first evaluation in a headache centre with respect to morning-type subjects. This aspect might be related to the different attacks frequency, because owl subjects with many attacks tend

Table 1 Baseline characteristic of the sample

Age (± SD)		39.51 (± 14.5)
Female sex (*n*, %)		131 (76.6%)
Number of attacks per month (± SD)		7.94 (± 7.71)
Years of migraine (± SD)		12.00 (± 10.82)
MEQ-SA score (± SD)		55.30 (± 8.43)
Attack intensity (*n*, %)	Mild	5 (2.9%)
	Moderate	90 (52.6%)
	Severe	76 (44.4%)
MEQ-SA category (*n*, %)	Early rising	17 (9.9%)
	Moderately early rising	55 (32.2%)
	Intermediate	65 (38.0%)
	Moderately late rising	24 (14.0%)
	Late rising	10 (5.8%)
Therapy before consultation (*n*, %)	NSAIDS	86 (50.3%)
	Paracetamol	40 (23.4%)
	Triptans	39 (22.8%)
	Others	6 (3.5%)
Suggested prophylaxis (*n*, %)	Beta-blockers	14 (8.2%)
	Calcium channel blockers	56 (32.7%)
	Antidepressants	34 (19.9%)
	Antiepileptic drugs	30 (17.5%)
	Vitamins	25 (14.6%)
	No therapy	12 (7.01%)
Suggested therapy (*n*, %)	NSAIDS	25 (14.6%)
	Paracetamol	26 (15.2%)
	Triptans	120 (70.2%)

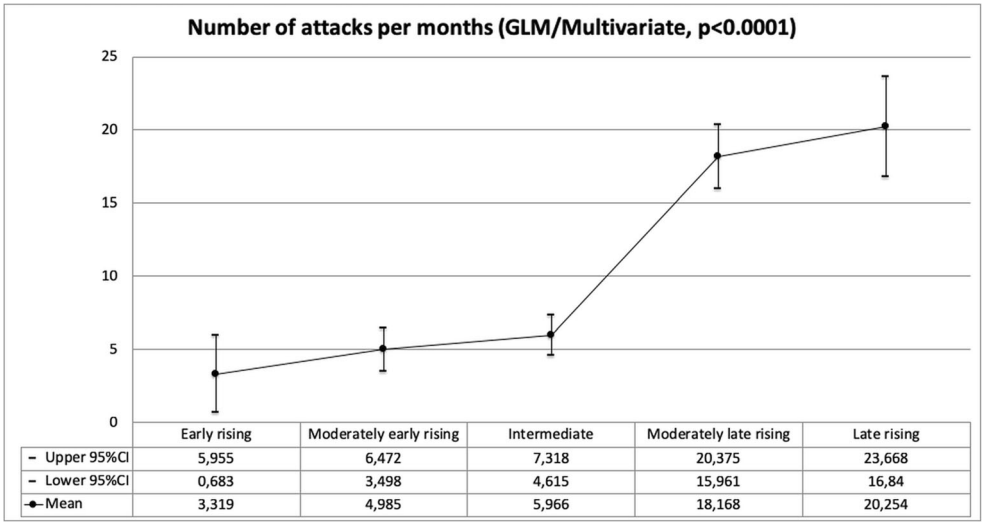

Fig. 1 Differences in the number of attacks per month in MEQ-SA categories (GLM/multivariate)

frequently to call on the emergency room or headache-specialized centres. Accordingly, an increased number of disabling attacks could stimulate patients to an earlier search for medical care [13].

Many different medical conditions, ranging from gastrointestinal diseases to autoimmune pathologies, show a clear oscillation in their clinical expression linked to the different phases of the day [14]. The same pattern is also evident in some neurological and psychiatric conditions, including Parkinson and Alzheimer's diseases, depressive and bipolar disorders and craving for alcohol or heroin. In this respect, the so-called 'chronodegeneration' is considered as a primary factor in disease progression [14–16]. The knowledge of such patterns is necessary in an attempt to improve patients' care by modulating timing for therapy administration or managing possible external temporal triggers.

