INTRODUCTION

Recent findings have suggested that neuronal potassium conductance may influence the sleep-wake cycle and REM sleep homeostasis (1,2).

The periodic paralyses (PP) are a group of rare disorders characterized by episodes of muscular weakness associated with changes in serum potassium levels and, therefore, with possible alterations in extracellular neuronal potassium conductance. The periodic paralyses (PP) are now classified on a genetic basis into sodium channel disorders (hyper-

Neuronal potassium conductance has been shown to influence the sleep-wake cycle and REM sleep homeostasis. The periodic paralyses (PP) are characterized by episodes of muscular weakness associated with changes in serum potassium levels and, therefore, with possible alterations in extracellular neuronal potassium conductance. We submitted a sleep questionnaire to the members of Periodic Paralysis International Listserv, an on-line support and information group for subjects with PP. Three control groups were made up of patients with untreated depression, patients with depression under treatment and healthy subjects. Both subjects with PP and those with untreated depression had a higher frequency of self-reported insufficient sleep quality and a higher number of nocturnal awakenings than patients with depression under treatment and healthy controls. PP subjects had more self-reported daytime sleepiness, sleep-related hallucinations and nightmares/abnormal dreams than the other three groups. Patients affected by PP may have disrupted sleep architecture and homeostasis. In particular, we suggest that the stereotypical abnormal dreams reported by several patients may reflect oneiric elaboration of nocturnal episodes of flaccid paralysis, while the increased frequency of sleep-related hallucinations may be due to enhanced REM sleep expression associated with alterations of neuronal potassium conductance.

KEY WORDS: Ion channel disorders, periodic paralysis, REM sleep, sleep disorders.

Giorgio Buzzi, Barbara Mostacci, Elisa Sancisi, Fabio Cirignotta

Sleep Medicine Unit, Department of Neurology, S. Orsola-Malpighi Hospital, University of Bologna, Italy

Reprint requests to: Dr Giorgio Buzzi, Unità Operativa Neurologia, Policlinico S. Orsola-Malpighi, Università di Bologna, Via Albertoni 15, 40138 Bologna, Italy. E-mail: gbuzzi@linknet.it

SLEEP COMPLAINTS IN PERIODIC PARALYSES: A WEB SURVEY

Neuronal potassium conductance has been shown to influence the sleep-wake cycle and REM sleep homeostasis. The periodic paralyses (PP) are characterized by episodes of muscular weakness associated with changes in serum potassium levels and, therefore, with possible alterations in extracellular neuronal potassium conductance. We submitted a sleep questionnaire to the members of Periodic Paralysis International Listserv, an on-line support and information group for subjects with PP. Three control groups were made up of patients with untreated depression, patients with depression under treatment and healthy subjects. Both subjects with PP and those with untreated depression had a higher frequency of self-reported insufficient sleep quality and a higher number of nocturnal awakenings than patients with depression under treatment and healthy controls. PP subjects had more self-reported daytime sleepiness, sleep-related hallucinations and nightmares/abnormal dreams than the other three groups. Patients affected by PP may have disrupted sleep architecture and homeostasis. In particular, we suggest that the stereotypical abnormal dreams reported by several patients may reflect oneiric elaboration of nocturnal episodes of flaccid paralysis, while the increased frequency of sleep-related hallucinations may be due to enhanced REM sleep expression associated with alterations of neuronal potassium conductance.

KEY WORDS: Ion channel disorders, periodic paralysis, REM sleep, sleep disorders.

FUNCT NEUROL 2001;16: 245-252
kalemic periodic paralysis and paramyotonia congenita), and the calcium channel disorder hypokalemic periodic paralysis. They are classified on a clinical basis, according to associated changes in serum potassium levels, into hypokalemic and hyperkalemic forms. A normokalemic form has also been described, but in most of these cases it is effectively a hyperkalemic periodic paralysis (3).

In hypokalemic periodic paralysis (hypoKPP), apparently normal subjects can awaken with severe weakness of the limbs. They are often unable to walk and at times may be quadriplegic. Consciousness is retained. Attacks typically occur while the patient is sleeping or following rest after exercise. Episodes of weakness usually resolve within a few hours but may occasionally persist for as long as 24 hours. Permanent weakness can develop after years of repeated attacks (3).

In hyperkalemic periodic paralysis (hyperKPP), attacks are frequent, last one to three hours, and are precipitated by rest after exercise and by emotional stress. After years of attacks, patients can develop persistent inter-attack weakness. Myotonia is often evident during attack-free intervals (3).

