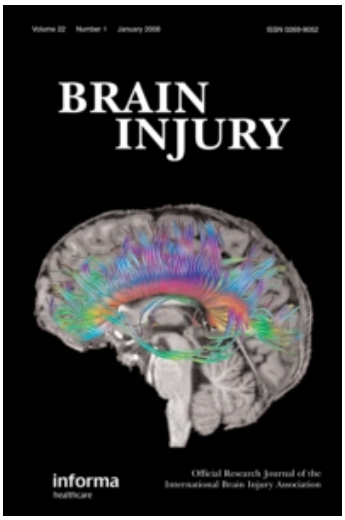

Brain Injury
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713394000

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Online Publication Date: 01 October 2009

To cite this Article Bekinschtein, T. A., Golombek, D. A., Simonetta, S. H., Coleman, M. R. and Manes, F. F.(2009)'Circadian rhythms in the vegetative state',Brain Injury,23:11,915 — 919
To link to this Article: DOI: 10.1080/02699050903283197
URL: http://dx.doi.org/10.1080/02699050903283197

Brain Injury, October 2009; 23(11): 915–919

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Circadian rhythms in the vegetative state

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(Received 26 March 2009; revised 13 August 2009; accepted 24 August 2009)

Abstract

Objective: To evaluate whether vegetative state patients maintain circadian rhythms.
Research design: An observational study of five single cases.
Methods and procedures: Five chronic vegetative state patients underwent clinical and neurological evaluations and 2-week continuous temperature measurements.
Main outcomes and results: The two patients with traumatic brain injury showed well-formed circadian temperature rhythms and had more reflexive behaviours and relatively low cortical and sub-cortical atrophy, whereas the three patients from anoxic-hypoxic origin demonstrated no cycles or rhythmic behaviour.
Conclusions: The presence of periods of wakefulness does not imply preserved sleep–wake cycling capacity, nor preserved circadian rhythms and it should not be taken as a distinguishing feature for the definition of the vegetative state.

Keywords: *vegetative state, circadian rhythms, body temperature, guidelines*

Introduction

The vegetative state (VS) is defined as a condition of wakefulness without awareness, characterized behaviourally by fluctuating arousal and only reflex responses to stimulation [1, 2]. International guidelines for the diagnosis of VS states that there are typically cycles of eye opening and closure giving the impression of a sleep–wake cycle [1, 2]. Together with evidence of eye opening, the presence of a sleep–wake cycle forms the threshold at which someone is said to have progressed from a comatose state to a vegetative state. However, despite the importance of this cycle to diagnosis, there is little empirical evidence that vegetative patients actually exhibit sleep phenomena on electroencephalogram or display a circadian rhythm.

Sleep–wake cycles are typically inferred by behavioural observations of long periods of eye closure or a change in respiratory pattern. Seldom is an electroencephalogram recorded clinically in this patient group to identify sleep phenomena. Previous research has recorded 24-hour variations in electroencephalographic patterns [3], hormones and blood pressure [4–6], obtaining variable results, but no study has addressed true cycling, circadian capabilities. To define the rhythmicity of a behavioural or physiological measure it is necessary to sample at least six points per day for 3 consecutive days [7] and this study is the first to follow these guidelines. One early study reported day/night brain state differences in eight out of 12 VS patients using continuous EEG and the remaining four patients showed the same EEG pattern during day and night [3]. Three other studies measured blood pressure, heart rate, temperature and urinary excretion hormones, blood pressure and heart rate and growth

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ISSN 0269–9052 print/ISSN 1362–301X online
DOI: 10.1080/02699050903283197

hormone, prolactine and cortisol. Significant day–night changes were found in body temperature and urine hormones, but not in blood pressure [5], significantly lower day–night difference in blood pressure as compared to normal volunteers [4] and shorter hormones mean peak duration in patients than in control subjects [6]. With previous research giving a mixed view on evidence for day–night differences in VS patients, the aim of this study was to evaluate whether patients meeting vegetative state criteria maintain a circadian rhythm consistent with changes in light intensity and environmental stimulation using temperature measurements.

Materials and methods

This study investigated five patients with brain injury, meeting the criteria defining the vegetative state (male $n=2$; at least 5 months post-ictus) with continuous skin temperature measurements recorded for 13–16 days to address circadian capabilities. Skin temperature was sampled every 15 minutes by means of a DS1921H iButton sensor [8]. These measurements were compared with nursing staff records, obtained approximately every 4 hours, detailing whether the patient had their eyes open or closed. Four points were assigned to the day period and two points to the night period for each day.