Migraine is a complex clinical condition with different aspects still to be fully defined [17]. According to one pathophysiologic hypothesis, migraine is considered a sort of "oscillopathy" of the pathway between thalamus and cortex. Transition between wakefulness and sleep is regulated by a thalamocortical oscillator that produces slow and synchronized oscillations (theta and delta rhythms). During sleep, the oscillator is activated, while in wakefulness, the oscillator is not functioning and fast rhythms are dominating [18]. Different studies hypothesized that thalamocortical dysrhythmia may be responsible for the altered synchronicity in migraine [19, 20]. Accordingly, a recent study showed that patients with migraine with aura have a peculiar connectivity pattern with an increased cortical activation after visual stimulation. A reduced cortical activation (susceptibility) is, on the contrary, present in patients not experiencing aura symptoms [21].

The relationship between sleep and headache is complex. While hypnic headache or paroxysmal hemicrania during REM sleep are strictly related to nocturnal rest [22], the correlation between sleep and migraine is less clear. Many studies reported that the majority of attacks occur in the morning, but this finding is still controversial [20, 23]. Sleep deprivation or

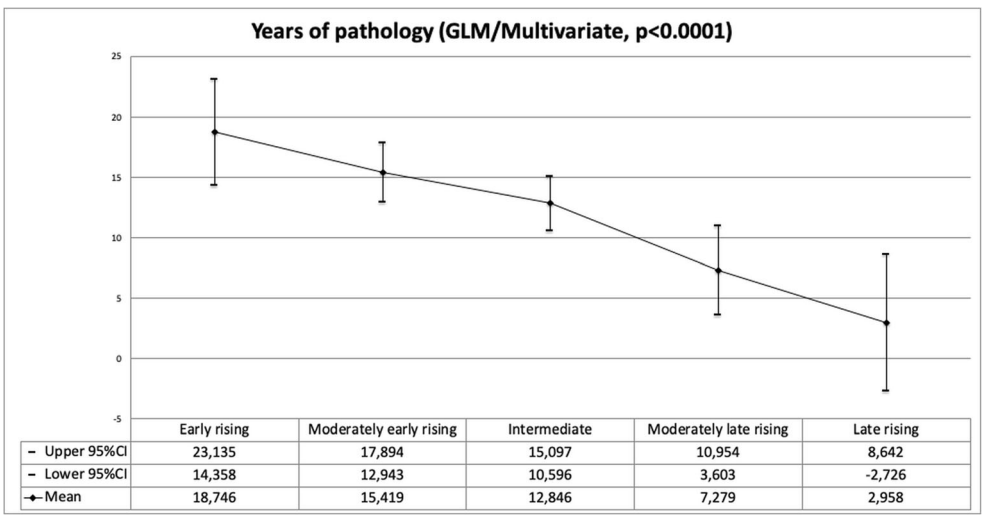

Fig. 2 Differences in the years of pathology among MEQ-SA categories (GLM/multivariate)

Table 2 Estimated marginal means of GLM/multivariate model adjusted for age and sex

	MEQ-SA category	Mean	SE	95%CI	95%CI
Attacks per month	Early rising	3.319	1.335	0.683	5.955
	Moderately early rising	4.985	0.753	3.498	6.472
	Intermediate	5.966	0.684	4.615	7.318
	Moderately late rising	18.168	1.118	15.961	20.375
	Late rising	20.254	1.729	16.84	23.668
Years of pathology	Early rising	18.746	2.223	14.358	23.135
	Moderately early rising	15.419	1.254	12.943	17.894
	Intermediate	12.846	1.14	10.596	15.097
	Moderately late rising	7.279	1.861	3.603	10.954
	Late rising	2.958	2.879	− 2.726	8.642
Intensity	Early rising	1.319	0.136	1.052	1.587
	Moderately early rising	1.391	0.076	1.24	1.542
	Intermediate	1.428	0.07	1.29	1.565
	Moderately late rising	1.46	0.114	1.235	1.684
	Late rising	1.524	0.176	1.177	1.871

marked alteration of bedtime could predispose to migraine [5, 24]. More in general, sleep alterations tend to increase all the typologies of morning headaches [25]. This is the reason for our choice to not include in the study night-shift work because these people presented a well-documented alteration of sleep cycles and a predisposition towards different types of headaches [26]. At the same time, we decided to avoid the inclusion of subjects with a positive anamnesis for sleep alterations [27, 28].

