Phasic Activities of Rapid Eye Movement Sleep in Vegetative State Patients

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INTRODUCTION

MORUZZI! IN 1965 WAS THE FIRST TO DISTINGUISH BETWEEN THE TONIC AND PHASIC COMPONENTS OF RAPID EYE MOVEMENT (REM) SLEEP. Tonic activities include electroencephalographic desynchronization, muscle atonia,1 and penile tumescence;2 phasic activities include rapid eye movements, skeletal muscle twitches, ponto-geniculo-occipital (PGO) waves,1 in addition to middle ear muscle activity,3 sawtooth waves,4 cardiorespiratory variability,5 and tongue movements.6 Most of our knowledge about the anatomical location of the neural generators of these activities has been provided by animal sleep studies.7 Studies in humans are limited and consist mainly of case reports of patients who, because of tumor or vascular lesions, showed either a decrease or absence of REM sleep or an alteration in its classical tonic and phasic components.8,9

The phasic activities of REM sleep are correlated with significant activation of various areas of the central nervous system.10 Accordingly, they tend to decrease in patients with neurological disorders in which mental functions are severely compromised but the sleep-wake cycle is preserved, such as Down syndrome11 or Alzheimer disease.12 For several years, our team has been conducting 24-hour polygraphic recordings of patients in vegetative state (VS) following traumatic brain injury.13—15 VS is a clinical entity resulting from severe organic brain damage and is characterized by serious disturbances of consciousness.16 Patients are able to open their eyes but unable to show signs of cognitive functions, presenting a peculiar state of wakefulness without awareness or detectable meaningful interaction with the environment. They are speechless, show severe motor abnormalities, and are totally dependent in activities of nutrition and personal hygiene. Brain trauma is one of the most common causes of this condition. Several neurodiagnostic tests have been assessed for outcome prediction in VS, but their contribution has been disappointing.17

Patients in VS have sleep-wake cycles. In a previous short report,13 we described the most prominent polygraphic characteristics of wakefulness and the different sleep stages in this condition. While periods of REM sleep were observed in all the patients, we were under the impression that the REM sleep phasic activities were reduced.

The aim of the present study was to assess the REM sleep phasic components in VS and to evaluate the possible relationship of these activities to patient outcome.

METHODS

Patients

Eleven patients in VS (10 males and 1 female) were included in the study. All but one had sustained a traumatic brain injury in a road accident. Their mean age was 28.4 years (range 17—53). The time elapsed from the accident to the polysomnographic (PSG) evaluation was two to five months. Recovered consciousness was defined as the ability to establish meaningful communicative contact with the environment by either a motor, visual, or verbal act. At six months after injury, six patients had recovered consciousness and five remained in persistent VS.
Control Subjects

The control group consisted of six normal adults (five males, one female) who were referred to our Sleep Disorders Unit for evaluation of snoring and suspected Obstructive Sleep Apnea (OSA). Nocturnal PSG evaluation yielded a diagnosis in all cases of Primary Snoring (i.e., normal sleep with no evidence of OSA). Mean age of the control group was 33 years (range 22—44), and their mean respiratory disturbance index (RDI) was 0.85±2.08.

Polysomnographic Evaluation

Authorization to perform PSG recording was obtained by the Head of the Intensive Care Unit from the family of each patient. All patients underwent a continuous 24-hour recording session. The basic PSG parameters always included 21 channels: four to six electrooculograms (EOG), two to three mental-submental electromyograms (EMG), six to nine electroencephalograms (EEG), and in addition, one EMG from the anterior tibialis of each leg, one electrocardiogram (ECG), lead 1, and two to three respiration channels. The recordings were performed at the bedside and usually began at noon and ended at noon the following day. Lights were off from 19:00 to 07:00 hour (nocturnal period). Sleep was scored manually according to standard criteria. In addition, the technician collected behavioral observations of the patients during the wake and sleep periods throughout the entire session.

Definition of REM Sleep Period

Two REM sleep periods were considered distinct if the time between the end of the first and the beginning of the next was 15 minutes or more. The REM sleep parameters evaluated for the present study included the number of REM sleep periods, their average duration, and the total REM sleep time.

