Fragmentation of Slow Wave Sleep after Onset of Complete Locked-In State

Surjo R. Soekadar, M.D.^{1,2}; Jan Born, Ph.D.¹; Niels Birbaumer, Ph.D.^{1,3}; Michael Bensch, Ph.D.⁴; Sebastian Halder, Ph.D.^{1,4}; Ander Ramos Murguialday, Ph.D.^{1,6}; Alireza Gharabaghi, M.D.⁷; Femke Nijboer, Ph.D.^{1,8}; Bernhard Schölkopf, Ph.D.⁹; Suzanne Martens, Ph.D.⁹

¹Institute of Medical Psychology and Behavioral Neurobiology, Eberhard Karls University Tübingen, Germany; ²Applied Neurotechnology Lab, Department of Psychiatry and Psychotherapy, University Hospital of Tübingen, Germany; ³Ospedale San Camillo, IRCCS, Venezia, Italy; ⁴Computer Engineering Department, Wilhelm-Schickard Institute for Computer Science, Eberhard Karls University Tübingen, Germany; ⁵Department of Psychology I, University of Würzburg; ⁶Health Technologies Department, TECNALIA, San Sebastian, Spain; ⁷Department of Neurosurgery, University Hospital of Tübingen, Germany; ⁸Research Group Human Media Interaction (HMI), Department of Electrical Engineering, Mathematics and Computer Science, (EEMCS) University of Twente, Enschede; ⁹Empirical Inference Department, Max Planck Institute for Biological Cybernetics, Tübingen, Germany

Locked-in syndrome (LIS) as a result of brainstem lesions or progressive neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), is a severe medical condition in which a person is fully conscious but unable to move or talk. LIS can transition into complete locked-in syndrome (CLIS) in which residual abilities to communicate through muscle twitches are entirely lost. It is unknown how CLIS affects circadian rhythm and sleep/wake patterns. Here we report a 39-year-old ALS patient who transitioned from LIS to CLIS while brain activity was continuously recorded using electrocorticography (ECoG) over one month. While we found no circadian rhythm in heart rate and body temperature,

transition into CLIS was associated with increased fragmentation of slow wave sleep (SWS) across the day. Total time in SWS did not change. SWS fragmentation might reflect progressive circadian system impairment and should be considered as a factor further limiting communication capabilities in these patients.

Keywords: Complete locked-in syndrome, sleep fragmentation, circadian rhythm, communication

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CASE REPORTS

Locked-in syndrome (LIS) is a neurobehavioral diagnosis referring to patients who are awake and cognitively aware of their environment, but unable to move their body or to speak.¹ Whereas *incomplete* LIS is characterized by remnants of voluntary movements, *complete* LIS (CLIS) is associated with total loss of any capability to communicate or voluntarily interact with the environment. The most common causes for LIS include brainstem lesions following trauma, cardiovascular accidents (CVA), tumors, or metabolic disorders such as central pontine myelinolysis. LIS can also be the consequence of a progressive neurodegenerative disorder, e.g., amyotrophic lateral sclerosis (ALS). Studies investigating sleep behavior in ALS-related LIS revealed reduced REM sleep and sleep efficiency as well as increased occurrence of insomnia in these patients.² Yet, there are no data available on circadian rhythm and sleep/wake behavior during the transition from LIS to CLIS. Such information is important, as it might indicate an involvement of the circadian system during advanced stages of the disease, and could point to further therapeutic constraints as to timing of communication attempts using for example brain-computer interfaces (BCI),³ which require the patient to be fully awake.

REPORT OF CASE

Here we present the case of a 39-year-old male patient who was diagnosed with ALS at the age of 29 and ventilated for 7 years. The patient was hospitalized after his capability to