Migraine attacks may be characterized by different temporal patterns, with several triggering factors determining diurnal or awakening onset, so configuring different phenotypes. Recent studies support the hypothesis of a central role of hypothalamus in migraine pathogenesis. Schulte et al. sustained that functional changes in hypothalamo-brainstem connectivity could be the real driver of migraine attacks [29].

Circadian rhythm sleep disorders (CRSDs) are described as chronic alterations of sleep–wake rhythm secondary to

Table 3 Pairwise comparison of estimated marginal means at GLM/multivariate model

(I) MEQ-SA	(J) MEQ-SA	(I–J)	SE	Sig.	95%CI	
					Low	High
Attacks per month						
Early rising	Moderately early rising	− 1.67	1.53	0.279	− 4.69	1.36
	Intermediate	− 2.65	1.50	0.08	− 5.62	0.32
	Moderately late rising*	− 14.8	1.74	0.00	− 18.3	− 11.4
	Late rising*	− 16.9	2.19	0.00	− 21.3	− 12.6
Moderately early rising	Early rising	1.67	1.53	0.28	− 1.36	4.69
	Intermediate	− 0.98	1.03	0.34	− 3.02	1.06
	Moderately late rising*	− 13.2	1.36	0.00	− 15.9	− 10.5
	Late rising*	− 15.3	1.88	0.00	− 18.9	− 11.5
Intermediate	Early rising	2.65	1.50	0.08	− 0.32	5.62
	Moderately early rising	0.98	1.03	0.34	− 1.06	3.02
	Moderately late rising*	− 12.2	1.30	0.00	− 14.7	− 9.63
	Late rising*	− 14.3	1.86	0.00	− 17.9	− 10.6
Moderately late rising	Early rising*	14.8	1.73	0.00	11.4	18.3
	Moderately early rising*	13.2	1.36	0.00	10.5	15.9
	Intermediate*	12.2	1.30	0.00	9.63	14.8
	Late rising	− 2.09	2.06	0.31	− 6.16	1.98
Late rising	Early rising*	16.9	2.19	0.00	12.6	21.3

Table 3 (continued)

(I) MEQ-SA	(J) MEQ-SA	(I–J)	SE	Sig.	95%CI	
					Low	High
	Moderately early rising*	15.3	1.88	0.00	11.5	18.9
	Intermediate*	14.3	1.86	0.00	10.6	17.9
	Moderately late rising	2.09	2.06	0.31	− 1.98	6.16
Years of pathology						
Early rising	Moderately early rising	3.33	2.55	0.19	− 1.71	8.36
	Intermediate*	5.90	2.50	0.02	0.95	10.8
	Moderately late rising*	11.5	2.89	0.00	5.75	17.2
	Late rising*	15.8	3.66	0.00	8.56	23.0
Moderately early rising	Early rising	− 3.33	2.55	0.19	− 8.37	1.71
	Intermediate	2.57	1.72	0.14	− 0.83	5.97
	Moderately late rising*	8.14	2.27	0.00	3.67	12.6
	Late rising*	12.5	3.14	0.00	6.26	18.6
Intermediate	Early rising*	− 5.90	2.50	0.02	− 10.8	− 0.95
	Moderately early rising	− 2.57	1.72	0.14	− 5.97	0.83
	Moderately late rising*	5.57	2.17	0.01	1.28	9.85
	Late rising*	9.89	3.09	0.00	3.78	15.9
Moderately late rising	Early rising*	− 11.5	2.89	0.00	− 17.2	− 5.75
	Moderately early rising*	− 8.14	2.27	0.00	− 12.6	− 3.67
	Intermediate*	− 5.57	2.17	0.01	− 9.85	− 1.28
	Late rising	4.32	3.43	0.21	− 2.46	11.09
Late rising	Early rising*	− 15.8	3.66	0.00	− 23.0	− 8.57
	Moderately early rising*	− 12.5	3.14	0.00	− 18.7	− 6.26
	Intermediate*	− 9.89	3.09	0.00	− 15.9	− 3.78
	Moderately late rising	− 4.32	3.43	0.21	− 11.1	2.46
Intensity						
Early rising	Moderately early rising	− 0.07	0.16	0.65	− 0.38	0.24
	Intermediate	− 0.11	0.15	0.48	− 0.41	0.19
	Moderately late rising	− 0.14	0.18	0.43	− 0.49	0.21
	Late rising	− 0.20	0.22	0.36	− 0.65	0.24
Moderately early rising	Early rising	0.07	0.16	0.65	− 0.24	0.38
	Intermediate	− 0.04	0.10	0.73	− 0.24	0.17
	Moderately late rising	− 0.07	0.14	0.62	− 0.34	0.20
	Late rising	− 0.13	0.19	0.49	− 0.51	0.24
Intermediate	Early rising	0.11	0.15	0.48	− 0.19	0.41
	Moderately early rising	0.04	0.10	0.73	− 0.17	0.24
	Moderately late rising	− 0.03	0.13	0.81	− 0.29	0.23
	Late rising	− 0.09	0.19	0.61	− 0.47	0.28
Moderately late rising	Early rising	0.14	0.18	0.43	− 0.21	0.49
	Moderately early rising	0.07	0.14	0.62	− 0.20	0.34
	Intermediate	0.03	0.13	0.81	− 0.23	0.29
	Late rising	− 0.06	0.21	0.76	− 0.48	0.35
Late rising	Early rising	0.20	0.22	0.36	− 0.24	0.64
	Moderately early rising	0.13	0.19	0.49	− 0.24	0.51
	Intermediate	0.09	0.19	0.61	− 0.28	0.47
	Moderately late rising	0.06	0.21	0.76	− 0.35	0.48

