Clinical Neurophysiology 127 (2016) 1445–1451

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

The prognostic value of sleep patterns in disorders of consciousness in the sub-acute phase

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ARTICLE INFO

Article history:
Accepted 17 October 2015
Available online 6 November 2015

Keywords:
Sleep
Vegetative state
Minimally conscious state
Coma
EEG

HIGHLIGHTS

- Regular sleep structure is a good predictor of clinical outcome in sub-acute DOC patients.
- Regular sleep structure is stronger than other known prognostic factors of DOC outcome.
- Visual-quantitative sleep analysis is helpful in the prognostic evaluation of DOCs.

ABSTRACT

Objective: This study aimed to evaluate, through polysomnographic analysis, the prognostic value of sleep patterns, compared to other prognostic factors, in patients with disorders of consciousness (DOCs) in the sub-acute phase.
Methods: Twenty-seven patients underwent 24-h polysomnography and clinical evaluation 3.5 ± 2 months after brain injury. Their clinical outcome was assessed 18.5 ± 9.9 months later. Polysomnographic recordings were evaluated using visual and quantitative indexes. A general linear model was applied to identify features able to predict clinical outcome. Clinical status at follow-up was analysed as a function of the baseline clinical status, the interval between brain injury and follow-up evaluation, patient age and gender, the aetiology of the injury, the lesion site, and visual and quantitative sleep indexes.
Results: A better clinical outcome was predicted by a visual index indicating the presence of sleep integrity ($p = 0.0006$), a better baseline clinical status ($p = 0.014$), and younger age ($p = 0.031$). Addition of the quantitative sleep index strengthened the prediction.
Conclusions: More structured sleep emerged as a valuable predictor of a positive clinical outcome in sub-acute DOC patients, even stronger than established predictors (e.g. age and baseline clinical condition).
Significance: Both visual and quantitative sleep evaluation could be helpful in predicting clinical outcome in sub-acute DOCs.

1. Introduction

The outcome of patients with disorders of consciousness (DOCs) remains difficult to predict. A key factor to consider is the duration of the DOC, as the prognosis worsens the longer the patient is in the condition (MSTF, 1994; Lammi et al., 2005; Katz et al., 2009). The identification, in the sub-acute phase, of further prognostic factors could allow better planning of treatment and rehabilitation for patients in the early stages of DOCs. The patient's age, the type of brain injury (Bernat, 2006; Monti et al., 2010), and the severity of the DOC (Katz et al., 2009; Luauté et al., 2010) are well-known prognostic factors in this setting; patients in the minimally conscious state (MCS) have been found to have a better prognosis than those in a vegetative state/unresponsive wakefulness syndrome (VS/UWS). Even though MCS patients showed a better prognosis

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http://dx.doi.org/10.1016/j.clinph.2015.10.042
1388-2457/

than VS/UWS patients, differential diagnosis between these two conditions continues to be challenging (Schnakers et al., 2009). Moreover, the boundaries between MCS and VS/UWS are elusive (Guldenmund et al., 2012) and there actually exist intermediate states between the two conditions (Monti et al., 2010). It is therefore believed that viewing DOCs as a continuum of different levels of consciousness may allow a more realistic assessment of patients' clinical status and prognosis.

The presence of regular sleep patterns could reflect preserved brain functioning, and the diagnostic and prognostic value of sleep in DOCs is a topic of growing interest (Cologan et al., 2010). However, most of the available studies were published before the definition of MCS (Giacino et al., 2002), and thus refer to a clinical framework that does not reflect current opinion. The studies conducted prior to the definition of MCS showed persistence of non-REM (NREM) sleep patterns (D'Aleo et al., 1994a,b; Evans and Bartlett, 1995; Giubilei et al., 1995; Oksenberg et al., 2001; Isono et al., 2002; Valente et al., 2002) and the sporadic presence of REM sleep markers (Gordon and Oksenberg, 1993; D'Aleo et al., 1994b; Oksenberg et al., 2001; Valente et al., 2002) in VS patients. In addition, the presence of organised sleep patterns was proposed as a reliable prognostic marker in post-traumatic coma patients (Valente et al., 2002) and in severe head-injured patients (Evans and Bartlett, 1995). However, none of these studies compared the prognostic value of sleep analysis with that of other, known prognostic markers.

Five studies (Landsness et al., 2011; Cologan et al., 2013; de Biase et al., 2014; Kang et al., 2014; Rossi Sebastiano et al., 2015) have been conducted since the definition of MCS (Giacino et al., 2002). Three of these (Landsness et al., 2011; de Biase et al., 2014; Rossi Sebastiano et al., 2015) focused on the diagnostic rather than the prognostic value of sleep analysis in DOCs. However, in one of them (Rossi Sebastiano et al., 2015), an assessment protocol based on multiple neurophysiological tests, including sleep evaluation, was found to provide significant information about residual functioning in chronic DOC patients.