Assessment of REM Sleep Phasic Activities

The following REM sleep phasic activities were evaluated: rapid eye movements (REMs), chin and leg muscle twitches, and sawtooth waves. The density of each of these activities was calculated for each REM sleep period. Each REM sleep period was divided into 30-second epochs, and each epoch was divided into three-second intervals. The percentage of three-second intervals containing at least one rapid eye movement, one muscle twitch, or three consecutive sawtooth waves was defined as the density score for that REM epoch. The average of the density scores for each phasic activity for all the 30-second epochs within a REM sleep period was the density score for that activity for that REM sleep period.19

Statistical Analysis

To compare the density scores of the REM sleep phasic activities between the VS patients and the control group, paired t-test was used when the data passed the normality test and the Mann Whitney rank sum test for data for which the normality test failed. All values are expressed as means ± SD. A p value of less than 0.05 was considered significant. Data analysis was performed with the SAS statistical package.

RESULTS

REM Sleep Data

Table 1 summarizes the REM sleep data of the patients and controls. All the patients had periods of REM sleep during the 24-hour recording session.

The total mean REM sleep time during the 24-hour session in the patient group was 66.5±34.9 min (range 1 to 107 min), and mean nocturnal sleep time was 37.3±19.7 min. Comparison with the control group (79.2±11.5 min) yielded a statistically significant difference only for nocturnal sleep time (t=4.75, df=15, p<0.0003).

The total number of REM sleep periods in the patient group was 69, with a similar distribution between nocturnal (34 periods) and diurnal (35 periods) hours. The range was 1 to 12 (mean 6.3±3.4). All patients had nocturnal REM sleep periods. Only three patients (one recovered and two nonrecovered) did not show period of REM sleep during the diurnal period. The total number of REM sleep periods in the control groups was 25, with a range from three to five (mean 4.2±0.8).

Mean duration of the REM sleep periods was 10.9±6.0 min (range 1—20.6 min) in the patient group and 19.6±4.9 min in the controls. This difference was statistically significant (t = 3.05,
Table 2—REM sleep data and REM phasic activities of recovered and norecovered vegetative state patients

<table>
<thead>
<tr>
<th></th>
<th>24 hours</th>
<th>Diurnal</th>
<th>Nocturnal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-VS</td>
<td>NR-VS</td>
<td>R-VS</td>
</tr>
<tr>
<td>Number of REMp</td>
<td>7.5±3.7</td>
<td>4.8±2.5</td>
<td>4.2±2.8</td>
</tr>
<tr>
<td>Total REM time</td>
<td>75.7±32.4</td>
<td>55.6±38.3</td>
<td>35.3±29.6</td>
</tr>
<tr>
<td>REMp duration</td>
<td>10.9±6.0</td>
<td>10.8±8.2</td>
<td>6.5±4.5</td>
</tr>
<tr>
<td>REMs D</td>
<td>8.2±3.5</td>
<td>6.5±6.0</td>
<td>8.5±5.8</td>
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<tr>
<td>Chin D</td>
<td>0.4±0.2</td>
<td>0.3±0.3</td>
<td>0.2±0.4</td>
</tr>
<tr>
<td>Leg D</td>
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<td>0.4±0.9</td>
</tr>
<tr>
<td>STW D</td>
<td>0.5±1.1</td>
<td>0.1±0.2</td>
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</tr>
</tbody>
</table>

R-VS=recovered vegetative state patients; NR-VS=norecovered vegetative state patients; REM=rapid eye movement; REMp=rapid eye movement sleep period, D=density, STW=sawtooth waves.

df=15, p<0.008). Comparison of this factor for the nocturnal period only did not yield a significant difference (p<0.09).

REM Sleep Phasic Activities

All the patients in VS had phasic activities during REM sleep. Figure 1 shows the densities of the REM sleep phasic activities for the two groups during the nocturnal period. Compared to controls, the patients had a significantly lower density of rapid eye movements (p=0.0003), chin twitches (p=0.0024), and leg muscle twitches (p=0.0392), and a non-significantly lower density of sawtooth waves (p=0.074). Similar results were obtained when the data for the whole 24 hours period were compared: rapid eye movements, p=0.001; chin twitches, p=0.002; leg twitches, p=0.023, and sawtooth waves, p=0.069.

Recovered vs. Nonrecovered Patients

Table 2 shows the REM sleep characteristics for the recovered and norecovered patients. There was no significant difference between these subgroups for any of the REM sleep characteristics or REM sleep phasic activities examined (24-hour, nocturnal and diurnal periods). It is possible that the lack of statistical significance found in REM sleep parameters between the two subgroups (recovered and norecovered) is likely due to the high variability of these parameters.

DISCUSSION

The present study shows that in patients with VS, the phasic activities of REM sleep are significantly reduced and that the number of these activities is unrelated to recovery from the clinical condition. In agreement with our previous studies,13-15 the PSG characteristics of the REM sleep periods in the patients with VS were similar to those of the control subjects.

