Vivid dreams, hallucinations, psychosis and REM sleep in Guillain–Barré syndrome


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We conducted a prospective controlled study of the clinical and biological determinants of the mental status abnormalities in 139 patients with Guillain–Barré syndrome (GBS) and 55 patients without GBS placed in the intensive care unit (ICU controls). There were mental status changes in 31% of GBS patients and in 16% of controls (odds ratio = 2.3; P = 0.04). In GBS patients, they included vivid dreams (19%), illusions (30%, including an illusory body tilt), hallucinations (60%, mainly visual) and delusions (70%, mostly paranoid). They appeared a median 9 days after disease onset (range 1–40 days, during the progression or the plateau of the disease), and lasted a median 8 days. Seven (16%) patients experienced the symptoms before their admission to the ICU. Hallucinations were frequently hypnagogic, occurring as soon as the patients closed their eyes. Autonomic dysfunction, assisted ventilation and high CSF protein levels were significant risk factors for abnormal mental status in GBS patients. CSF hypocretin-1 (a hypothalamic neuropeptide deficient in narcolepsy) levels, measured in 20 patients, were lower in GBS patients with hallucinations (555 ± 132 pg/ml) than in those without (664 ± 71 pg/ml, P = 0.03). Since the mental status abnormalities had dream-like aspects, we examined their association with rapid eye movement sleep (REM sleep) using continuous sleep monitoring in 13 GBS patients with (n = 7) and without (n = 6) hallucinations and 6 tetraplegic ICU controls without hallucinations. Although sleep was short and fragmented in all groups, REM sleep latency was shorter in GBS patients with hallucinations (56 ± 115 min) than in GBS patients without hallucinations (153 ± 130 min) and in controls (207 ± 179 min, P < 0.05). In addition, sleep structure was highly abnormal in hallucinators, with sleep onset in REM sleep periods (83%), abnormal eye movements during non-REM sleep (57%), high percentages of REM sleep without atonia (92 ± 22%), REM sleep behaviour disorders and autonomic dysfunction (100%), reminiscent of a status dissociatus. The sleep abnormalities, that were almost absent in non-hallucinated GBS patients, were not exclusively related to ICU conditions, since they also appeared out of ICU, and were reversible, disappearing when the mental status abnormalities vanished while the patients were still in ICU. In conclusion, the mental status abnormalities experienced by GBS patients are different from the ICU delirium, are strongly associated with autonomic dysfunction, severe forms of the disease and possibly with a transitory hypocretin-1 transmission decrease. Sleep studies suggest that mental status abnormalities are wakeful dreams caused by a sleep and dream-associated disorder (status dissociatus).

Keywords: Guillain–Barré syndrome; hallucinations; hypocretin; ICU syndrome; REM sleep; REM sleep behaviour disorders; status dissociatus

Abbreviations: CSF = cerebrospinal fluid; GBS = Guillain–Barré syndrome; ICU = intensive care unit; REM sleep = rapid eye movement sleep

Introduction

Guillain-Barré syndrome (GBS) is an acute autoimmune polyradiculoneuritis with sensory and motor impairment. Since GBS may also cause autonomic dysfunction, aspiration pneumonia and respiratory failure, some patients undergo intensive care including invasive ventilation. Although GBS is generally restricted, clinically and pathologically, to the peripheral nervous system, central dysfunctions have also been documented. They include hyponatraemia caused by abnormal antidiuretic hormone secretion (Hochman et al., 1982), single reports of rapid eye movement sleep (REM sleep) motor behaviour disorders (Schenck et al., 1986), excessive daytime sleepiness (Guilleminault and Mondini, 1986) and abnormally low CSF hypocretin-1 (a hypothalamic neuropeptide) levels (Nishino et al., 2002, 2003).

In addition, patients with GBS may experience mental status abnormalities. Such signs were incidentally noted in early clinical studies of the disease (Guillain, 1953), and were described with various names, including personality changes and mental disturbances (McFarland and Heller, 1966), hallucinatory experiences and onerieu states (De (1973; Goulon et al., 1975), dream-like scenic hallucinations (Schmidt-Degenhard, 1986), and psychotic symptoms (Weiss, 1991; Weiss et al., 2002). Although such mental status abnormalities are unexpected in a disease of the peripheral nervous system, and disturbing for the patient, their relatives and the medical staff, they have not been well studied. They are generally referred to as ‘ICU delirium’, a heterogeneous syndrome including confusion and agitation in aged patients with metabolic disorders (Wilson, 1972; Geary, 1994). We planned to determine the mechanisms of these mental status abnormalities in GBS patients. We previously described a series of patients with GBS, autonomic dysfunction and psychotic signs (Bolgert, 1991) and reported an unconfused patient with GBS, with vivid dreams and hallucinations of which he was aware (Wegener et al., 1995). In the present study, we describe a typical case report and present the results of a prospective study of the nature, chronology and clinical determinants of the mental status abnormalities in a large series of GBS patients. In addition, because of the dream-like aspects of these signs, we examine their association with REM sleep (using sleep monitoring) in 13 GBS patients.