Most of the above studies investigated heterogeneous samples that included DOC patients in the acute, sub-acute or chronic stages. Cologan et al. (2013), studying a group of sub-acute DOC patients, found that a large amount of standard spindles was associated with a better clinical outcome. However, the prognostic value of sleep integrity compared to other prognostic factors was not assessed. Finally, Kang et al. (2014) recently proposed a bedside scoring system for predicting awareness recovery in sub-acute UWS patients. Their score (Kang et al., 2014) includes clinical and neurophysiological parameters, such as the presence/absence of sleep spindles. However, their study did not include MCS patients.

The present study set out to compare the potential prognostic value of sleep/wake patterns (their persistence and various features) to that of other, known prognostic factors in sub-acute DOCs. To this end, we combined clinical evaluation with the use of a sleep-structure integrity index, created on the basis of relevant literature data. We also explored whether and how quantitative EEG spectral analysis parameters might be of prognostic value. Both VS/UWS and MCS patients were included in the study. These conditions were considered to lie on a continuum of different levels of consciousness.

2. Methods

2.1. Patients

The study involved 31 non-sedated, spontaneously breathing DOC patients, admitted consecutively to the Coma Unit at the "S. Maugeri" Foundation (Pavia, Italy) over a period of 30 months. The patients underwent neurological examination, brain imaging (CT or MRI) and standard EEG studies. The Italian version of the Coma Recovery Scale-Revised (CRS-R) (Sacco et al., 2011) was used for clinical assessment. Once the patients were in a stable condition, they were admitted to the Coma Unit and sleep–wake patterns were investigated by means of 24-h polysomnography (PSG) at the bedside. The time needed to achieve clinical stabilisation varied among the patients. Thus, the interval between brain injury and PSG recording also varied (range: 1–11 months; mean: 3.5 ± 2).

Twenty-seven of the 31 patients were in the sub-acute stage (1–6 months since anoxic/haemorrhagic brain injury or 1–12 months since traumatic brain injury) at the time of PSG and were therefore included in the study (18 males, mean age: 52.6 ± 19.4 years). These patients were repeatedly evaluated using the CRS-R during standard clinical management and, for the purposes of this study, the last available data were considered. The duration of the follow-up after PSG ranged between six and 38 months (mean: 18.5 ± 9.9). Eight patients died; the follow-up in these patients lasted between six and 37 months (mean: 20 ± 11), and they were assigned a CRS-R score of 0. Table 1 reports the main demographic and clinical characteristics of the patients included in the study. The study protocol was approved by the local ethics committee and an informed consent form was signed by all the participants, or by their legal guardians, in compliance with the Helsinki Declaration of 1975.

2.2. Sleep

Polysomnography was carried out at the Neurorehabilitation Unit of the S. Maugeri Foundation by neurophysiology technicians with expertise in the recording of sleep and consciousness. The recordings were then evaluated at the Sleep Unit of the C. Mondino National Institute of Neurology Foundation (Pavia, Italy). Sleep scoring was performed by neurologists specialised in sleep medicine (R.M. and M.T.). All the patients were continuously recorded for 24 h in the Coma Unit environment by means of a portable PSG system at the bedside (BS Pocket Polygraph 2100, Micromed, Treviso, Italy). A 24-h log was used to record information about nursing interventions, light–dark timing and other environmental parameters. EEG electrodes (*F*3, *F*4, *C*3, *C*4, *O*1, *O*2, *A*1, *A*2) were positioned according to the 10–20 international system, referred to a common electrode placed in *Fz* and with a ground electrode placed in *Fpz*. Even though DOC patients often present skull wounds, in all our cases the EEG electrodes were successfully placed in at least one hemisphere. Disposable cup electrodes with conductive paste were used. Electrode impedances were checked at the beginning of the recording and values of up to 5 kΩ were allowed. Acquired EEG signals were then re-referenced to the contralateral earlobe, and signals from bipolar (frontocentral and centro-occipital) derivations were also computed for the subsequent visual and quantitative analysis. Electro-oculographic (EOG) electrodes (horizontal bipolar montage) and electromyographic (EMG) chin electrodes were placed according to standard criteria (Iber et al., 2007). All signals were stored with a sampling rate of 128 Hz after band-pass filtering at 0.3–35 Hz for EEG and EOG, and 10–50 Hz for EMG. Standard markers of both NREM sleep (spindles, K-complexes and slow waves) and REM sleep (rapid eye movements, saw-tooth waves and muscle atonia) were used, whenever possible, to identify and characterise sleep patterns and to allow us to score recording epochs according to the current criteria (Iber et al., 2007). We then used an index of sleep structure, created by us on the basis of the current literature (Valente et al., 2002; Cologan et al., 2010, 2013), to classify each recording, as a