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Original Article

Evening melatonin timing secretion in real life conditions in patients with Alzheimer disease of mild to moderate severity

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ABSTRACT

Background: Circadian dysfunction is thought to take part in the pathogenesis of sleep disorders in Alzheimer's disease (AD) and in AD pathophysiology itself.
Objective: Our study aims to calculate dim light melatonin onset (DLMO) secretion in order to define the circadian phase in patients with AD at an early stage of the disease.
Methods: Twenty-one patients (M/F: 11/10; mean age 74.1 ± 5.4 years; mean disease duration 3.4 ± 1.6 years) with a diagnosis of AD and 17 healthy controls (HC; M/F: 10/7; mean age 67.47 ± 3.8 years) were investigated for subjective nocturnal sleep quality and chronotype, for DLMO and quantitative aspects of the evening melatonin secretion by means of a 5-point in-home evening melatonin saliva test.
Results: Subjective sleep quality score on the Pittsburgh Sleep Quality Index questionnaire (PSQI) above 5 ($p = 0.24$), insomnia frequency as measured by Sleep Condition Indicator Questionnaire ($p = 0.823$) and the subjective chronotype according to Morning Evening Questionnaire (MEQ) scores distribution ($p = 0.464$) did not differ between AD and HC. However, DLMO occurred significantly later (55 min; $p = 0.028$), and melatonin secretion following DLMO was significantly decreased in AD patients compared to HC.
Conclusion: Initial evening secretion of melatonin proves to be delayed and mildly impaired in patients with a mild/moderate form of Alzheimer disease while patients' subjective sleep parameters and chronotype are reported to be similar to those of HC. These results indicate that subclinical altered patterns of melatonin secretion occur in subjects with AD at an early stage of the disease.

1. Introduction

Circadian dysfunction is thought to contribute to the pathogenesis of sleep disorders in Alzheimer's disease (AD) as well as in AD pathophysiology itself [1]. Neurodegeneration of the suprachiasmatic nucleus (SCN) with decreased output to the pineal gland, decreased melatonin MT1 receptor expression and lesser central nervous system (CNS) responsivity to light for entrainment [2], account for circadian dysfunction in AD. Accordingly, reduced melatonin amplitude and increased variation of melatonin peak secretion time were reported in AD [3,4]. Currently, less is known about the timing of melatonin onset secretion. Our study aimed to determine dim light melatonin onset (DLMO) in non-institutionalized AD patients investigated using an in-home saliva melatonin test.

2. Material and methods

2.1. Participant selection

The patients were consecutively enrolled at the Alzheimer's Disease Assessment Unit of the IRCCS C. Mondino Foundation of

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Pavia from October 2016 to March 2017 among AD outpatients with a diagnosis of AD according to standard criteria [5]. The patients were enrolled using these exclusion criteria: score less than 14 or more than 24 on the Mini-Mental State Examination (MMSE) [6]; visual deficits and glaucoma; diabetes, renal, hepatic or thyroid diseases; abuse of alcohol or other substances; use of hypnotics; use of antidepressants; long distance trans-meridian flight(s) in the previous three months; intake of melatonin or drugs altering endogenous melatonin secretion; bipolar disorders; seasonal affective disorder or major depression diagnosed according to DSM V criteria [7]; a score of more than 13 on the Beck Inventory II [8]; and sleep disorders (eg, sleep apnea, narcolepsy, or restless legs syndrome). As for obstructive sleep apnea (OSA), AD patients and controls with snoring or with other clinical symptoms/signs suspected for OSAS underwent an out-of-center full-night polygraphic testing with a cardiorespiratory channel (Embletta X 100, Embla) and they entered the study only if they had an AHI of less than five.

Twenty-one out of the 30 AD patients screened agreed to participate in the study; their demographic and clinical characteristics were as follows: M/F: 11/10; mean age 74.2 ± 5.4 years, range 61–84; mean disease duration 3.4 ± 1.6 years, range 1–6; MMSE range: 14–24, mean 20.39 ± 3.8; ADL range: 4–6 functions preserved, mean 5.6 ± 0.6; IADL range: 4–6 functions preserved, mean 4.2 ± 1.1; NPI range: 3–10, mean 5.8 ± 2.2; CDR range: 1–2, mean 1.1 ± 0.6.

All patients were on treatment with acetylcholinesterase inhibitors (donepezil or rivastigmine); the dosage of donepezil ranged between 5 and 10 mg/day in a single oral daily administration; the dosage of rivastigmine transdermal patch ranged between 4.6 and 9.5 mg.

