Article abstract

Seven patients with "locked-in" syndrome were studied by prolonged polygraphic recordings. Severe alterations in the sleep pattern were observed in five patients who had bilateral extensive pontine lesions resulting in tetraplegia, facial and pseudobulbar paralysis, and absence of conjugate horizontal gaze. Rapid eye movement (REM) sleep was entirely absent while non-rapid eye movement (NREM) sleep was absent, reduced, or altered. The remaining two patients, both of whom had relative sparing of horizontal gaze and apparently either no or minimal pontine tegmental involvement, showed both REM and NREM sleep with only a minimal alteration in the sleep pattern. The study suggests that, in human beings as in animals, pontine structures near the midline are essential for control of sleep states.

Sleep abnormalities in patients with brain stem lesions

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ecent work has refuted the traditional view regarding sleep as a unitary passive state opposite to waking. Aserinsky and Kleitman¹ discovered that sleep consisted of two successive functional phases, usually called rapid eye movement (REM) and non-rapid eye movement (NREM) states. Animal studies have suggested that both REM and NREM sleeping states are dependent on active neural mechanisms located in the brain stem.^{2,3} In man, only scanty data, largely based on single case reports, are available on the alteration of sleep patterns in patients with brain stem lesions.⁴⁻⁷ Although they do suggest that extensive and bilateral brain stem lesions produce severe alterations in sleep states, these studies have given variable results; the patients studied have been few, and the results are not comparable because of the extreme variability in the anatomic extent and the pathologic process afflicting the brain stem. Furthermore, the time of the sleep study in relation to the onset of the brain stem insult has varied from a few weeks to several years. In an attempt to overcome some of these problems, the authors carried out prolonged polygraphic recordings, often

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serially on several occasions, on seven patients who had "locked-in" syndrome caused by bilateral brain stem lesions.

Methods and case reports. The study included seven patients with brain stem lesions admitted to the Indiana University Hospitals in the years 1973 to 1975. We included only those patients who had extensive brain stem lesions resulting at least in tetraplegia and pseudobulbar paralysis, because restricted or unilateral lesions may not produce significant sleep abnormalities. Furthermore, we confined the study to those patients who had definite evidence of alertness because, both behaviorally and electroencephalographically, the identification of sleep patterns would be easier in such patients than in deeply comatose subjects with extensive tegmental lesions. All patients showed features typical of "locked-in syndrome" as originally described by Plum and Posner⁸ that included tetraplegia, pseudobulbar palsy, mutism, and varying degrees of alertness at some stage of the illness. In five patients, the lesion was probably at the midpontine level on both sides because there was, in addition, a severe restriction of horizontal eye movements and the presence of bilateral upper motor neuron facial paralysis. One patient had a lesion in the lower brain stem, most likely below the midpons because of the intact eye movements and the lack of paralysis of the facial and masticatory muscles. The remaining patient had a lesion of the basis pontis on both sides with extension in the

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pontine tegmentum on the left, resulting in peripheral facial and abducens palsies on the same side.

In one patient, the brain stem lesion was a spontaneous hemorrhage that was confirmed at autopsy. In the remaining six patients, the lesion was probably an ischemic infarction. Cerebral angiography demonstrated occlusive disease in the vertebrobasilar system in three patients, and autopsy confirmed the brain stem location of the infarct in one of them. The diagnosis was entirely clinical in three patients.

Routine electroencephalograms (EEGs) were recorded on each patient prior to the polygraphic studies. The electrode placement was according to the international "10-20" system. Silver-silver-chloride electrodes were held on the scalp by collodion. Both bipolar (scalp to scalp) and monopolar (referential) derivations were used. Clinical and EEG responses to various stimuli including photic, auditory, and somesthetic were studied during recording in each patient.

All patients had continuous polygraphic recordings, usually extending to 24 hours, on one or more occasions. To retain as far as possible the patient's normal hospital routine, recordings were made at the bedside with the patient in his usual bed. These studies were done on a 8-9 channel Grass electroencephalograph, usually using two channels for electro-oculogram (one each for horizontal and vertical eye movements), one channel for chin electromyogram, and five or six channels for EEG. EEG channels recorded activities from frontal, central, and occipital electrodes connected to the ipsilateral ear (FP1-A1, FP2-A2, C3-A1, C4-A2, O1-A1, and O2-A2). Photic stimulation was carried out on one or more occasions during each study. A paper speed of 30 mm per second was most commonly used, but a slower paper speed was used for short intervals. To promote sleep, the lights were turned off and the patient was disturbed as little as possible. The records were interpreted visually, page by page. Sleep was scored into different stages according to the criteria of Rechtschaffen and Kales.⁹ The clinical behavior of the patient was carefully observed and noted in detail on the tracing.