The aim of this study was to investigate the subjective sleep quality and self-reported sleep-waking disorders in patients affected by either form of PP.

MATERIALS AND METHODS

A sleep questionnaire was submitted to the members of Periodic Paralysis International Listserv, an on-line support and information group for PP patients, families, researchers and physicians (http://www.calexplorer.com/list/ppsite.htm).

At the time of the survey the list included about 130 members with all types of PP. List members can have a genetically-defined form of PP, a clinically-defined form of PP or a diagnosis of possible PP (strongly suggested by clinical characteristics only). The clinically-defined members have been diagnosed through one or more of the following methods: symptoms plus known family history, documented potassium level variation, insulin/glucose challenge, EMG, muscle biopsy, and response to medication. The Listserv members use e-mail to discuss clinical and non-clinical issues pertaining to PP.

With the permission of the Listserv owners, on August 23, 1999, we mailed to the Listserv a sleep questionnaire investigating general characteristics of sleep, insomnia, snoring, parasomnias (in particular, sleep paralysis, nightmares and hypnagogic/hypnopompic hallucinations), awakenings with PP attacks and daytime vigilance. Patients were also required to report their sex, age, nationality, PP type, degree of diagnostic certainty (genetically defined; clinically defined; possible), age at first attack and whether they had permanent weakness. A space for comments or additional information on patients’ sleep was also available.

An Italian version of the same questionnaire (items regarding PP excluded) was administered to all patients with a diagnosis of depressive disorder without psychotic traits evaluated in a primary care psychiatric center in Ravenna, Italy, over two consecutive months. Patients’ relatives and caregivers were also asked to fill out the questionnaire as healthy controls.

Patients with PP were compared with each of the following groups: patients with untreated depression, patients with depression under treatment, and healthy controls. Patients with untreated depression were chosen as a control group since this condition is known to be highly associated with sleep complaints. Patients with depression under treatment were chosen since, according to recent studies, subjects taking sleep-inducing medication or anxiety/anti-depressant medication are more likely to report sleep-related hallucinations and sleep paralysis.
than other subjects (4,5). In this report we compare the items listed in Table I.

We defined “insomniacs” patients who selected “insufficient” in response to question one.

Patients who gave the answer “often” or “usually” plus “at any time” to question three were regarded as being affected by excessive daytime sleepiness.

Question five was intended as a means of investigating how often the patients experienced hypnagogic/hypnopompic hallucinations, while question six was intended to investigate how often the patients experienced sleep paralysis.

Student’s t-test was used to compare the mean of clinical characteristics between patients with PP and each of the other groups. The z-test or Fisher exact test was used to compare differences in proportion. Significance was defined as p<0.05.

RESULTS

Forty-two patients (approximately 32 percent of the List members) filled out the questionnaire. Four were excluded (two cases had a very dubious diagnosis, one also had a severe sleep apnea syndrome and one was a 6-year-old child whose questionnaire was filled out by his mother); 38 questionnaires were analyzed. Twenty-seven respondents were females, 11 were males. Mean age was 42.6 years. Twenty-eight had hypoKPP, 10 had hyperKPP (5 with paramyotonia congenita). The patients’ characteristics are summarized in Table II (see over). At the time of the survey, 17 patients were taking carbonic anhydrase inhibitors (15 were taking acetazolamide, 2 dichlorphenamide), and 3 were taking potassium-sparing diuretics (information available for 31 out of 38 respondents). Eight patients were taking antidepressants (in particular, 7 were taking selective serotonin reuptake inhibitors, 1 a very small dose of a tricyclic).

The control groups were composed of 34 patients with untreated depression (22 F, 12 M; mean age 38.9 years); 48 patients with depression under treatment (28 F, 20 M; mean age 45.7 years); and 37 healthy subjects (23 F, 14 M; mean age, 46.2 years).