Patients and methods

From 1990 to 2004, ~170 patients were hospitalized with suspected GBS in the Neurology Department of the Pitié-Salpêtrière Hospital, a tertiary care university hospital in Paris. All of the patients were examined by the same neuropsychiatrist (F. Bolgert) in order to confirm the diagnostic criteria and to decide whether they should be placed in the intensive care unit (ICU), a unit open to day light through large windows. For homogeneity, only patients meeting the criteria for definite GBS (Asbury, 1990) were included in the prospective study of mental status abnormalities. Patients with subacute forms of polyradiculoneuritis (extension of the symptoms for >4 weeks), purely sensory forms, Miller–Fisher syndrome and patients with cellular reactions in the CSF were excluded.

Table 1 Characteristics of patients with GBS and controls (patients without GBS placed in the ICU)

<table>
<thead>
<tr>
<th>Patients</th>
<th>GBS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>139</td>
<td>55</td>
</tr>
<tr>
<td>Mental status</td>
<td>31%*</td>
<td>16%</td>
</tr>
<tr>
<td>Vivid dreams</td>
<td>5.7%</td>
<td>11%</td>
</tr>
<tr>
<td>Illusions</td>
<td>9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>18.6%*</td>
<td>3.6%</td>
</tr>
<tr>
<td>Delusions</td>
<td>21.6%*</td>
<td>0%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 ± 19*</td>
<td>57 ± 18</td>
</tr>
<tr>
<td>Male sex</td>
<td>57% (51%)</td>
<td>65% (67%)</td>
</tr>
<tr>
<td>Placed in ICU</td>
<td>75% (84%)</td>
<td>100% (100%)</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>45%* (100%)</td>
<td>5% (33%)</td>
</tr>
<tr>
<td>Assisted ventilation</td>
<td>32% (60%)</td>
<td>35% (22%)</td>
</tr>
<tr>
<td>Urinary troubles</td>
<td>17% (19%)</td>
<td>5% (0%)</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>25% (30%)</td>
<td>18% (44%)</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>10%* (9%)</td>
<td>34% (56%)</td>
</tr>
<tr>
<td>Psychoactive drugs</td>
<td>14%* (14%)</td>
<td>42% (33%)</td>
</tr>
</tbody>
</table>

The characteristics of patients experiencing mental status changes in both groups are indicated in parentheses; *Significant difference between GBS and ICU control groups; †Significant difference between GBS and non-GBS patients with mental status abnormalities.

Thus, 139 patients with definite GBS, aged from 16 to 84 years, were included over a 14 year period. Their demographic and clinical characteristics are shown in Table 1. Three patients died. Patients went back to work a mean 224 days (range 80–562 days) after GBS onset. None of the patients had a prior history of psychosis. In addition, 55 consecutive patients without GBS placed in the ICU were interviewed similarly by the same medical and paramedical team during winter 2004 (Table 1). They suffered from various acute diseases, including respiratory insufficiency (n = 34), renal insufficiency (n = 5), sepsis (n = 2), diseases affecting brain (n = 8, brain contusion, status epilepticus, suicidal attempt, encephalitis) and peripheral nervous system (n = 6, spinal cord traumaism, amyotrophic lateral sclerosis, myasthenia, myopathy).

Collection of mental status abnormalities and symptoms

After having observed the first GBS patient with vivid dreams in 1990, F.B. encouraged his medical team and nurses to systematically gather data on mental status changes in GBS patients. They prospectively interviewed all patients daily concerning abnormal sensations, visions, sounds, strange visions and unusual dreams. When the patients were able to speak, their answers were recorded in their medical file, and using a video camera in the last years. When patients were able to speak because they were on assisted ventilation, lip reading and writing on slate were used. In addition, the behaviour of the patients was observed hourly in the ICU. Some patients later recorded their experiences on paper or tape. All patients were again interviewed when leaving the ICU by F.B. and S. Demeret. The experiential and mental status abnormalities were classified as vivid dreams (unusually clear, long dreams with elaborate scenario and possibly strong emotions, that occurred only when sleeping and were acutely remembered), illusions (distortion of perceived images, sounds or sensations), hallucinations (short-lasting perception
Hallucinations in Guillain–Barré syndrome

without object to be perceived, occurring either with open or closed eyes, in clear consciousness). In addition, we classified delusions as the real perceptual experiences of non-confused patients that were long (day)-lasting, poorly criticized despite nurse’s intervention and caused observable behavioural changes.

