Epilepsy & Behavior 61 (2016) 132–137

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

# Circadian phase typing in idiopathic generalized epilepsy: Dim light melatonin onset and patterns of melatonin secretion—Semicurve findings in adult patients

Raffaele Manni [a,*], Roberto De Icco [a], Riccardo Cremascoli [a], Giulia Ferrera [b], Francesca Furia [c], Elena Zambrelli [c], Maria Paola Canevini [d], Michele Terzaghi [a]

[a] Unit of Sleep Medicine and Epilepsy, C. Mondino National Neurological Institute, Pavia, Italy
[b] Medical School, Insubria University, Varese, Italy
[c] Epilepsy Center — Sleep Medicine Center, San Paolo Hospital, Milan, Italy
[d] Department of Health Sciences, University of Milan, Milan, Italy

ARTICLE INFO

*Article history:*
Received 8 March 2016
Revised 16 May 2016
Accepted 18 May 2016
Available online 23 June 2016

*Keywords:*
Idiopathic generalized epilepsy
Sleep
Chronotype
DLMO

ABSTRACT

*Objective/background:* It has been debated in the literature whether patients with idiopathic generalized epilepsy (IGE) have a distinctive, evening-oriented chronotype. The few questionnaire-based studies that are available in the literature have conflicting results. The aim of our study was to define chronotype in patients with IGE by determining dim light melatonin onset (DLMO).

*Patients/methods:* Twenty adults diagnosed with IGE (grand mal on awakening [GM] in 7 cases and juvenile myoclonic epilepsy in 13 cases) were investigated by means of a face-to-face semistructured sleep interview, Morningness–Eveningness Questionnaire (MEQ), Pittsburgh Sleep Quality Index (PSQI) questionnaire, and a melatonin salivary test with DLMO determination. Eighteen healthy subjects (HC) and 28 patients affected with cryptogenic focal epilepsy (FE) served as controls.

*Results:* The mean MEQ score was significantly lower in patients with IGE than that in patients with FE (49.1 ± 5.9 versus 56.1 ± 8.7 $P < 0.01$) but not significantly lower than that in HC (49.1 ± 5.9 versus 49.3 ± 8.6). Midsleep on free days corrected for sleep duration did not differ significantly between the three subject groups (04:59 ± 01:21 h, 04:37 ± 01:17 h, 04:29 ± 00:52 h). The mean DLMO time in patients with IGE (22:13 ± 01:34 h) occurred 49 min later than that in HC (21.24 ± 1 h), and the melatonin surge within the 30-minute time interval after DLMO in patients with IGE was significantly lower than that in HC (1.51 ± 2.7 versus 3.8 ± 3.6 pg/mL $P = 0.045$).

*Conclusions:* Subjective measures of chronotype do not indicate a definite evening-oriented chronotype in patients with IGE. However, the data concerning endogenous melatonin secretion indicate that patients with IGE tend to have a late circadian phase. Further studies are warranted in order to better define the late pattern of endogenous melatonin secretion in patients with IGE and to ascertain the role of this pattern in influencing behavioral chronotype in these subjects.



*Abbreviations:* IGE, idiopathic generalized epilepsy; GM, grand mal on awakening; JME, juvenile myoclonic epilepsy; DLMO, dim light melatonin onset; MEQ, Morningness–Eveningness Questionnaire; PSQI, Pittsburgh Sleep Quality Index Questionnaire; HC, healthy subjects; FE, cryptogenic focal epilepsy; AEDs, antiepileptic drugs; MIDwd, midsleep on workdays; MIDf, midsleep on free days; MIDfc, midsleep on free days corrected for sleep duration; SJL, social jet lag; Post-DLMO measure, melatonin salivary concentration of the first post-DLMO melatonin sample; Post-DLMO surge, melatonin surge in the 30-minute time interval after DLMO occurrence; AUC, the under-the-curve area of the post-DLMO semicurve AUC; $AUC^{30}$, the under-the-curve area specifically about the 30-minute time interval of melatonin secretion after DLMO occurrence $AUC^{30}$; SPSS, The Statistical Package for the Social Sciences; DSPS, delayed sleep phase syndrome.

* Corresponding author at: C. Mondino National Neurological Institute, 27100 Pavia, Italy.
*E-mail addresses:* raffaele.manni@mondino.it (R. Manni), rob.deicco@gmail.com (R. De Icco), cremaz@hotmail.it (R. Cremascoli), giulia.ferrera1@gmail.com (G. Ferrera), francesca.furia@asst-santipaolocarlo.it (F. Furia), elena.zambrelli@asst-santipaolocarlo.it (E. Zambrelli), maria.canevini@asst-santipaolocarlo.it (M.P. Canevini), michele.terzaghi@mondino.it (M. Terzaghi).

http://dx.doi.org/10.1016/j.yebeh.2016.05.019
1525-5050/

## 1. Introduction

Nycthemeral timing of the seizures as well as that of the interictal epileptiform abnormalities in idiopathic generalized epilepsy (IGE) indicate that circadian rhythms play a role in the pathophysiology and clinical phenotype of this form of epilepsy [1–3].

To maintain regular sleep patterns is considered important for neural function in patients with epilepsy. In fact, sleep deprivation and circadian rhythm disruption may increase neuronal excitability [4]. Furthermore, it is known that chronotype matters with respect to individuals' psychosocial adjustment: those with evening chronotypes show poorer sleep quality, higher social jet lag, and sleep deprivation accumulation than those with morning types [5].