Tables III and IV (see over) show the results for the analyzed items in the four groups of sub-

---

Table I - Questions analyzed in the present report.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Item grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  How would you define the quality of your nocturnal sleep?</td>
<td>Excellent-good-sufficient-insufficient</td>
</tr>
<tr>
<td>2  How many times do you awake during a typical night’s sleep?</td>
<td></td>
</tr>
<tr>
<td>3  Do you feel that you are excessively sleepy during the day?</td>
<td>Never-sometimes-often-usually</td>
</tr>
<tr>
<td>If yes: only after lunch; at any time.</td>
<td></td>
</tr>
<tr>
<td>4  Do you ever experience nightmares or abnormal dreams?</td>
<td>Never-sometimes-often-usually</td>
</tr>
<tr>
<td>5  Do you ever experience intense dream-like imagery just before falling asleep or just after awakening?</td>
<td>Never-sometimes-often-usually</td>
</tr>
<tr>
<td>6  Do you ever experience brief episodes of inability to move, at sleep onset or upon awakening, which differ from PP attack because of a spontaneous and complete cessation within seconds or a few minutes?</td>
<td>Never-sometimes-often-usually</td>
</tr>
</tbody>
</table>
Table II - Patients’ characteristics.

<table>
<thead>
<tr>
<th>Period paralysis type and no. of subjects</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Nationality</th>
<th>Age (years)</th>
<th>Age at 1st attack (years)</th>
<th>Disease duration (years)</th>
<th>Permanent weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 HypoKPP</td>
<td>6 genetically defined</td>
<td>27 F</td>
<td>27 USA</td>
<td>42.6 ± 12.8 (range: 18-73)</td>
<td>15.0 ± 13.6 (range: 0-47)</td>
<td>27.6 ± 18.2 (range: 1-72)</td>
<td>19 yes 19 no</td>
</tr>
<tr>
<td>10 HyperKPP (5 with PMC)</td>
<td>25 clinically defined</td>
<td>11 M</td>
<td>2 Canadian 2 Australian 1 British 1 Norwegian</td>
<td>47.4%</td>
<td>14.6%</td>
<td>19.6%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HypoKPP = hypokalemic periodic paralysis; HyperKPP = hyperkalemic periodic paralysis; PMC = paramyotonia congenita.

Table III - Insomnia, self-reported number of nocturnal awakenings, and daytime sleepiness in PP patients and control groups.

<table>
<thead>
<tr>
<th>Periodic paralyses</th>
<th>Untreated depression</th>
<th>Depression under treatment</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>36.8%</td>
<td>35.3% ns</td>
<td>14.6% p 0.02</td>
</tr>
<tr>
<td>Nocturnal Awakenings *</td>
<td>2.7 ± 2.4</td>
<td>1.9 ± 1.5 ns</td>
<td>1.2 ± 1.2 p 0.0004</td>
</tr>
<tr>
<td>EDS</td>
<td>47.4%</td>
<td>17.6% p 0.005</td>
<td>18.7% p 0.004</td>
</tr>
</tbody>
</table>

Abbreviations: EDS= excessive daytime sleepiness; ns = not significant  
* Mean ± standard deviation. p values, in comparison with the periodic paralyses group

Table IV - Nightmares/abnormal dreams, hypnagogic/hypnopompic hallucinations, and sleep paralysis in PP patients and control groups.

<table>
<thead>
<tr>
<th>Periodic paralyses</th>
<th>Untreated depression</th>
<th>Depression under treatment</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nightmares at least “sometimes”</td>
<td>81.6%</td>
<td>64.7% ns</td>
<td>70.8% ns</td>
</tr>
<tr>
<td>Nightmares “often/usually”</td>
<td>34.2%</td>
<td>14.7% p 0.05</td>
<td>14.6% p 0.04</td>
</tr>
<tr>
<td>HH at least “sometimes”</td>
<td>63.2%</td>
<td>38.2% p 0.03</td>
<td>35.4% p 0.009</td>
</tr>
<tr>
<td>HH “often/usually”</td>
<td>23.7%</td>
<td>5.9% p 0.03</td>
<td>8.3% ns (0.057)</td>
</tr>
<tr>
<td>SP at least “sometimes”</td>
<td>34.2%</td>
<td>23.5% ns</td>
<td>27.1% ns</td>
</tr>
<tr>
<td>SP “often/usually”</td>
<td>7.9%</td>
<td>5.9% ns</td>
<td>6.2% ns</td>
</tr>
</tbody>
</table>

Abbreviations: HH = hypnagogic/hypnopompic hallucinations; SP = sleep paralysis; ns = not significant  
p values, in comparison with the periodic paralysis group
No significant differences were observed between hypoKPP and hyperKPP patients. Patients affected by PP do not differ statistically from subjects with untreated depression as regards insomnia and the mean number of nocturnal awakenings. Both subjects with PP and untreated depression have a higher frequency of self-reported insufficient sleep quality and a higher number of nocturnal awakenings than patients with depression under treatment and healthy controls. PP subjects have more self-reported daytime sleepiness, sleep-related hallucinations (both when considering this item positive for patients reporting such experiences at least “sometimes,” and when regarding it as positive in the case of those answering “often”-“usually”) and nightmares or abnormal dreams (when considering this item positive for patients reporting them “often”-“usually”) than the other three groups. Patients with PP also tend to report experiencing sleep paralysis more frequently than the other three groups, but the difference fails to reach statistical significance.