Clinical and biological measures

As the clinical status of GBS patients and ICU controls may rapidly deteriorate and become life-threatening within a few hours, the clinical signs (interview, evaluation of motor weakness, sensory defect, measures of respiratory function and subcutaneous oxygen saturation, heart and respiratory rate, arterial blood pressure) were performed a minimum of three times a day. Arterial blood gases, blood glucose, hepatic transaminases, albumin, haematocrit, and sodium, potassium and chloride ion levels were measured daily. All treatments used by the patients during their hospitalization were obtained from their medical files. We gave particular attention to the use of psychoactive drugs before and during mental status abnormalities. Autonomic dysfunction was defined as systolic blood pressure changes >40 mmHg in 1 day, fever-free heart rate >120 beats/min or decrease in heart rate of at least minus 20 beats within 1 min. During the mental status abnormalities, we checked for metabolic changes known to induce psychotic manifestations (Geary, 1994), such as arterial carbon dioxide pressure >44 mmHg, arterial oxygen pressure <80 mmHg, venous blood sodium level <130 mmol/l, glucose level <3.9 mmol/l and 2-times increase above normal values of transaminases. Lumbar punctures were performed in the 139 patients on the first day of hospitalization to determine CSF protein levels and cell count, and in one patient during the hallucinations. CSF hypocretin-1 levels were measured in 20 patients, with (n = 9) and without (n = 11) mental status abnormalities, by direct radioimmunoassay (Phoenix Pharmaceuticals, Belmont, CA).

Sleep studies

Between 2002 and 2004, 13 patients with GBS and 6 tetraplegic patients without GBS (suffering from myasthenia gravis, cervical tumour and post-traumatic cervical lesion) in the ICU agreed to undergo sleep monitoring (Table 4A, Supplementary data). Seven GBS patients had elaborate mental status abnormalities (Table 4B, Supplementary data) at time of the first sleep monitoring, of whom four underwent a second sleep recording after the hallucinations stopped. All patients had no disease or drug treatments affecting the central nervous system 48 h before and during the sleep monitoring and were subject to the same ICU conditions, including assisted ventilation, except one GBS patient who experienced hallucinations before ICU placement and was recorded in the neurology ward. Sleep was monitored using a portable Holter device with bipolar frontocentral and temporoccipital electroencephalography, electrooculography, and chin electromyography. The 31 sleep recordings lasted from 8 to 24 h, depending on ICU conditions, with 26 during the night, from 10 p.m. to 8 a.m. and 5 during the day. Four recordings could not be scored owing to artefacts of ICU devices on the encephalogram. The other recordings were scored according to international guidelines (Rechtschaffen and Kales, 1968; American Sleep Disorders Association, 1992) by a neurologist (I.A.) blind to the mental status of the patients. In addition, the presence of REM sleep without atonia was scored as previously described (Arnulf et al., 2005). When abnormal rapid eye movements occurred during sleep Stages 1 and 2, these periods were scored as Stage 1 in the absence of saw-tooth waves and Stage 2 as soon as spindles appeared rather than REM sleep. We also quantified the number of eye movement bursts per minute in sleep Stage 2, as previously described for REM sleep (Arnulf et al., 2002).

Statistical analysis

The characteristics of GBS patients and ICU controls, with and without mental status abnormalities, were compared by χ²-test (qualitative measures, with Yates correction when appropriate) and Student’s t-test (quantitative measures). Statistical threshold for significance was set at P < 0.05. A model of logistic regression was then computed, including all variables for which the level of significance was 0.05, using SAS 8.0 software (SAS Institute, Cary, NC). The sleep measures obtained in GBS and ICU controls were compared using Kruskall–Wallis test, and those obtained during and after the hallucinations using the Wilcoxon rank test. Data were expressed as mean ± SD.