communicate through eye movements decreased from over an hour 3-4 days per week to less than an hour 1-2 days per week. Long before admission to the hospital, the patient and the legal representative gave informed consent for implantation of electrocorticogram (ECoG) electrodes to eventually enable communication via a brain-computer interface (BCI) system in case the ability to communicate through eye movements completely ceased.³ A multichannel grid of platinum electrodes was implanted epidurally covering the left brain hemisphere (Ad-Tech Medical Instruments, Wisconsin, USA) (**Figure 1A**). ECoG data was sampled continuously at 500 Hz (BrainAmp, BrainProducts, Gilching, Germany). Although immediately after implantation the patient could communicate for up to 30 minutes through eye movements, this ability vanished on day 4, indicating complete transition from LIS to CLIS. Circadian environmental conditions, such as time of light exposure (08:00-22:00) and timing of artificial feeding and interactions with caregivers and visitors on each day, were kept constant throughout the 30 days of ECoG recordings. We evaluated the time in SWS and numbers of SWS epochs (> 2.6 min) across the day and, using autocorrelation analyses, the circadian rhythm in SWS, heart rate, and body temperature. (Days 5 and 8 were excluded from this latter analysis because the patient acutely exhibited complete insomnia, i.e., SWS < 5.2 min/d). Time in SWS was compared between nighttime (20:00-08:00) and daytime (08:00-20:00). Values were compared between the first and second 15-day intervals.

Figure 1

(A) X-ray image of the patient's head after implantation of the epicortical grid. (B) Number (upper panel) and distribution across days (lower panel) of slow wave sleep periods > 2.6 min. Note the increasing sleep fragmentation after transition from locked-in to *complete* locked-in state (CLIS). $p < 0.001$ indicated by ***.

Time in SWS was normal but highly variable, and did not differ between days 1-15 and 16-30 (mean $\pm$ SEM across all days: 349.73 ± 46.81 min; day₁₋₁₅: 321.20 ± 49.87 min; day₁₆₋₃₀: 378.27 ± 44.02 min; one-way ANOVA: $p = 0.389$). The patient spent distinctly more time in SWS during the night (256.36 ± 34.61 min) than during daytime (98.04 ± 26.88 min; $p < 0.001$), with no changes across the two 15-day intervals ($p = 0.179$, two-way ANOVA with factors "day/night" and "days₁₋₁₅/days₁₆₋₃₀" indicated no interaction between the factors, $p = 0.930$). However, SWS fragmentation as measured by the number of SWS periods increased across the two 15-day intervals ($p < 0.001$; day₁₋₁₅: 7.6 ± 0.99 ; day₁₆₋₃₀: mean: 15.33 ± 1.67), with this increase equally present during nighttime and daytime (two-way ANOVA with factors "day/night" and "days₁₋₁₅/days₁₆₋₃₀" showed no interaction between both factors, $p = 0.849$). Autocorrelation analyses indicated a circadian rhythm in SWS with a period length of 24.18 h in the first and 24.35 h in the second 15-day interval, which was accompanied by a nonsignificant ($p = 0.501$) decrease in amplitude towards the second 15-day interval. We found no periodicity of body temperature or heart rate.

DISCUSSION

Our findings indicate that transition into CLIS can be associated with a progressive fragmentation of SWS across both nighttime and daytime. SWS fragmentation is a common symptom of various sleep disorders such as obstructive sleep apnea and restless legs syndrome, as well as of normal aging,⁴ where it can be a consequence of a flattened amplitude of the circadian rhythm. On the backdrop of missing circadian rhythmicity in heart rate and body temperature, despite highly constant cycling in light/dark and social stimulation, we assume that increasing SWS fragmentation across the 24-h period reflects a progressive impairment of the brainstem circadian system accompanying the transition into CLIS. This finding has important clinical implications, as more frequent transitions into SWS even dur-

ing daytime obviously interferes with the patient's attention to therapeutic approaches and might substantially impede attempts to establish communication via a BCI system. Thus, our data indicate that accompanying sleep recording is mandatory in the context of BCI use in CLIS patients.

ABBREVIATIONS

ALS, amyotrophic lateral sclerosis
ANOVA, analysis of variance
BCI, brain-computer interface
CLIS, complete locked-in syndrome
CVA, cerebral vascular accident
ECoG, electrocorticography
LIS, locked-in syndrome
REM, rapid eye movement
SEM, standard error of the mean
SWS, slow wave sleep

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Address correspondence to: Surjo R. Soekadar, M.D., Institute of Medical Psychology and Behavioral Neurobiology & Applied Neurotechnology Lab, Department of Psychiatry and Psychotherapy, University Hospital of Tübingen, Calwerstr. 14, D-72076 Tübingen, Germany; Tel: +49-7071-29 82640; Fax: +49-7071-29 82625; E-mail: surjo.soekadar@uni-tuebingen.de

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