Thus, the knowledge of the chronotype in patients with IGE is of importance with possible pathophysiological and clinical implications. Nevertheless, to date, the study of chronotype in patients with IGE has only been addressed by a few papers in the literature, and these have conflicting results. An evening sleep and behavioral preference was initially signaled by Janz [6] as a distinctive trait in subjects with juvenile myoclonic epilepsy (JME), a prototypical form of IGE. This was confirmed later by Pung and Schmitz [7]. More recently, patients with IGE have been reported significantly more likely to be evening types than patients with focal epilepsy (FE) [8,9].

By contrast, morning type was reported to be the most represented chronotype in patients with IGE as well as in patients with FE by other authors [10,11].

However, all the available data are questionnaire-based and feature only the subjective, behavioral component of the chronotype that may not reflect the actual circadian phase, especially in patients with epilepsy [12].

The aim of our study was to define chronotype in patients with IGE by determining dim light melatonin onset (DLMO), a well-known biological marker of circadian phase in humans.

## 2. Material and methods

### 2.1. Setting and participants selection criteria

Subjects who were 18 years or older with a definite diagnosis of IGE according to the 2010 ILAE classification [13] and attending a scheduled appointment at the epilepsy outpatient clinic of the C. Mondino Institute of Neurology of Pavia or of San Paolo Hospital of Milan in Italy were evaluated for inclusion into the study over a six-month period in 2015.

The patients were consecutively enrolled after screening for the following exclusion criteria: night shift work, long-distance transmeridian flight(s) in the previous month, cardiopulmonary and/or metabolic diseases (such as diabetes or renal or hepatic failure), obstructive sleep apnea, narcolepsy, restless legs syndrome, major visual deficits, alcohol or substance abuse, use of hypnotics, use of antidepressants, melatonin or prescription or over-the-counter drugs known to affect endogenous melatonin secretion, use of oral contraceptive medications, and mood disorders such as major depression or seasonal affective disorder. The presence of major depression disorder was assessed according to DSM-IV criteria, based on clinical history integrated by SCID I [14] and 20-item Beck Inventory II [15]. A score over 13 using Beck Inventory II was taken as consistent with depression and let us to exclude him/her from the enrollment.

Twenty-two out of 30 screened patients were eligible to be enrolled and underwent DLMO determination by salivary samples. Two patients showed low melatonin secretion after a salivary test and retest. These patients were excluded from enrollment because it was impossible to determine their DLMO.

Healthy subjects and subjects with cryptogenic focal epilepsy (FE) who came from the same epilepsy outpatient clinics were selected from our clinical series database to serve as controls. They had to meet the abovementioned exclusion criteria and be comparable to the patients with IGE for age, sex, low caffeine and alcohol use, and employment status. Eighteen HC and 28 subjects with FE were selected.

No subject received financial compensation for taking part in the study. Consent forms were signed prior to patients' participation. The protocol was approved by the Ethics Committee of the C. Mondino National Neurological Institute as a part of a research project funded by the Italian Ministry of Health - RC 2014-16.

### 2.2. Clinical features of the study participants

The demographic and clinical features of the patients with IGE and FE and those of the healthy controls "HC" are shown in Table 1.

Idiopathic generalized epilepsy consisted of forms of GM on awakening in 7 cases and of JME in 13 cases. The mean disease duration at the time of the study was 26.7 years (±14.4) with 72.7% of the patients being seizure free for at least a year.

In all the patients with focal epilepsy, their disease was cryptogenic with no patient having previously undergone surgery for epilepsy. The mean disease duration at the time of the study was 10.0 years (±9.6) with 64.3% of the patients being seizure free for at least a year.

All the patients were treated with antiepileptic drugs (AEDs) with the most used AEDs being valproic acid in patients with IGE and levetiracetam and carbamazepine in patients with focal epilepsy. Both patients with IGE and those with FE consumed part of the therapy (half to two-thirds of the daily dose) or the entire daily dose at dinnertime or at bedtime. Patients who were on valproate and carbamazepine were taking long-acting versions of these drugs. The blood levels of AEDs were within the therapeutic range of values in all the subjects.

### 2.3. Procedures

During the screening visit, the patients took part in a face-to-face semistructured sleep interview and were given a validated Italian version of the Morningness–Eveningness Questionnaire (MEQ) [16] and the Pittsburgh Sleep Quality Index (PSQI) [17]. A physician was on site to provide any clarification and do a final check of the questionnaires. The participants were then instructed to keep a sleep diary on graph paper at home for two weeks, maintaining their usual lifestyle habits and sleep schedule. On the 15th day, they returned to the outpatient clinic, were given an at-home saliva melatonin sampling kit, and instructed to perform the test according to specific, published procedures [18] and to return it within 24 h in an ice chest. In the event of a seizure, patients were required to wait at least 72 h before performing the salivary melatonin test.

### 2.4. Questionnaires and tests used

#### 2.4.1. Semistructured sleep interview and sleep diaries

The aim of the semistructured sleep interview was to assess the timing and duration of sleep on workdays and free days, sleep hygiene, and symptoms of sleep disorders, including daytime sleepiness, snoring, sleep apnea, and sleep-related motor disorders and parasomnias.

The following variables were derived from the sleep interview and diaries:

- Mean sleep onset and end time, sleep duration;
- Accumulated sleep deprivation (difference between the average sleep duration and the sleep duration on workdays);
- The time of midsleep (midtime between sleep onset and sleep end) on workdays (MIDwd) and on free days (MIDf) and the time of midsleep on free days corrected for sleep duration (MIDfc), in accordance with literature conventions [19]; and
- Social jet lag (SJL), calculated as the difference between MIDf and MIDwd and intended to quantify the discrepancy between biological