Results

Case report

Mrs M, a 41-year-old woman with GBS was hospitalized for 78 days. She experienced hallucinations and delusions from day 11 (6 days after onset of invasive ventilation) to day 25, and suffered from autonomic dysfunction during the same period. She experienced weird dreams, illusions, hallucinations and even a mild paranoid delusion. She dreamed that her body was floating above the bed, then was standing up in a moving cart, with the picture of her son in front of her. The cart was moving in a background of music by Mozart, then the picture turned into a movie of her son walking or playing, and other, unfamiliar, persons. In the background, she could hear the conversations of the ICU nurses. Later in the afternoon, she saw herself standing on a sheet pulled across the floor by an invisible system (she even felt the bumps in the floor under her feet) that took her to visit a bustling street in Paris in the spring with people walking around in her right visual hemifield (in the ICU, the door and walking visitors were also on her right). When awake, she saw three contortionists coming out of the arms of the respiratory device. She believed they were in her bedroom to amuse her (see Video 1, Supplementary data). Two of them were children; one of them had blond hair and looked like ‘Jesus of the manger’, whereas the second one was ill and had a tube in his nose. The third character was a woman dancing with her arms. She had very long nails and was dressed like an actress. During the hallucinatory period, the patient imagined having a hypernormal ability to hear distant conversations, and believed that the conversations were about her. The patient was never confused. As she was intrigued by these strange psychic experiences, she agreed to undergo five night-time sleep studies within 1 month, two during the hallucinations and three after they stopped. During the dreams and hallucinations, there was first a major insomnia (total sleep was restricted to 37 min, on a 600 min recording), a 14 min REM sleep latency (normal >50 min), frequent (2.0 per min) abnormal rapid eye movements during non-REM sleep and the REM sleep was entirely without atonia. After 11 days, as she still experienced hallucinations, total
sleep time was 341 min, REM sleep latency was 213 min, but there were still frequent (2.3 per min) rapid eye movements during non-REM sleep and REM sleep entirely without atonia. The hallucinations stopped together with autonomic dysfunction on day 26, as she was still in the ICU. The same night, total sleep time was 200 min, REM sleep latency was 148 min, and 100% of REM sleep was still without muscular atonia. There were frequent (2.1 per min) eye movements during non-REM, which were no longer rapid, but slow and rolling. One month after the hallucinations disappeared, as she was no more in the ICU, total sleep time was 504 min, REM sleep latency was still short, but there were no longer any rapid or slow eye movements during non-REM sleep, and muscle tone was abolished as it is normal during REM sleep.

Prevalence of mental status abnormalities

Among the 139 GBS patients, 43 (31%) experienced mental status abnormalities, versus 16% of ICU controls (odds ratio = 2.3, 95% confidence interval = 1.5–3.1; P < 0.05). The onset and duration were accurately determined in 30/43 GBS patients (Fig. 1). They appeared a median 9 days after disease onset (range 1–40 days, during the progression or plateau of the disease), 6 days after hospitalization, and lasted a median 8 days (range 1–133 days). There was no difference in age, sex, percentages of intubation, disease severity, impaired cranial nerves, infection, pain, liver dysfunction, myelinic versus axonal lesions, CSF levels of protein and hypocretin-1 or use of psychoactive drugs, between patients myelinic versus axonal lesions, CSF levels of protein and impaired cranial nerves, infection, pain, liver dysfunction, myelinic versus axonal lesions, CSF levels of protein and hypocretin-1 or use of psychoactive drugs, between patients with short-onset (≤9 days) and late-onset (>9 days) mental status abnormalities.

Phenomenology of mental status abnormalities

Vivid dreams

Eight (19%) of those with mental status abnormalities GBS patients reported on awakening recurrent, unusual, vivid dreams that they experienced intensely and remembered accurately (Table 2). The dreams occurred several times a day, as soon as the patients closed their eyes. Short naps were very frequent during the day. The patients were spontaneously aware of the dream-like mentation, indicating that it intruded upon and disrupted a flow of consciousness characteristic of wakefulness with unusual and elaborate dreams. These dreams were strange, colourful and highly emotional. The patients often reported the feeling of going away on a boat trip, swimming and flying over places. Some patients had the impression that they left their bodies empty at the hospital while they went away on a trip. Nightmares with themes of death and illness also occurred. The patients, when questioned months after the events, accurately remembered these strange dreams. In contrast, the 6/9 (66%) ICU controls had less detailed vivid dreams, including three nightmares about murder, war, and insects, and two pleasant dreams of parents and travel to China.

Table 2 Examples of mental status changes experienced by 43/139 patients with GBS

<table>
<thead>
<tr>
<th>Mental status abnormalities</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivid dreams</td>
<td>Floating over the streets of New York early in the morning and seeing people taking out their garbage</td>
</tr>
<tr>
<td>Auditory</td>
<td>The gentle sound of the nasogastric feeding system heard as a voice whispering: left, left, right indicating which lung to breathe with</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Rats, ants, blue dwarfs, pink elephant, white and blue whale, family members, babies, coloured flags, dust-bunnies</td>
</tr>
<tr>
<td>Delusions</td>
<td>A patient believed he was a prisoner of the Germans during World War II trying to cross a border, and continually asked for his passport. Another thought that the nurse was bringing all patients out in a pick-up to the restaurant, where the other guests turned into giant homosexual lizards and made them flee</td>
</tr>
</tbody>
</table>
illusory body tilt ‘dreamt’ that his son had bought a house with a front door that was not vertical but like the trap door of a coal bin. Some patients lost the sense of their body and reported the illusion of floating weightlessly. Two ICU controls saw, when treated by morphine, that the ceiling was changed to a pleasant surface of tiny pink marbles that oscillated as waves, and that animals slowly crawled in the light.