Healthy control (HC) subjects coming from the same geographic area and in the same age range of AD patients (60–85 years) were selected from our database to serve as controls. All the controls scored more than 24 on the Mini-Mental State Examination (MMSE) and met the above-mentioned exclusion criteria. Seventeen HC were selected (M/F: 10/7; mean age was 67.47 ± 3.8 years, range 61–78).

No subject was financially compensated. All participants signed a consent form before entering the study. The protocol was approved by the Ethics Committee of the IRCCS C. Mondino Foundation.

The following quantitative instruments were used to describe the AD population:

- MMSE for global cognitive evaluation;
- Activities of Daily Living (ADL), maintained functions were considered [9].
- Instrumental Activities of Daily Living (IADL), maintained functions were considered [10].
- Neuropsychiatric Inventory (NPI) [11].
- Clinical Dementia Rating (CDR) [12] to evaluate disease severity.

2.2. Procedures

The participants underwent a semi-structured sleep interview and filled in a validated Italian version of the Morningness-Eveningness Questionnaire (MEQ) [13], the Pittsburgh Sleep Quality Index (PSQI) [14] and the Sleep Condition Indicator (SCI) [15] while a physician expert in sleep disorders was available for any clarification and check of the questionnaires. The participants were then instructed to keep a graphic sleep log at home for two weeks, maintaining their usual living conditions. On the 15th day, they were instructed to do an in-home saliva melatonin test (Bühlmann Laboratories AG, Schonenbuch, Switzerland) according to the specific, published procedures [16] and described below.

2.2.1. Sleep questionnaires

2.2.1.1. Semi-structured sleep interview and sleep logs. The semi-structured sleep interview assessed the timing and duration of sleep, sleep hygiene, and symptoms of sleep disorders, including daytime sleepiness, snoring, sleep apnea, cataplexy, sleep-related motor disorders and parasomnias.

2.2.1.2. Morningness-Eveningness Questionnaire. The MEQ evaluated the subjective/behavioral chronotype. Chronotype was defined according to the standard range of scores: 41 or less "evening type," 59 and more "morning type," scores between 42 and 58 "intermediate type".

2.2.1.3. Pittsburgh Sleep Quality Index. The PSQI evaluated subjective sleep quality, with poor sleep quality indicated by a score higher than five (maximum score: 21).

2.2.1.4. Sleep Condition Indicator. The Sleep Condition Indicator was used in identifying a condition of insomnia. A global score of less than 16 was taken as indicative of the existence of a condition of insomnia.

2.2.2. Melatonin test

Melatonin testing was done during a period of daylight saving in April 2017. The participants had to collect five saliva samples in a dark (<10 lux) environment, at hourly intervals with the first sample collected three hours before their usual bedtime.

Melatonin concentration in saliva samples was measured using a commercial ELISA kit (Direct Saliva MELATONIN– Buhlmann), according to the manufacturer's instructions. Briefly, saliva samples were pre-treated with a pretreatment solution, and 100 μl of each sample was added to the wells. Each ELISA test included control (low and high) samples.

The optical density at 450 nm was determined using a microplate reader (Biotek). DLMO was calculated by linear interpolation across the time points before and after the melatonin concentration increased to and stayed above three pg/mL. DLMO was expressed in 24-hour clock time and single DLMO values with respect to the circadian phase definition were interpreted according to the published range of values indicating that: values before 7:30 pm are indicative of an early circadian phase, values between 7:30 pm–10 pm of an intermediate phase and values after 10 pm of a late circadian phase [17].

To compare saliva melatonin secretion patterns, we aligned each of the five saliva samples according to its temporal relationship to the first saliva sample before DLMO. A 7-point curve (three pre- and four post-DLMO) was obtained. The following parameters were taken as a measure of the melatonin secretion pattern following DLMO:

- The saliva melatonin concentration of the first post-DLMO melatonin sample (post-DLMO measure) (pg/mL);
- The melatonin secretion rate shortly after DLMO, expressed as the melatonin surge in the 30-minute time interval following DLMO (post-DLMO surge) (pg/[mL*h]);
- The area under the curve of the post-DLMO semi-curve (AUC) ([pg*h]/mL);
- The area under the curve specifically about the 30-minute time interval of melatonin secretion after DLMO occurrence (AUC30) ([pg*h]/mL);

2.3. Outcome measures

2.3.1. Sleep questionnaire and tests

- MEQ, PSQI and SCI scores.