Though the total REM sleep time for the 24-hour period was similar in the patients and controls, the patients had a significantly shorter nocturnal sleep time and shorter duration of REM sleep periods. These findings could be attributable to our allowing the VS patients to sleep practically "ad libitum" during the entire recording session. Furthermore, as REM sleep phasic activities may be involved in the maintenance or continuity of REM sleep periods,20 the decreased REM sleep phasic activities in the VS patients may also explain their reduced duration of REM sleep periods.

The consistency of the reduction in the phasic activities in all the patients is notable. Specifically, the reduction in the density of the rapid eye movements and chin and leg twitches was significant, whereas the reduction in the sawtooth waves was not. A similar consistency, though in the opposite direction, was reported in narcoleptic patients, who showed an increase in rapid eye movements and muscle twitches with no change in sawtooth waves.21 These data support the concept of different brain generators in the regulation of REM sleep phasic activities.

An alteration in REM sleep phasic activities has also been described in other neurological and mental disorders. Early studies conducted in the 1960s documented a reduction in REM density (mainly burst of REMs) in mentally retarded children. This finding led to the concept of REMs density as an index of intellectual level,11 and is consistent with the reduction in REM sleep and REMs density found in patients with Alzheimer disease.12 Our finding of a marked reduction in REM sleep phasic activities in VS patients may be considered in accordance with this notion. It could be of interest to investigate this issue in patients who recovered from this condition and to evaluate the relationship between REM sleep phasic activities and the improvement of their cognitive functions. A suggestion that this could be the case was provided by Ron et al.22 who showed a parallelism between amount of REM sleep and improvement in cognition in traumatic brain injury patients.

VS results from overwhelming damage to the cerebral hemispheres producing a massive loss of cortical activities, but with preservation of a functional brainstem, which allows for continued regulation of primitive reflexes and vegetative functions.16 Several studies have evaluated the possible contribution of neurodiagnostic tests to the prediction of recovery in VS. Unfortunately, neither EEG, evoked potentials, cerebral blood flow studies nor CT assessment has proven useful.23-25 Although we showed a significant reduction in REM sleep phasic activities in VS patients, we did not find differences between those who recovered and those who did not.

While the brainstem mechanisms responsible for the sleep-wake cycles and for the appearance of REM sleep are preserved in VS, the marked reduction in REM sleep phasic activities in our patients suggests that other brainstem mechanisms are impaired. The neural source of REM sleep tonic and phasic activities appears to be located within the pons inasmuch as REM sleep signs are abolished rostral to transections at the pontomesen-
cephalical junction and caudal to transections at the pontomedullary junction.\textsuperscript{7} Moreover, several studies have shown that the neural generators of phasic and tonic REM sleep components are localized in the pontine tegmentum.\textsuperscript{26-28}

The decrease in the densities of the rapid eye movements and muscle twitches during REM sleep may reflect possible damage to the cholinergic mechanisms of the pedunculopontine tegmentum (PPT). In animal studies, these have been demonstrated to be critical for rapid eye movements and PGO waves, but not for EEG desynchronization and REM sleep atonia.\textsuperscript{29} Nevertheless, lesions in the PPT do not affect the duration of REM sleep episodes suggesting that cholinergic cells do not play a critical role in the maintenance of REM sleep. On the other hand, lesions in the subcerulesus—mainly the peri-locus ceruleus alpha area, the crucial region for the atonia of REM sleep\textsuperscript{30} not only eliminated the atonia but also reduced the duration of REM sleep and increased the number of phasic events.\textsuperscript{30} Activation of serotonergic cells in the dorsal noradrenergic cells in the locus cerulesus area has been also implicated in the suppression of phasic events.\textsuperscript{26} Interestingly, a recent magnetic resonance imaging study showed that lesions in the corpus callosum and dorsolateral brainstem are significant in predicting nonrecovery in post-traumatic VS patients.\textsuperscript{31} In humans, the involvement of cholinergic mechanisms in the control of REM sleep phasic activities was recently supported by showing that transplantation of Scopolamine (a potent anticholinergic agent) reduces REM sleep phasic activity.\textsuperscript{32}

Although the integrative mechanism controlling the phasic activities during REM sleep remains unclear, the synergistic relationship between cholinergic and noradrenergic cells of the pontomesencephalic tegmentum appears to be critical for most REM sleep components. However, as Shouse and Siegel\textsuperscript{29} suggest, the involvement of other noncholinergic, nonadrenergic cells in the unifying mechanism for REM sleep onset and maintenance seems likely.

REFERENCES

29. Shouse MN, Siegel JM. Pontine regulation of REM sleep components in cats: integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. Brain Res 1992;571:50-63.