**Hallucinations**

Hallucinations were experienced by 26 (60%) GBS patients, who mostly saw tiny, colourful moving figures, such as goblins or animals of various sizes and colours crossing the room and sometimes entertaining them. One patient asked to take off his imaginary tights or gloves, another asked why he felt soap or noodles on his hands. The hallucinations generally occurred as soon as the patients closed their eyes, as the patients were still awake, and continued for a few seconds after they opened them again. These patients were rapidly aware of their hallucinations, although they were transitorily panicked by what happened to them. Several patients reported that they were afraid to close their eyes because the images immediately appeared and could not be avoided. In contrast, two ICU controls said they experienced an isolated hallucination, one of a barking dog and another of something he could not remember exactly.

**Delusions**

It was rapidly recognized by nurses that when GBS patients developed delusions, their faces changed. They seemed to have imaginary experiences. They looked scared or astonished or followed invisible objects with their eyes or recounted incomprehensible events. Thirty (70%) GBS patients presented transient abnormal behaviours that stemmed from a dream-like state. Most delusions were paranoid (Table 2). A patient thought he had been intubated in the middle of the street during a fair, attached to a chair by two doctors. A woman looked scared and agitated. She wrote to the nurse that her friend Françoise, the secretary of the municipal council was here in the ICU and had killed her husband and children. The nurse reassured her, but a few minutes later ‘Françoise’ was back and was trying to kill her by drilling her heart with needles (see Video 2, Supplementary data). The theme of the delusions tended to remain the same over a period of several days, as if they were episodes of the same event. The patients remembered perfectly the ‘awake nightmares’ several months after. They were not associated with confusion. In contrast, no delusion was reported in ICU controls.

**Risk factors for the mental status abnormalities**

On monovariate analysis (Table 3), GBS patients with mental status abnormalities had more frequent autonomic dysfunction (P = 0.0001). Other factors associated with mental status abnormalities were disease severity (A: able to walk, P = 0.0001), and impairment of cranial nerves (P = 0.0001). In contrast, no delusion was reported in ICU controls.
dysfunction, higher severity of the disease and CSF protein levels, and lower CSF hypocretin-1 levels (Fig. 2) than other GBS patients. Lower CSF hypocretin-1 levels were not associated with higher protein levels ($r^2 = 0.12, P = 0.14$, linear regression). All of them had been admitted in the ICU, but seven (16%) experienced the mental status abnormalities a few days before their transfer to the ICU. Conversely, 17% of non-ICU patients experienced hallucinations versus 37% of ICU patients ($P = 0.02$). CSF hypocretin-1 level was normal (450 pg/ml) in the single patient who accepted a second lumbar puncture during her hallucinations. In contrast, there was no difference in age, sex ratio, frequency of infection prior to GBS, pain, upper-body motor deficits, cranial nerve impairment, sensory disorders, urinary troubles, liver dysfunction, metabolic disorders, myelinic polyneuropathy, Lasegue’s sign or use of immunosuppressive and psychoactive treatments between patients with and without mental status abnormalities. Eight (19%) patients with mental status abnormalities were treated with psychotropic drugs (zolpidem, midazolam, lorazepam, clonazepam, fentanyl, amitriptyline), six had hypoxaemia and one had hypercapnia.

The multivariate logistic analysis model included all variables that were different between groups, except autonomic dysfunction which occurred in 100% of patients with mental status abnormalities. Only the grade C (assisted ventilation; odds ratio: 3; 95% confidence interval: 1.2–8, $P = 0.02$) and the CSF protein levels (partial correlation coefficient $r = 0.08$, $P < 0.05$) were significant risk factors (Table 3). At time of mental status changes, ICU controls had more frequent metabolic disorders (56% versus 9%, $P = 0.005$) and less frequent autonomic dysfunction (33% versus 100%, $P < 0.0001$) than GBS patients.