Case descriptions

Patient S1 was hospitalized after being hit by a car. She was rendered unconscious immediately. Two months later, she scored very low on behavioural scales, presenting just a few spared reflexes. Patient consciousness level was assessed following the Task Force on PVS Guidelines [1] and she was diagnosed with PVS. In the fifth month post-ictus, following 3 weeks of pro-dopaminergic drug administration, the patient briefly oriented to sound and voices on her left side and exhibited inconsistent visual fixation. According to the CRS guidelines fixation is considered a criteria for MCS but not for the Royal College of physicians [2], which this study follows. Some weeks later, the patient developed extreme sweating and other side-effects to the medication and, when continuous temperature measurements started, the patient was no longer under medication and her behavioural range regressed to basic reflexes.

Patient S2 suffered severe head trauma following a motor vehicle accident and post-operative ischemic events which resulted in PVS. He scored low on behavioural scales in the first 3 months. During the 4th month, following the administration of pro-dopaminergic medication, the patients' behavioural portfolio increased. When this evaluation was conducted the patient could fixate briefly to a bright object if presented in his line of view; he also showed mechanical vocalization, such as a yawn or sigh. The patient's MRI revealed cortical atrophy, diencephalic contusion, a left temporoinsular contusion haemorrhage spreading into the putamen and a semioval centre contusion. Due to open head injury, he also showed frontal lobe damage.

Patient S3 suffered cardiac arrest during surgery leading to anoxic events in the brain. The patient was reanimated but never regained consciousness from anaesthesia. He had a Glasgow Coma Scale of 4/15 when first evaluated and has remained in VS for several years. A full behavioural evaluation observed preserved taste, eyeblink, startle and withdrawal reflexes, the patient also showed facial grimacing to noxious stimuli but no localization. The anatomical MRI revealed severe cortical and sub-cortical atrophy and ventriculomegaly.

Patient S4 had severe cardiac arrest during cosmetic surgery resulting in a comatose state progressing to vegetative in the course of 4 weeks after the hypoxi-anoxic event. She had low responsiveness during behavioural assessments, limited to arousal fluctuations when tilted vertically. The patient demonstrated relatively preserved withdrawal, threat and eyeblink reflexes on the left side but inconsistently on the right side. The MRI showed severe cortical atrophy with basal ganglia hyperintensities due to ischemic encephalopathy.

Patient S5 was taken to the hospital where investigations determined she had meningococcal meningitis. CT scan on acute admission showed generalized cerebral swelling with signal changes in the brainstem and bilateral temporal lobes. A week later she suffered a massive left hemisphere stroke. Two weeks later the patient was opening her eyes, but no other responses were noted. During hospitalization, she was diagnosed as being in a vegetative state. Upon behavioural examination, she appeared to fixate; however, over prolonged and repeated assessment, this behaviour was not reproducible and disappeared in the following weeks. She demonstrated head rolling, facial grimacing, teeth grinding and groaning occurring spontaneously. She had preserved reflexes to tactile, olfactory and painful stimuli; reflex responses to threat were inconsistent. Her MRI scan showed dilated lateral ventricles (more on the left side), severe cortical atrophy and left subcortical displacement.

Atrophy

This study assessed the degree of cortical and subcortical atrophy using a visual scale inspired in the scale developed by Galton et al. [9]. It first defined,

using T1-3D anatomical images, atrophy levels from 0–4 (0 = no atrophy, 1 = very low, 2 = mild, 3 = severe and 4 = highly severe atrophy) in a group of 12 patients with neurodegenerative disorders and applied the scale to the VS patients (see Table I). Patients' T1-weighted and T2/PD images were assessed by two experienced raters (T.B. and F.M.). Briefly, hard copies of the coronal MRI images of 12 patients of mixed diagnoses were assessed by blinded raters (T.B. and F.M.) with the names of the patients obscured. The scans were presented randomly. The scale used a handful of single measure per region based on the initial measures which had the best agreement between raters in the pilot studies [10].

The indices for the different lobes were calculated from the centre of the thalamus to the most distant cortical gyrus. The depth of the atrophy was calculated from the top part of three gyri in each lobe to the bottom of the adjacent sulci. Sub-cortical structures were rated from 0–4 based on the putamen and caudate length and combined perimeter and thalamus diameter.

A signed assent from the patient's next of kin was obtained prior to participation. The Ethics and Research Committee in Buenos Aires approved the study. None of the patients' family withdrew assent. All five patients met the clinical diagnostic criteria defining the vegetative state and signs of awareness were checked to rule out minimal conscious processing in agreement with the Aspen Neurobehavioural Conference Workgroup guidelines [11] and the Royal College of Physicians Guidelines [2]. All patients were evaluated with the Revised Coma Recovery Scale (CRS-R) [12]. Demographics and basic neurological and behavioural data from the patients are shown in Table I.