DISCUSSION

This study suggests that a subgroup of patients affected by PP may have a disrupted sleep pattern, with nocturnal awakenings, recurrent nightmares or abnormal dreams and sleep-related hallucinations, resulting in a self-reported poor quality of nocturnal sleep and in excessive daytime sleepiness.

Several patients (either with hypoKPP or hyperKPP) report recurrent nightmares or abnormal dreams associated with nocturnal attacks of paralysis. These dreams are described as “stranger than normal”, “more vivid and memorable” and they almost always involve a sensation of difficult moving or of getting help in an emergency. Some patients say that they have learned to recognize these dreams as signs of an episode and of the fact that they must wake up and get potassium (some examples of dream experiences associated with nocturnal PP attacks are reported in the Appendix).

Periodic paralyses are characterized by episodes of flaccid paralysis that, when occurring during sleep, may resemble REM sleep atonia. Generalized muscle atonia occurs during REM sleep due to strong hyperpolarization of motor neurons in the brainstem and spinal cord. This prevents motor activity associated with dream mentation. In spite of the fact that during REM sleep the cortex is as activated as during wakefulness (with high neuron firing and possible occurrence of gamma range activity, typical of attentive wakefulness), in normal conditions the subject is unaware of muscle atonia, and the dreaming condition has been defined as “a state of hyperattentiveness in which sensory input cannot address the machinery that generates conscious experience” (6). In fact, unlike the wakeful state, although gamma range activity can be present, during REM sleep there is no reset by peripheral stimulation. Moreover, the late components of the sensory-evoked potentials (which partly correspond to what nowadays are called event-related potentials and reflect cortical processing and integration of sensory information) are suppressed (7). When REM sleep atonia occurs out of normal REM sleep, the subject experiences a condition known as “sleep paralysis”, which may be associated with terrifying hallucinatory or dream-like experiences. According to the International Classification of Sleep Disorders (8), “hypokalemic paralysis is perhaps the only condition that closely mimics sleep paralysis”. We suggest that the occurrence of episodes of flaccid paralysis out of REM sleep may generate the stereotypical “periodic paralysis nightmare” that somehow resembles the dream imagery associated with sleep paralysis.

Patients clearly discriminate the above reported nightmares/abnormal dreams from hallucinations occurring during sleep-related attacks (see the Appendix).
Sleep-related (hypnagogic/hypnopompic) hallucinations have been pathophysiologically related to dissociated REM sleep intruding into wakefulness (9). Conditions enhancing the REM sleep propensity, such as periods of REM sleep rebound following pharmacologic REM sleep suppression, may facilitate the occurrence of these phenomena.

Recently, neuronal potassium conductance has been shown to influence the sleep-wake cycle, and the REM sleep propensity in particular. Benington et al. (1) have administered small doses of apamin (a selective blocker of a class of Ca\(^{2+}\)-dependent K\(^+\) channels, the small conductance SK channels) into the lateral ventricle in rats, and characterized the resultant effects on REM sleep expression. Apamin produced a dose-dependent reduction in REM sleep expression, with a small REM rebound after each dose. In a subsequent study, Gandolfo et al. (2) found that intracerebroventricular injections of low doses of apamin in rats induced insomnia and a long-lasting suppression of deep, slow sleep and paradoxical sleep. Injected animals showed a late but important rebound of paradoxical sleep. Even after the recovery of a normal sleep amount, the circadian cycle remained disturbed throughout the recording duration (96 h). The authors state that the effects of apamin on sleep are spectacular and that they are certainly associated with a blockade of SK-type Ca\(^{2+}\)-activated K\(^+\) channels since apamin is very specific for SK channels.

In PP, changes in serum potassium levels during the attacks may result in an altered extracellular neuronal potassium conductance.