**Sleep measures**

The quantity and quality of sleep were similarly poor in all groups (Table 4), with on average one-third of the night spent

![Fig. 2 Lumbar cerebrospinal hypocretin-1 levels (pg/ml) in 20 patients with and without mental status abnormalities. The mean of each group is indicated by a horizontal line ($*P = 0.03$, Student’s $t$-test).](https://academic.oup.com/brain/article-abstract/128/11/2535/339518/128/11/25353518/51873518)

**Table 4** Night-time sleep measures in 19 tetraplegic patients with and without GBS (controls), according to mental status changes

<table>
<thead>
<tr>
<th>Patients</th>
<th>GBS</th>
<th>Controls with normal mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With abnormal mental status</td>
<td>With normal mental status</td>
</tr>
<tr>
<td></td>
<td>During episode</td>
<td>After episode</td>
</tr>
<tr>
<td>Number of patients</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Days in ICU before sleep recordings</td>
<td>11 ± 13</td>
<td>27 ± 20</td>
</tr>
<tr>
<td>Total sleep period (min)</td>
<td>407 ± 193</td>
<td>490 ± 96</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>220 ± 110</td>
<td>345 ± 158</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>57 ± 22</td>
<td>69 ± 25</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>201 ± 146</td>
<td>133 ± 132</td>
</tr>
<tr>
<td>Arousals per hour</td>
<td>29 ± 12</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>Latency in minutes to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep onset</td>
<td>92 ± 106</td>
<td>19 ± 19*</td>
</tr>
<tr>
<td>REM sleep onset</td>
<td>56 ± 115†</td>
<td>96 ± 96</td>
</tr>
<tr>
<td>SOREMP (at night % patients)</td>
<td>86%†</td>
<td>25%</td>
</tr>
<tr>
<td>Duration in % TST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>25 ± 16</td>
<td>6 ± 3*</td>
</tr>
<tr>
<td>Stage 2</td>
<td>49 ± 12</td>
<td>57 ± 26</td>
</tr>
<tr>
<td>Stages 3 and 4</td>
<td>14 ± 12</td>
<td>17 ± 10</td>
</tr>
<tr>
<td>REM sleep</td>
<td>12 ± 8</td>
<td>20 ± 17</td>
</tr>
<tr>
<td>REM sleep without atonia (%) REM sleep</td>
<td>92 ± 22†</td>
<td>0 ± 0*</td>
</tr>
<tr>
<td>Eyes movements during non-REM sleep (%)</td>
<td>57†</td>
<td>0</td>
</tr>
</tbody>
</table>

REM, rapid eye movement; TST, total sleep time; WASO, wakefulness after sleep onset; SOREMP, sleep onset in REM periods, i.e. REM sleep latency <15 min; $*P = 0.06$ for paired comparisons of patients during and after the episodes of abnormal mental status; $†P < 0.05$ for comparisons between groups of patients.
awake, high percentages of sleep Stage 1, normal amounts of deep slow wave sleep and low percentages of REM sleep, when compared with age- and sex-matched norms (Williams et al., 1974). As shown in an example in Fig. 3, sleep was extremely fragmented and unstable during the period of mental status abnormalities, with frequent shifts between REM sleep, wakefulness, Stage 1 and Stage 2 sleep. In 4/7 patients, sleep was also monitored during the daytime and contained daytime sleep onset in REM periods (SOREMPs, i.e. REM sleep latency <15 min in sleep episodes separated by at least 15 min of wakefulness) are indicated by arrows.

REM sleep latency was abnormally short in 6/7 patients with mental status abnormalities (0, 3, 10, 12, 14 and 29 min, respectively, when norms are longer than 50 min), but was extremely delayed (316 min) in one patient. The 3 min REM sleep latency was observed in Patient 7, when monitored out of the ICU. All but one patient (with GBS) in the other two groups had a REM sleep latency >50 min, which is considered a normal threshold. The mean REM sleep latency was twice shorter in the group of GBS patients with mental status abnormalities than in the other GBS patients and ICU controls (P < 0.05). The REM sleep latency normalized in all but one patient after cessation of mental status abnormalities.

A major morphological abnormality, observed in 4 out of these 7 patients (and absent in the other two groups) consisted of abnormal bursts of polymorphic, rapid and then slow eye movements that occurred during sleep Stage 2 (Fig. 4A and B). They had a frequency of 1.8–2.3 bursts per minute, close to the 1.2–2.3 per min frequency observed during REM sleep in these same patients. They were absent during Stages 3 and 4. The eye movements totally disappeared after recovery from the hallucinations (Fig. 4C).

Another remarkable abnormality was the frank increase in muscle tone in patients with mental status abnormalities during 100% of REM sleep in 6/7 patients and during 47% of REM sleep in 1/7 patients. It normalized when the mental status abnormalities disappeared, while the patients were still in the ICU, and submitted to the same assisted ventilation. The abnormal tonic loss of atonia during REM sleep was also observed in an 18-year-old GBS patient without mental status abnormalities. The 11 remaining patients had a normal atonia during REM sleep.