Case 1. A 62-year-old man began to have difficulty in hearing, deviation of the mouth to the right, and slurred speech on the morning of November 1, 1973. Within the next few hours, he became unresponsive and paralyzed on both sides. Neurologic evaluation at the time of admission showed flaccid tetraplegia and decerebrate posturing, particularly on painful stimuli. Muscle stretch reflexes were hyperactive and Babinski sign was elicited on both sides. Though the patient appeared "comatose," he could open his eyes and stare straight ahead on loud commands. He could move his eyes vertically but had entire absence of horizontal eye movements. Doll's-eye maneuver and cold caloric stimulation failed to deviate the eyes to either side. Ocular bobbing was evident bilaterally but was more prominent on the left. Facial and bulbar musculature was paralyzed on both sides. The patient was clinically thought to have "locked-in" syndrome secondary to a brain stem infarct at the pontine level. No contrast studies were carried out. He died on February 5, 1974, after more than 3 months.

Case 2. A 55-year-old man was admitted on March 30, 1974, after being found lying on the floor unresponsive on that day. On

admission he was unconscious and had irregular respirations. Vertical eye movements were intact but horizontal eye movements were absent. Ocular bobbing was present bilaterally. Oculocephalic reflex and caloric stimulation did not produce deviation of the eyes in the horizontal direction. Motor system examination revealed total facial and bulbar paralysis with flaccid tetraplegia. Reflexes were hyperactive but symmetrical. Babinski sign was present bilaterally. Signs of meningeal irritation were absent.

Four-vessel cerebral angiography disclosed neither evidence of occlusive disease nor mass lesion. Spinal fluid was slightly hemorrhagic. The patient was diagnosed as having had a pontine hemorrhage. In spite of several bouts of pneumonia, the patient became progressively more alert and regained some motor strength.

Six months after the neurologic insult, he started making attempts to communicate by speaking in a whisper. He could move his head and all his extremities to some extent. His eyes still showed severe limitation of horizontal movements, but the vertical eye movements were full.

The patient died on March 2, 1975, due to rupture of an aneurysm of the abdominal aorta. Autopsy disclosed an old resolving hematoma in the midpons, situated almost exactly at the point of division between the basis pontis and the tegmentum, somewhat more extensive on the right side (figure 1).

Case 3. A 45-year-old man who had a history of hypertension, arteriosclerotic heart disease, and type III hyperlipidemia was hospitalized on July 17, 1974, because of confusion, disorientation, and diplopia of 5 days' duration. Three days after admission, the patient was found to be stuporous but could open his eyes and move his right upper limb on command. He had skew deviation of the eyes; the right eye was midline and deviated slightly downwards while the left eye was upwards and slightly abducted. The patient could move his eyes vertically on command but not horizontally. There was tetraplegia except for minimal movements on the right side. Babinski sign was elicited bilaterally. Bilateral upper motor neuron type of facial and bulbar paralysis was noted, the former more severe on the left side.

Four-vessel cerebral angiography showed complete occlusion of the basilar artery 1 cm distal to its origin. The patient progressively improved in spite of *Proteus* pneumonia. At the time of discharge to a nursing home after 3 months of hospitalization, he still had disconjugate eye movements and restriction of horizontal movements. In spite of some improvement in his motor strength, he was still markedly weak on the left side and had bilateral Babinski signs. He was able to communicate by moving his eyes up and down and by some movements of the right side of his body. It was later learned that he died in November 1974. Autopsy was not obtained.

Case 4. A 60-year-old man with a history of chronic obstructive lung disease, chronic cor pulmonale, diabetes mellitus, and aortoiliac by-pass was admitted in an unresponsive state to a local hospital on August 3, 1974. Blood sugar was 750 mg percent. Brain scan showed a definite area of increased uptake in the left cerebellum. Two days later, he responded to one of us during the physical examination by opening his eyes on command. He could look up and down on request but was otherwise entirely immobile. Painful stimuli elicited decerebrate posturing. The right carotid pulse was absent and a bruit was heard over the left carotid. His eyes were disconjugate at rest, the right eye being somewhat abducted and the left eye in midline. The right eye showed fine intermittent horizontal nystagmus

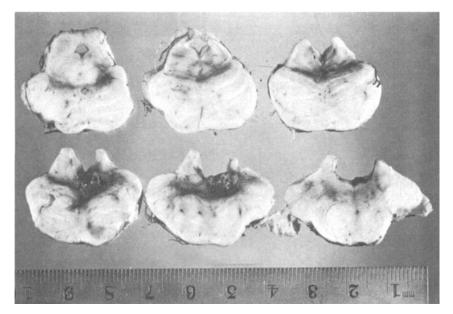


Figure 1. Serial cross sections of the brain stem of a 55-year-old patient with "locked-in" syndrome showing resolving hematoma in the pons, involving the region at the junction of basis pontis and tegmentum, more extensively on the left side.