In hypoKPP, the occurrence of nocturnal episodes of hypokalemia, typical of this condition, may result in a reduced extracellular neuronal potassium conductance and this, in turn, may cause a reduction in REM sleep expression, followed by compensatory REM rebounds.

Several patients report an improvement of their nocturnal sleep (and in particular a reduction of their sleep-related hallucinations) following treatment with acetazolamide. Interestingly, a recent report (10) has suggested that the therapeutic effects of acetazolamide in the K-deficient diet rat (an animal model of human hypoKPP) can be mediated by activation of the KCa\(^{2+}\) channel. Therefore, the beneficial effect of acetazolamide on the sleep of subjects with PP could confirm the importance of neuronal K\(^+\) conductance in REM sleep homeostasis.

On the other hand, in hyperKPP, transitory episodes of weakness are associated with an increase in the serum potassium level which may enhance REM sleep propensity.

A recent report (11) described a 24-year-old man with hyperKPP who presented with moderate excessive daytime sleepiness and transitory episodes of weakness, which occurred during and after sleep. The multiple sleep latency test (MSLT) demonstrated the presence of five sleep onset REM periods (SOREMPs) and a sleep latency of five minutes. Treatment with a diuretic that decreases serum potassium resolved all the clinical symptoms and a new MSLT showed the absence of SOREMPs and a sleep latency of 13.5 minutes. The authors suggest that SOREMPs in their hyperKPP patient might be explained by an increased extracellular neuronal potassium conductance. This could also be the case of a 59-year-old man with a clinically-defined diagnosis of hyperKPP and paramyotonia congenita who participated in our survey and reported brief episodes of hallucinations occurring regularly during each sleep-related attack and not at other times.

In summary, our survey suggests that symptoms indicating possible concomitant sleep/wake disorders may be common in PP. This study has obvious limitations: due to the web-survey technique, the diagnoses of individual patients could not be validated and some patients could have had a coexisting psychi-
atric disorder. Moreover, the results may be biased by the fact that patients with sleep complaints could have been more motivated to fill in the questionnaire. However, given the conceivable pathophysiologic basis for a disrupted sleep architecture and sleep homeostasis in subjects with PP – as described above – we believe that our findings deserve further investigation.

ADDENDUM

We contacted by e-mail the seven patients who had a diagnosis of “possible” PP at the time of the survey. Eighteen months later, four of them have been confirmed as hypoKPP, one as hyperKPP with paramyotonia congenita, one has been diagnosed as Andersen’s Syndrome (a PP variant with cardiac involvement and skeletal anomalies) and the seventh has been classified as a “novel variant” of PP, associated with malignant hyperthermia.

ACKNOWLEDGEMENTS

We thank the Periodic Paralysis International Listserv owners (Mr Don Anderson and Mrs Deborah Cavel-Greant) for giving us permission to conduct this survey, the List members who filled out the questionnaire, and Mrs Donna Lindsay who revised the manuscript.

APPENDIX

Examples of dream experiences associated with nocturnal PP attacks

“I have very vivid dreams when I’m going into an episode and will dream that I’m having difficulty walking, or unable to move, or trying to call for help and no sound comes out…”.

“I might actually dream that I was in an episode, but most often I’d have a dream where my body would slow down”.

“I had the same dream in which I could not move… and someone would come and help me… and then I managed to come out of this and realized I was in a serious episode”.

“I am always weak in my dreams”.

“I recognize from the character of the dream that I am entering an episode, and that I need to awaken and get some potassium”.

“I have learned to recognize these dreams as signs of an episode and can now say to myself, even asleep, ‘You’re having an episode. Wake up.’ And then I wake myself, and if I can move I will get up and get potassium”.

“I’ll realize that I am going into an episode and I’ll wake myself up enough to flail around to get my husband’s attention”.

Hallucinatory experiences associated with nocturnal PP attacks

“In that state I can’t tell reality from hallucination, and I have no idea I’m paralyzed, whereas in my dreams I recognize that I am having an episode immediately”.

“The difference between dreams and hallucinations is I recognize a dream for what it is. A ‘hallucination’ appears so realistic, even if it isn’t anything ‘real,’ that I often can’t sort out if it actually happened or if it just happened in my head”.

REFERENCES

2. Gandolfo G, Schweitz H, Lazdunski M, Gottesmann C. Sleep cycle disturbances induced by apamin, a selective blocker of
Ca^{2+} activated K^{+} channels. Brain Res 1996;736:344-347


