Experimental Gerontology 72 (2015) 45–49

Contents lists available at ScienceDirect

Experimental Gerontology

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

# The diurnal profile of melatonin during delirium in elderly patients—preliminary results

Karolina Piotrowicz [a,*], Alicja Klich-Rączka [a], Agnieszka Pac [b], Anna Zdzienicka [c], Tomasz Grodzicki [a]

[a] Department of Internal Medicine and Gerontology, Jagiellonian University Medical College, Krakow, Poland
[b] Chair of Epidemiology and Preventive Medicine, Jagiellonian University Medical College, Kraków, Poland
[c] Department of Clinical Biochemistry, Jagiellonian University Medical College, Kraków, Poland

ARTICLE INFO

*Article history:*
Received 27 May 2015
Received in revised form 31 August 2015
Accepted 7 September 2015
Available online 11 September 2015

Section Editor: Christian Humpel

*Keywords:*
Delirium
Melatonin
Circadian rhythm
Elderly
Pathophysiology

ABSTRACT

Delirium is an acute-onset syndrome that exacerbates patients' condition and significantly increases consequential morbidity and mortality. There is no comprehensive, cellular and tissue-level, pathophysiological theory. The melatonin hormone imbalance has been shown to be linked to circadian rhythms, sleep–wake cycle disturbances, and delirium incidence. There has been relatively little research about melatonin in delirium, and there has been no such study done in the group of elderly patients of a general medicine ward yet.

The aim of our study was to compare melatonin hormone concentration in relation to the presence of delirium in elderly patients hospitalized in the general medicine ward.

Blood samples were collected four times a day for two days (at 12:00, 18:00, 00:00 and 6:00), on the day when delirium was diagnosed and 72 h after the delirium resolution. Delirium was diagnosed with the Confusion Assessment Method and the criteria of the Diagnostic and Statistic Manual of Mental Disorders, 4th Revision.

The mean age of 30 patients (73.3% women) was 86.5 ± 5.2 years. Delirium was diagnosed most often on the second and third day of hospitalization. A lot of predisposing and precipitating factors for delirium were identified. There was a significant difference in the melatonin hormone concentration measurement at 12:00 when patients had acute delirium and after its resolution [18.5 (13.8, 27.5) vs 12.9 (9.8, 17.8), $p < 0.01$]. Different patterns of the melatonin hormone concentration were shown in analyses in the subgroups defined according to the patients' diagnosis of dementia.

We found that the delirium recovery was, in fact, associated with the alteration of the daily profile of melatonin.



## 1. Introduction

### 1.1. Background

Delirium is an acute-onset syndrome that substantially exacerbates patients' condition, impedes their recovery process and significantly increases consequential morbidity and mortality (NICE, 2010).

It is known that delirium in hospital settings may affect up to 20–30% of elderly patients, and therefore as a prevalent, both a symptom and also a risk factor for negative clinical outcomes, is under the scope of both geriatricians and researchers in gerontology and geriatrics (NICE, 2010; Meagher et al., 2014).

Numerous causes and circumstances may contribute to the incidence of delirium. The strong relationship between delirium and advanced age, prior brain degeneration and cognitive impairment, acute medical states resulting in dehydration and hypoxemia, severe concomitant diseases attributing to the acid–base imbalance and metabolic disturbances as well as drugs, have all been listed (Inouye, 2006; Vasilevskis et al., 2012; Michaud et al., 2007).

The question is, which cellular and tissue-level mechanisms may be linked to the occurrence of delirium, its manifestation and resolution.

Despite the wide knowledge about delirium, there has still been no comprehensive theory describing its pathophysiology.

One of the mechanisms responsible for delirium development might be the change in the circadian rhythms of the melatonin hormone.

Melatonin is a hormone produced and secreted by the pineal gland. Melatonin has several effects. This hormone regulates the sleep–wake cycle and other circadian rhythms, and also has antioxidative and immunomodulating properties (Reiter et al., 2013; Reiter et al., 2011).

Some studies investigating the relationship between disturbed melatonin rhythms and delirium have been conducted in the Intensive Care Unit (ICU) (Elliott and Nathaney, 2014; Li et al., 2013). There is some research in melatonin among elderly patients in the perioperative periods (Miyazaki et al., 2003; Yoshitaka et al., 2013; Shigeta et al., 2001).

We hypothesized that melatonin hormone circadian rhythm disturbances are linked to delirium onset, and melatonin circadian rhythm restoration is important in delirium recovery. We considered a 72-hour time period to be sufficient for recovery of the melatonin circadian

* Corresponding author at: Department of Internal Medicine and Gerontology, Jagiellonian University Medical College, Śniadeckich 10 Str., 31-351 Krakow, Poland.
*E-mail address:* zona3@interia.pl (K. Piotrowicz).

http://dx.doi.org/10.1016/j.exger.2015.09.007
0531-5565/

rhythms with minimum risk for prolonged hospitalization and in-hospital medical complications.

We decided to examine the patients at the age of 75 and older who, according to the World Health Organization's (WHO) definition, constitute a growing population of those of middle old age and very old age. Those patients are the most vulnerable to delirium and due to the aging process, represent a distinct clinical and pathophysiological entity.

### 1.2. Objective

The aim of the study was to compare melatonin hormone concentration in relation to the presence of delirium in elderly patients hospitalized in the general medicine ward.