**Discussion**

Mental status abnormalities, including vivid dreams, illusions, hallucinations and paranoid delusions, affected one-third of a large group of GBS patients. These symptoms were consistently associated with autonomic dysfunction and were more frequent in patients with severe GBS. They
occurred during the progression or the plateau phase of GBS, with a peak on day 9, and disappeared as the patients recovered from GBS. In addition, the GBS patients with mental status abnormalities had major REM sleep abnormalities when monitored, that included shortened REM sleep latencies, REM sleep without atonia and abnormal bursts of eye movements during non-REM sleep. The sleep abnormalities were not exclusively related to the ICU conditions, because they were also found in one patient out of the ICU, and not observed in other GBS and ICU controls. They were transitory and reversible, disappearing in parallel with mental status normalization.

Some dreams and illusions in GBS contained recurrent themes, such as travelling dreams, illusory body tilt or tactile illusions (like wearing gloves, having dislocated limbs or a floating body) that may be caused by sensory deafferentation in GBS and the continuous lying position. They indeed resemble the illusory tilt evoked by weightlessness in astronauts (Brown et al., 2002), and the perceptual distortion of the limbs during limb or spinal anaesthetic blocks (Paqueron et al., 2003) or by phantom limb (Ramachandran and Hirstein, 1998).

The mental status abnormalities were early recognized in the initial description of the disease by Guillain (1953), and reported thereafter in isolated case reports. In the two previous prospective studies of psychic symptoms in GBS, 7 out of 8 patients had illusions or hallucinations (Eisendrath et al., 1983) and 12 out of 49 patients had a brief reactive psychosis (Weiss et al., 2002), with frequencies of mental status changes close to our findings. The mental status changes are private experiences that can go unnoticed in ICU patients physically unable to verbalize them, if the medical team does not insist to obtain them. In contrast, what can be classically observed in ICU is the ‘ICU delirium’, that includes fluctuating levels of consciousness, poor orientation, hallucinations, delusions and aggressiveness or passivity. The risk factors for the delirium are ageing, metabolic disorders, use of psychoactive drugs and placement in windowless ICUs (Inouye, 1993; Kishi et al., 1995; Granberg et al., 1999). The ICU conditions cannot, however, be the unique cause of the mental status abnormalities in the GBS patients, because (i) although they were twice rarer in non-ICU GBS patients, changes in mental status started in 16% of GBS patients out of the ICU; (ii) the risk factors for ICU delirium were not found in GBS patients; (iii) the dreams, illusions and hallucinations were qualitatively more elaborate, more severe and more frequently associated with delusions in GBS patients than in ICU controls; (iv) they were twice more frequent in GBS than in ICU controls, despite GBS patients being younger and less exposed to psychoactive drugs and metabolic disorders than controls. It seems, therefore, that suffering from GBS in an ICU provides an important additional risk for experiencing mental status changes.

The risk factors for abnormal mental status in GBS were autonomic dysfunction, requirement for assisted ventilation (but not tetraplegia or impairment of cranial nerve, to the difference of Weiss series) and important CSF inflammatory signs, indicating a more severe form of the disease and motivating placement in the ICU. This could create an artificial link between ICU and abnormal mental status, whereas on the contrary one may imagine that more aggressive forms of GBS might affect the central nervous system. Maier et al. (1997) found degenerative and inflammatory cell reactions in the central nervous system, particularly in the periventricular areas, associated with changes in the blood–brain barrier in post mortem GBS brains. The strongest risk factor for
mental status changes in GBS was autonomic dysfunction, a syndrome whose exact cause is unknown. Some authors have suggested that visceral afferent fibres or parasympathetic and sympathetic efferent fibres may be altered by the polyradiculoneuritis (Goulon et al., 1975), whereas others have reported that the brainstem vagus nerve nucleus and hypothalamus may be affected by GBS (Lichtenfeld, 1971; Maier et al., 1997). If this last mechanism is proved to be true, this would suggest that autonomic dysfunction and mental status abnormalities are co-occurring markers of central impairment in GBS.

Fully cognizant patients reported dreaming as soon as they closed their eyes, and the transient persistence of the hallucinatory images after reopening them, a phenomenon similar to hypnagogic hallucinations. Furthermore, the mental status changes resembled wakeful dreams, like the prominent hypnagogic hallucinations and wakeful dreams experienced by patients suffering from primary narcolepsy, a disorder of REM sleep. Of interest, hypocretin-1, a hypothalamic peptide which is abnormally low in the CSF of patients with narcolepsy (Nishino et al., 2000), was transiently absent or could even decrease after initial normal to high levels in some patients with severe GBS (Nishino et al., 2003). Unfortunately, mental status abnormalities were not searched out in this series. In our study, CSF hypocretin-1 levels were lower in the patients with mental status abnormalities than in other GBS patients, suggesting that decreased hypothalamic hypocretin-1 transmission could promote mental status changes the following days. Hypocretin-1 levels were never <200 pg/ml, a threshold for deficiency in narcolepsy (Mignot et al., 2002), nor absent in the patients, but CSF was collected at the time of GBS diagnosis, and, except for one patient, not during the vivid dreams and hallucinations. It is, therefore, unknown how the kinetics of hypocretin-1 might change with time, in particular around the ninth day of the disease. Since the difference in hypocretin-1 levels between hallucinators and non-hallucinators was mild, it is also possible that it is not the autoimmune attacks against these cells, but against another, yet unknown part of the hypothalamus controlling REM sleep systems that would be responsible for the abnormal mental status and REM sleep.