2.3.2. Melatonin test

DLMO was taken as an objective circadian phase marker.

Other measures of melatonin secretion, namely the post-DLMO measure, post-DLMO surge, AUC, and AUC30, were also taken into consideration in evaluating melatonin secretion patterns.

2.4. Statistical analysis

To calculate the sample size for this study, we referred to the indications of the "Open Source Epidemiologic Statistics for Public Health" (www.openepi.com). Based on literature data and our previous experience [18], we took as meaningful a difference of 45 min in DLMO time between AD patients and HC. The sample size was calculated according to the following parameters: confidence interval (two-sided) 95%, power 80%, ratio of sample size 1, mean difference 45 min, and standard deviation of 60 min for both groups. The suggested minimum number of subjects to be enrolled was 56 (28 per group). The Statistical Package for the Social Sciences (SPSS) for Windows, version 21.0, was used for the statistical analysis with the normality of distribution of all our variables being assessed in terms of "skewness" and "excess kurtosis." All data proved to have a Gaussian distribution. Categorical variables were submitted to cross-tabulation, and statistical significance was evaluated using the chi-square test or Fisher's exact test, where appropriate. As far as continuous variables were concerned, they were expressed as mean values ± standard deviation and differences between groups were tested with ANOVA (analysis of variance) followed by a post hoc Bonferroni test. The level of significance was set at 0.05. AD patients and HC differ significantly for age, AD patients being older. Since age may influence sleep as well as melatonin parameters, any significant difference between AD patients and HC using univariate/bivariate analyses was further tested in a linear regression analysis.

3. Results

Sleep measures and subjective measures of chronotype are detailed in Table 1.

3.1. Sleep measures

Subjective sleep quality did not differ between groups. The percentage of subjects with a PSQI score above 5 did not differ between patients and controls (AD: 38.1%, HC: 29.4%, $p = 0.57$) and neither did the mean PSQI score (AD: 6.24 ± 5.4, HC: 4.47 ± 3.0, $p = 0.24$). AD patients went to bed earlier compared to HC both on workdays (AD 22:42 ± 00:56 vs. HC 23:51 ± 00:27) and free-days (AD 22:44 ± 00:58 vs. HC 23:58 ± 00:58), with the difference being statistically significant ($p < 0.01$). As for SCI, the mean SCI score did not differ significantly between AD patients and HC (26.29 ± 9.1vs 25.45 ± 7.3; $p = 0.08$). The percentage of subjects with an SCI score <16 did not differ between AD patients and HC (11.8% versus 9.1%; $p = 0.823$).

3.2. Subjective measures of chronotype

The mean MEQ score (61.14 ± 7.9 versus 61.14 ± 7.9, $p = 0.116$), as well as the subjective chronotype distribution by global MEQ score, did not differ between Ad patients and HC.

3.3. Melatonin measurements

We failed to calculate DLMO in five patients: in one patient because the quantity of saliva sampling was insufficient to allow a correct melatonin determination; in two patients because the melatonin concentration was consistently below the saliva melatonin threshold of 3 pg; in two other patients because the melatonin concentration proved to be either far higher than the saliva melatonin threshold of 3 pg or showed bizarre fluctuations. Thus DLMO could be calculated in 17 out of the 21 patients examined (86.6%) while it could be calculated in all the controls.

Dim light melatonin onset time and melatonin secretion parameters are detailed in Table 2. On average DLMO occurred significantly later in AD patients than in controls (55 min; $p = 0.028$), with its single values falling within the range of DLMO values indicative of evening chronotype in AD patients and within the range of an intermediate-type in controls (16). Analysis of the semi-curve of saliva melatonin secretion before and after DLMO showed that post-DLMO melatonin measures were significantly lower in AD patients (Fig. 1). This result was confirmed by evaluating the single and global melatonin AUC semi-curve between groups (Fig. 2; $p = 0.001$). The linear regression analysis showed that DLMO was independent from age, while it was statistically related to AD diagnosis (Age, beta: −0.146, $p = 0.501$; AD patients/HC, beta: −0.466, $p = 0.038$, $R = 0.387$).

3.4. Sleep parameters and melatonin measurements according to disease severity

Patients with a global MMSE score >18, indicating a mild cognitive impairment, were compared to those with a global MMSE score ≤18. Neither differences in subjective and objective sleep parameters, nor DLMO and melatonin secretion pattern were found (MEQ mean score $p = 0.827$; Pittsburgh score $p = 0.645$; SCI $p = 0.179$; DLMO $p = 0.698$; AUC $p = 0.605$). No correlation was found between melatonin measurements and NPI.