Results

Two patients (S1 and S2) showed well-formed circadian temperature rhythms according to autocorrelation and Chi-square periodograms (S1, $Qp = 650$, $p < 0.05$; S2, $Qp = 443$, $p < 0.005$) with peaks at 24 hours and 45 minutes and 24 hours and 35 minutes (Figures 1(a) and (b)), which were in agreement with eyes open/close cycle charts. A clear 24-hour peak was detected in the temperature autocorrelograms (Figures 1(a) and (b), right hand column), while robust cosine waveforms were significantly fitted to the data. Patient S3's rhythmicity approached significance (S3, $Qp = 340$, $p = 0.07$) (Figure 1(c)), consistent with behavioural observations. S4 and S5 showed no open/close eyes cycling or skin temperature rhythm (Chi-square periodogram, N.S., no 24-hour component in the autocorrelogram) with high variability for both day and night hours and low autocorrelation (Figures 1(d) and (e)). This study compared day and night nurse's chart results for each patient, finding significant differences in S1 ($p < 0.001$), S2 ($p < 0.001$) and S3 ($p < 0.05$, Mc Nemar's Test, two tailed) but not for S4 and S5.

Cortical atrophy (Table I) in the patients was severe (S3 and S5) or highly severe (S4). Sub-cortical atrophy was severe (S5) or highly severe (S3, S4) in the three anoxic-hypoxic patients. In contrast, cortical and sub-cortical atrophy in the TBI patients was mild (S1) or very low (S2). Also in agreement with rhythms and degree of atrophy, S1 and S2 showed a wider repertoire of reflexive behaviours and less cortical and sub-cortical atrophy.

Discussion

This study found a preserved circadian rhythm in only two out of five patients meeting the criteria defining the vegetative state. The preserved circadian rhythm was observed in the two patients with traumatic brain injuries, absent in two patients with non-traumatic hypoxic injuries and one anoxic patient showed weak rhythmicity. This finding is consistent with previous observations using electroencephalography [3] and suggests circadian rhythms are not maintained by all patients in the vegetative state. Nevertheless, not all the evidence converges

Table I. Patients' demographic data and behavioural scores.

	Months from ictus	Age	CRS	Outcome	Cortical atrophy	Sub-cortical atrophy	Aetiology
S1	13	30	9 (2+1+2+2+0+2)*	VS	1	1	TBI
S2	5	24	8 (2+1+2+1+0+2)	VS	2	2	TBI
S3	6	22	6 (1+1+1+1+0+2)	VS	3	4	Anoxic-ischemic (cardiac arrest)
S4	24	25	5 (1+1+1+0+0+2)	VS	4	4	Anoxic-ischemic (cardiac arrest)
S5	7	67	6 (2+1+1+0+0+2)	VS	3	3	Anoxic-ischemic (stroke)

CRS = Coma Recovery Scale (Revised) Scores are expressed as total score (auditory + visual + motor + oromotor + communication + arousal sub-scales). The usual criteria for VS is a CRS of 8 or less, only S1 showed a score of 9 (Fixation in the visual sub-scale). The atrophy visual scale goes from 0 (no atrophy) to 4 (highly severe atrophy). *S1 highest CRS score was 9 but when temperature was measured he regressed to a score of 6 due to adverse events and subsequent withdrawal of pro-dopaminergic medication.