*Significant results

alterations of the circadian timing system or to disagreement between endogenous circadian rhythm and the sleep–wake times ruled by school or work activities [2]. According to our data, we could hypothesize that migraine is a sort of CRSD generated by an alteration of circadian rhythm imposed by living and working activities in predisposed subjects. On the contrary, when the sleep–wake rhythm is similar to the endogenous rhythm, migraine subjects may present a low frequency of severe headaches. According to some authors, migraine could be interpreted as the result of a main effort to maintain homeostasis contrasting the desynchronization between circadian phenotype and lifestyle [30].

Therapeutic implications of circadian rhythms in neurological diseases presenting with paroxysmal events as epilepsy have been largely investigated. Different studies, evaluating the influence of circadian typologies, showed that different time of drug administration could modify the effectiveness and tolerability of treatment [31, 32]. Migraine and epilepsy share different pathophysiologic aspects including an alteration in the brain electric connections. Both present paroxysmal crisis and share some treatment approaches. Based on these considerations, a "chronotherapy" could also be taken into consideration for migraine patients. Accordingly, a personalized time for drug administration could improve treatment effectiveness.

Different studies showed low melatonin levels in subjects with chronic migraine [33]. In migraine patients, higher levels of melatonin are dosed in the days free from headache [34, 35]. Based on these data, some trials evaluating melatonin as a possible therapeutic approach for migraine were performed, but the results were controversial. Only a dose of 3 mg/day was significantly associated to a positive effect [34] but a more rational employment of melatonin therapy, based on patients' chronotype, should be considered to fully evaluate the potentiality of this therapeutic approach.

Study limitations

The present study has several limitations. The most relevant one is related to the fact that we did not associate the MEQ-SA score to any other instrumental evaluation as actigraphy, body temperature rhythm, melatonin secretion rhythm or polysomnography. However, some studies show that MEQ-SA score is a reliable instrument to define ideal sleep time, which is not related to sleep phase but to sleep quality [12]. Moreover, we did not perform a follow-up because our study had a cross-sectional design. This approach did not allow to fully determine the temporal ordering of the various items and the exact causality in the relationship between chronotype and migraine characteristics. Moreover, by excluding patients with sleep alterations reduced the possibility to generalize our results to all migraine subjects. In this respect, we decided to include only patients affected by migraine without aura to obtain a homogeneous sample.

Conclusions

In conclusion, our findings suggest that chronotype may be considered an influencing factor on some, relevant migraine characteristics and could represent a significant aspect to evaluate and consider in the attempt to increase the possibilities to optimize the therapeutic management of patients.

Compliance with ethical standards

The ethics committees of Marche Polytechnic University and Campus Bio-Medico University of Rome approved the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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