## 2. Materials and methods

### 2.1. Study population and study methods

The patients for the study were recruited from elderly patients of the general medicine ward of the tertiary teaching hospital in Kraków. All the patients who were admitted to a hospital at the time of the research and agreed to participate in the study were assessed by a geriatrician. This examination was performed within the first 24 h of hospitalization or within a maximum of 72 h on weekends. Two doctors (KP, AKR), of whom one is an expert in geriatrics, did the patients' daily assessment and discussed the results with the leading physicians. In the case of delirium being presented on the day of admission, the patient's caregivers were questioned, in a structured way, in accordance with the Confusion Assessment Method (CAM) shortened version worksheet, in order to confirm the diagnosis of delirium.

Inclusion criteria:

- age ≥ 75 years,
- acute delirium diagnosed on the day of admission to hospital or diagnosed later on during hospitalization.

Exclusion criteria:

- life expectancy <24 h,
- subacute or chronic delirium.

We got the informed consent and obtained melatonin measurements on the day of delirium onset from 65 patients who met the inclusion and exclusion criteria, out of the total number of 2495 patients who were hospitalized in our ward and asked for consent from September 2008 to December 2011. 30 of them had a follow-up observation and 8 measurements of melatonin hormone carried out (data presented in our paper).

The screening for delirium was conducted with a shortened, 4-item Confusion Assessment Method Diagnostic Algorithm once a day. Additionally, information about patients' behavior, which might have been indicative for delirium, was gathered from the nurses' daily reports and taken into consideration. Delirium was diagnosed using the Confusion Assessment Method and the criteria of the Diagnostic and Statistic Manual of Mental Disorders, 4th Revision (DSM-IV) (Inouye, 2003; DSM-IV Diagnostic Codes). CAM is a standardized, 9-item detection tool designed for physicians without training in psychiatry (Inouye, 2003). Both raters, employed in the study, had followed the recommended training procedures for CAM prior the research. CAM questionnaire, training manual and coding guide (Inouye, 2003) had been translated into Polish and tested in the pilot study (Klich-Rączka and Piotrowicz, 2009). The blood samples were collected four times a day for two days, that is on the day when delirium was detected and 72 h after delirium resolution, at 12:00, 18:00, 00:00 and 6:00 (10-min shift of time was acceptable). Blood was obtained via venipuncture. The concentration of melatonin hormone was measured in the serum samples with the radioimmunoassay method (*Labor Diagnostika Nord GmbH & Co. KG*) with a limit of detection of 2 pg/ml (intra-assay precision CV = 9.7%, inter-assay precision CV = 10.9%). Blood samples were stored at −80 °C. All the steps for blood collection, specimen storage and test procedures were performed according to the manufacturer's instructions. Light protocol was applied. Except life-threatening situations, strong-light avoidance during sleeping hours was strongly recommended. Dim lights were suggested to be the only source of artificial light between 22:00 and 6:00. Maximum recommended illuminance was no stronger than 100 lx measured with a portable light meter (*Standard ST-1301*). The study was conducted throughout the year with the seasonal sun-light exposure typical for the Central Europe countries.

Information on chronic diseases, acute somatic states and other precipitating factors for delirium, as well as the reasons for current admission to the hospital were gathered from the patient's medical charts. The diagnosis of dementia had been made according to the DSM-IV criteria and was documented in the medical records. All demographic data and medical history was collected from the patients' medical records retrospectively. The median number (Q1;Q3) of chronic diseases was calculated for: hypertension, cardiovascular disease, chronic heart failure, atrial fibrillation, diabetes mellitus t2, chronic obstructive pulmonary disease, chronic kidney diseases, dementia, stroke (in the past medical history), other neurologic disorders, and neoplasm.

The study was performed according to the Helsinki Declaration with the approval of the Ethics Committee of the Jagiellonian University Medical College in Kraków (KBET/115/B/2008). Written consents were obtained from all examined patients or their representatives. The project was registered in the internal database of research projects of the Jagiellonian University Medical College with the symbol of K/ZDS/000627.

### 2.2. Statistical analysis

We used medians and quartiles because of the non-normal distribution of melatonin hormone concentration, as well as a small number of patients, to describe the melatonin hormone concentration.

We used the nonparametric Wilcoxon test for paired data to compare the results between two time periods — the period of acute delirium with the period 72 h after delirium resolution. We performed some analyses in the subgroups defined according to patients' diagnosis of dementia (demented vs non-demented).

Statistical analyses were performed using STATASE 12 [StataCorp., Texas, USA]. The level of statistical significance was set at 0.05.

## 3. Results

The examined group consisted of 30 patients at the mean age of 86.5 ± 5.2 years; median: 85, min.–max.: 78–98 years. The group included 22 women (73.3%); none of the patients had been institutionalized before the hospital admission. There was no difference in age between men and women.

Delirium was diagnosed most often on the second and third day of hospitalization (40%). The time of follow-up was between 3 and 21 days (median: 4.5 days).

Baseline characteristics of the patients, including chronic concomitant diseases, acute medical conditions, medication use and other found precipitating factors for delirium, were presented in Table 1.

There was a significant difference in the melatonin hormone concentration measurement at 12:00 when patients had acute delirium and after its resolution. There were no differences in melatonin hormone concentration in the time of acute delirium and 72 h after its resolution was measured at any other specified time (18:00, 00:00 and 6:00). The results were shown in Table 2.