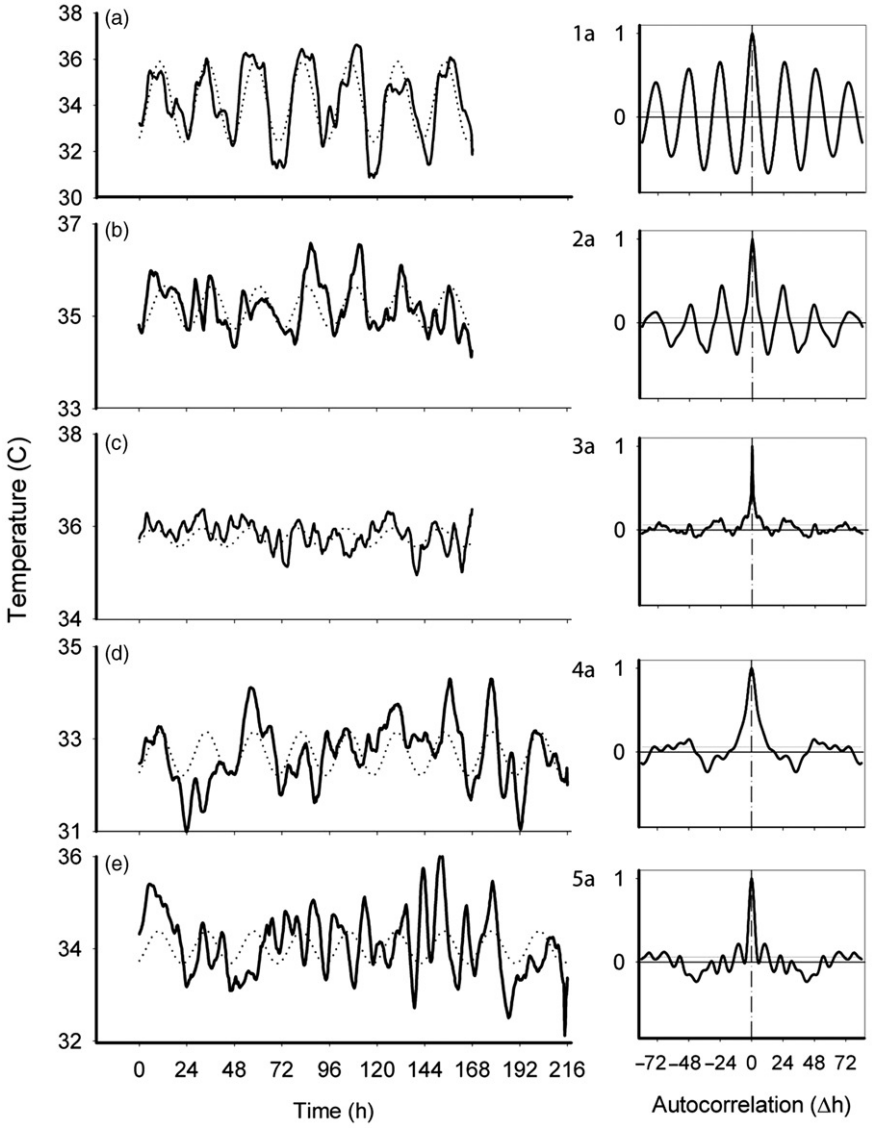

Figure 1. Temperature patterns in five vegetative state patients. Graphs on the left show each patient's 1-week temperature measurements and a fitted cosine function. Only S1 and S2 show circadian patterns. Graphs on the right are autocorrelograms of the temperature data, S1 and S2 show 24, 48 and 72 hours peaks consistent with circadian rhythmicity.

to the same results; there have been reports of temperature rhythmicity in comatose patients in the ICU [13].

Cause of injury may play a role in explaining the differences this study suggests between TBI and non-TBI vegetative state patients. Indeed, TBI tends to be more circumscribed to lesions in the cortex and thalamocortical/corticortical connections, not necessarily related to the establishment and maintenance of circadian rhythmicity. These results support, in a neurophysiologic manner, a common finding in severely disabled and vegetative state patients—i.e. that hypoxic brain injury is often more disruptive (physiologically and cognitively) than TBI. This is probably related to differences in the underlying pathology. After TBI, this mainly comprises contusional and diffuse shearing axonal and vascular injury, with relative sparing of the cerebral cortex. After ischemic and anoxic brain injury, however, the pathology comprises more diffuse cortical, basal ganglia and hippocampal damage [14], perhaps affecting medial or inner parts of the brain first, including autonomic regulation areas of basic functions such as biological rhythms. In particular, models of hypoxia-related brain injury have been reported to exhibit critical impairments in sleep–wake regulation [15] and neuropeptide rhythms [16], as well as in clock gene expression [17]. In particular, a key regulator of clock gene expression is the hypoxia-inducible factor 1α (HIF-1α) [18,19], which might be implied in the circadian changes observed in patients with hypoxic brain injury.

Wakefulness assessment is a key feature to define the patient's state of consciousness and for

diagnostic criteria of VS. Its detection in clinical settings typically requires medical charts that do not suffice to define the different types of wakefulness that can be found in pathologies of consciousness. Patients showing no sleep–wake cycles but spontaneous eye opening and preserved reflexes (like S4 and S5) may still be classified as being in vegetative state, since they show minimal responsiveness and do not fit in the chronic coma definition. Circadian rhythms may be used as a measure of physiological state and/or prognosis [20], since hypothalamic and midbrain functions can be inferred from different circadian parameters.

This study represents a first attempt to characterize the VS from a circadian point of view. Nevertheless, the small sample size in this study represents a limitation for the conclusions, since these patients represent only a few cases in the highly heterogeneous population of patients with disorders of consciousness. However, even with a small sample, the disparity between TBI and hypoxia-related brain injury patients is striking and suggests a clear differentiation between both groups of subjects. Moreover, as has recently been reported elsewhere [21], the circadian prognosis in each case might predict the potential outcome of the diverse disorders of consciousness, therefore becoming an important tool when assessing diagnostic and therapeutic measurements as well as steps to be taken with these patients.

Further large scale studies are needed to characterize circadian rhythms in VS patients and to examine the impact of different aetiologies (i.e. TBI or hypoxic) on circadian parameters.

Acknowledgements

This research was supported by the following grants: Antorchas Foundation (TAB) and PICT (DAG). We thank the patients and their families for their participation.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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