Although sleep quality and quantity were poor in all patients monitored in ICU, whether they had GBS or other causes of tetraplegia, only GBS patients, and particularly those who experienced hallucinations, had striking abnormalities in sleep morphology (frequent eye movements during non-REM, sleep onset in REM periods, REM sleep without atonia). Shortened REM sleep latency has been occasionally observed in critically ill patients (Cooper et al., 2000), and putatively ascribed to sleep (and particularly REM sleep) deprivation and ultradian redistribution of sleep across day and night (Freedman et al., 2001). Although controversial (Dyer et al., 1995; McGuire et al., 2000) and measured rather than as a consequence than as a cause (Harrell and Othmer, 1987), sleep deprivation is also reported as a risk factor for ICU delirium. Interestingly, one GBS patient had identical REM sleep abnormalities although not yet placed in ICU, suggesting they are caused or at least amplified rather by the disease than by the ICU conditions. The rapid oscillations between encephalographic patterns of wakefulness, Stages 1 and 2 with rapid eye movements, and REM sleep without atonia characterize the status dissociatus. Status dissociatus represents a major breakdown of the polysomnographic markers for REM sleep, non-REM sleep and wakefulness, with admixtures of these states being present, but with conventional sleep stages not being easily identifiable during sleep monitoring (American Academy of Sleep Medicine, 2005). Initially described by Mahowald and Schenck in 1991, status dissociatus has been identified in rare cases of narcolepsy, parkinsonism, dementia, protracted alcohol withdrawal, status post-cardiac surgery, brainstem involvement of human immunodeficiency virus infection and fatal familial insomnia (Montagna and Lugaresi, 2002). The patients with fatal familial insomnia were, however, continuously confused, agitated, reported hallucinations and had signs of sympathetic hyperactivity, whereas our patients were not confused, as shown by their excellent memory of the dreams, hallucination and delusions. The GBS patients were insomniac rather than hypersomniac, another characteristic of status dissociatus rather than of narcolepsy. Status dissociatus is consistently associated with abnormal dreaming and hypnagogic hallucinations (Mahowald et al., 1998), as observed in our patients.

Since the REM sleep executive mechanisms are located within the brain, the presence of abnormal REM sleep (in particular REM sleep without atonia and rapid eye movements during non-REM sleep) in GBS provides strong evidence that the disease affects not only the peripheral nervous system, but also central targets. Since there is an association between autonomic dysfunction and hallucinations in GBS patients, the putative central target of the antibodies may be the lateral hypothalamus, which is (i) close to the third ventricle, where the blood–brain barrier is weaker and thereby more exposed to autoimmune attack (Maier et al., 1997); (ii) where hypocretin neurons controlling wake/non-REM/REM sleep transitions are located; (iii) where the paraventricular nucleus (Loewy and Neil, 1981; Akine et al., 2003) and the median preoptic nucleus (Patel and Schmid, 1988; Westerhaus and Loewy, 1999) controlling the autonomous system are located. The central dysfunctions causing status dissociatus and REM sleep behaviour disorders are unknown, but this last syndrome has been reproduced in animal models with lesions of the locus coeruleus alpha and peri-alpha in the pons. This small group of mainly cholinergic neurons has not yet been examined in GBS brains, despite the fact that one of the first cases of REM sleep behaviour disorder described in the literature was a GBS patient (Schenck et al., 1986).

Finally, we found that the sleep and dream-related mental status abnormalities observed in some GBS patients were wakeful dreams associated with specific wakefulness/non-REM/REM sleep state dissociation. Although limited to
one-third of the patients affected by this rare disease, these abnormalities may provide clues to understand psychoses in other neurological diseases associated with hallucinations, increased dream-like imagery and sometimes autonomic dysfunction. These results indicate that GBS can affect the central nervous system. They also suggest that hallucinations in GBS are manifestations of a sleep and dream-related disorder. This should also reassure doctors, patients and families as to the nature of this disturbing experience.

Supplementary data

Supplementary data are available at Brain Online.

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References


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