Table 1
Sleep parameters and subjective chronotypes in AD patients and HC.

		Alzheimer Disease Patients	Healthy Controls	p-value
Age		74.14 ± 5.4	67.47 ± 3.8	**0.001**
Male Sex (%)		11 (52.4%)	10 (58.8%)	0.691
MEQ mean values		61.14 ± 7.9	56.88 ± 8.3	0.116
MEQ	Morningness	11 (52.4%)	7 (41.2%)	0.464
Categorial values	Intermediate	10 (47.6%)	9 (52.9%)	
	Eveningness	0 (0.0%)	1 (5.9%)	
PITTSBURGH SCORE		6.24 ± 5.4	4.47 ± 3.0	0.237
PITTSBURGH SCORE> 5		8 (38.1%)	5 (29.4%)	0.575
SCI		26.29 ± 9.1	25.45 ± 7.3	0.800
SCI < 16		2 (11.8%)	1 (9.1%)	0.823

Bold signifies statistically significant value.

Table 2
Melatonin secretion parameters in AD patients and HC.

		Alzheimer Disease Patients	Healthy Controls	p-value
Age		74.14 ± 5.4	67.47 ± 3.8	**0.001**
Male Sex (%)		11 (52.4%)	10 (58.8%)	0.691
DLMO		22:04 ± 01:31	21:09 ± 00:40	**0.028**
Chronotype according to DLMO	Matt.	0 (0%)	0 (0%)	**0.019**
	Int.	9 (52.9%)	16 (88.9%)	
	Ser.	8 (47.1%)	2 (11.1%)	
AUC-1		1.78 ± 0.7	2.90 ± 0.8	**0.002**
AUC-2		3.19 ± 1.2	5.38 ± 1.9	**0.001**
AUC-3		5.52 ± 2.7	8.5 ± 3.4	**0.012**
AUC-4		6.04 ± 3.0	11.71 ± 5.2	**0.009**
AUC-TOTAL		11.75 ± 6.12	26.11 ± 10.1	**0.001**
AUC-Theoric		4.46 ± 1.4	4.92 ± 1.58	0.386
MELATONIN-1		1.76 ± 0.7	2.14 ± 0.7	0.162
MELATONIN-2		4.70 ± 2.3	4.62 ± 1.2	0.901
MELATONIN-3		6.10 ± 3.8	9.12 ± 6.2	0.107
MELATONIN-4		6.60 ± 3.4	11.09 ± 6.4	0.096
SECRETION		2.92 ± 2.7	3.84 ± 3.2	0.386

Bold signifies statistically significant value.

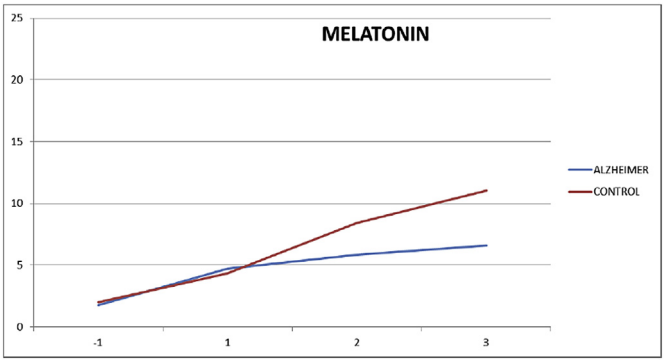

Fig. 1. Melatonin secretion curve in AD patients (blue line) and controls (red line). The X axis represents 60- minute consecutive intervals in relation to DLMO (pre and post-DLMO). The Y axis represents the melatonin concentration in saliva at each point of determination. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

The few literature reports concerning melatonin secretory patterns in AD refer to in-hospital or community-dwelling patients, with overt sleep disturbances in AD patients investigated while kept in standardized conditions. Random, variable patterns of reduced melatonin secretion were reported in 24-hour plasma level melatonin determinations in such AD patients compared to regular nictemeral patterns in controls [3,4]. We investigated the secretory patterns of endogenous melatonin in patients with AD of mild to moderate degree and without comorbidities.

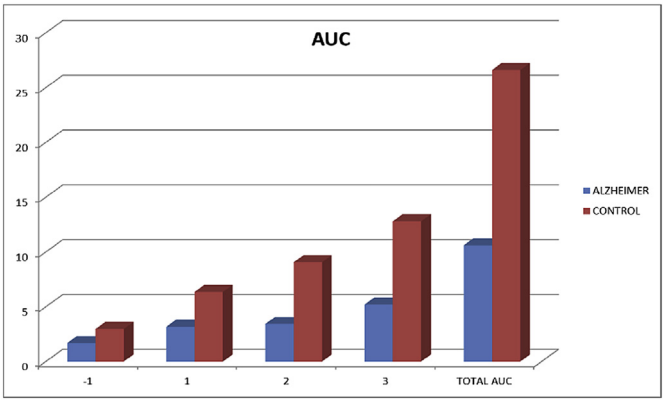

Fig. 2. Under-the-curve area of the melatonin secretion curves (AUC) in relation to DLMO (pre and post-DLMO) in AD patients (blue) and controls (red). ($p = 0.001$). X axis represents 60- minute consecutive intervals in relation to DLMO. The Y axis represents the melatonin concentration in saliva at each point of determination. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Our patients reported mild sleep or no sleep complaints, which is at odds with the high prevalence of sleep disorders reported in AD in the literature [19]. This discrepancy is likely due to the fact that the literature data refers to samples including AD patients with comorbidities and a greater degree of disease severity, while our data pertains to AD patients of a mild to moderate degree of severity and without comorbidities, such as depression and sleep apnea.

In investigating endogenous secretive melatonin patterns, we focused on the timing of melatonin secretion by determining DLMO according to standard melatonin saliva testing. Our data indicate that DLMO tends to occur on average an hour later in AD patients than in HC. Despite this, AD patients tend to go to bed earlier than HC do and in any event, early in respect to their DLMO clock time. This may be due to their withdrawal from social and family activities with a tendency to isolation. To go to bed early with respect to DLMO clock time was reported to play a role in causing insomnia [20]. The discrepancy between bedtime and DLMO clock time in AD could be a potential determinant of insomnia development over time in these patients.

Pre- and post-DLMO values show that melatonin secretion is mildly decreased in our AD patients compared to HC, in keeping with data from the literature documenting a globally decreased melatonin secretion in AD [2,3]. It is known that circadian phase tends to physiologically advance with aging, as documented in studies comparing peak time of plasma melatonin in healthy young and older adults investigated in regular routines as well as in standardized daily routine conditions [21]. By contrast, we found a trend to a delay of the circadian phase in our AD patients in spite of the fact that they were older than HC. Our findings are in keeping with studies documenting delayed rest-activity actigraphic patterns [22] and delayed core body temperature in AD [23].

Circadian phase shifting is reportedly associated with cognitive decline progression in older adults [20], disordered sleep and sleep-related abnormal behavior such as sundown in advanced forms of AD [24].

Our data indicate that altered melatonin secretion may occur in AD patients at an early stage of the disease and who do not have

overt sleep complaints. Based on subjective data, AD patients show a sleep quality similar to that of HC, with only one-third of the patients reporting mildly poor sleep quality. Accordingly, the frequency of an insomnia disorder as assessed by the SCI is low in our AD patients and not statistically different from that of HC.

MEQ scores are similar in patients and controls and indicate an intermediate subjective chronotype. Albeit within the limits of AD patients potential misjudgment due to cognitive deficits and anosognosia [25], the data indicate a well-preserved sleep quality and neutral subjective chronotype in our AD patients. Thus, the melatonin secretion alterations we found would represent an early sign of melatonin secretion dysregulation in AD. Additional and longitudinal data are warranted to confirm the present findings and to clarify their ultimate neurobiological meaning and clinical importance in AD. These data could pave the way to new therapeutic strategies in AD by exploiting the chronobiotic properties of melatonin in resetting circadian rhythms.

Our paper suffers from some limitations. Seven-day actigraphic monitoring would have provided a more reliable evaluation of sleep-wake patterns in patients and controls. Even though instrumental monitoring is not required during the in-home melatonin saliva test, actigraphic monitoring along with a light sensor would have provided reliable measures of rest-activity patterns of the patients and their compliance concerning staying in a dark environment while performing the test.

5. Conclusions

Initial evening secretion of melatonin proves to be delayed and mildly impaired in patients with a mild/moderate form of AD while patient's subjective sleep parameters and chronotype are reported similar to those of healthy controls. This data indicates that subclinical altered patterns of melatonin secretion occur in subjects with AD at an early stage of the disease.

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Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.04.018.

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