unaccompanied by similar movements of the left eye. Ocular bobbing was seen bilaterally, was more pronounced on the left side. Horizontal eye movements were entirely lacking, but vertical movements were fully intact. Cold caloric stimulation produced no significant deviation of the eyes. Motor system examination revealed flaccid tetraplegia and bilateral facial and bulbar paralysis of the upper motor neuron type. Muscle stretch reflexes were hyperactive and symmetrical. Plantar responses were extensor on both sides. The clinical impression was that he had "locked-in" syndrome due to ventral pontine infarction.

Cerebral angiography demonstrated occlusion of the right carotid and both vertebral arteries. Only the left carotid artery was visualized above the neck. The neurologic state remained essentially unchanged until his death on August 9, 1974. Autopsy showed bilateral pontine infarction, predominantly involving the ventral pons, though the tegmental region was also minimally affected. There were bilateral cerebellar hemispheric infarcts, more extensive in the left side. The basilar and both vertebral arteries were completely occluded.

Case 5. A 47-year-old woman had a sudden onset of dizziness and inability to stand on September 23, 1973. She was taken to a local hospital where she was found to have complete paralysis of her upper and lower extremities with inability to speak. During the patient's entire illness, she was completely aware of her surroundings and was able to communicate by blinking her eyes using two blinks for "yes" and one blink for "no." She was transferred to the Indiana University Medical Center on April 29, 1974. Neurologic examination on admission showed spastic tetraplegia except for some voluntary activity of the hands. She showed marked emotional instability and inappropriate crying. Except for weakness of the palate and the tongue, the musculature innervated by the cranial nerves was intact. Muscle stretch reflexes were hyperactive including the jaw reflex, and there was sustained ankle and knee clonus bilaterally. Babinski sign was present on both sides. The patient did not produce any words but she understood simple commands and communicated fairly well with the examiner. Deep and superficial sensations were not affected. The patient was clinically diagnosed to have a brain stem infarction. It was presumed to be in the lower brain stem because of the intact ocular, facial, and jaw motility.

Case 6. A 55-year-old woman who had a previous history of

myocardial infarction and angina pectoris, woke up with a headache on the night of November 1, 1974. Later that morning her husband found her unable to talk, move, and respond. She was admitted to the local hospital, where she was found to be alert, able to comprehend what was spoken to her, and able to move her eyelids on command. She exhibited ocular bobbing for the first 2 or 3 days. She had tetraplegia, severe pseudobulbar paralysis, and bilateral pyramidal signs. Cerebral angiography showed complete occlusion of her basilar artery. On March 24, 1975, she was transferred to the Indiana University Stroke Unit for evaluation and rehabilitation. On neurologic examination at the time of admission, she was emotionally labile and severely dysarthric. She could utter only a few words but could understand very well. There was a lateral rectus palsy and a severe peripheral facial paralysis on the left side. Corneal reflex was diminished on the left. Moderately severe paralysis of palate, tongue, and sternocleidomastoids was noted on both sides. She had severe tetraplegia with some restoration of flexion-extension movements of the elbow and wrist bilaterally. Virtually no movements were possible in the legs. All muscle stretch reflexes were hyperactive and Babinski sign was elicited bilaterally. Superficial and deep sensibilities were completely intact. After intensive physical therapy, she was able to feed herself with the help of mechanical devices at the time of discharge on May 17, 1975.

Case 7. A 65-year-old woman was admitted to a local hospital in the last week of May 1975 for pain in the right upper abdomen. While in the hospital, she developed slurred speech and right hemiparesis on June 1, 1975, followed the next day by paralysis of all four limbs, and inability to speak. At the time of her transfer to the Indiana University Hospital, the patient was tetraplegic but able to respond to simple commands by slightly nodding her head appropriately and signalling by moving her eyes. She had bilateral facial and pseudobulbar paralysis. Horizontal eye movements were entirely lacking but vertical gaze was intact. Attempts on left lateral gaze induced monocular horizontal nystagmus of the left eye. Ocular bobbing was observed initially for a few days. Painful stimuli elicited minimal flexion of the right upper limb. There was spasticity of all four limbs and muscle stretch reflexes were symmetrically hyperactive. Plantar reflex demonstrated Babinski sign bilaterally. Sensations were grossly intact.

Age, sex	Date of onset	Date and duration (hours) of polygraphic study		Sleep patterns	Remarks
62, M	11.01.73	11/19/73	16.0	No behavioral or EEG sleep	_
		11/24/73	23.0	Same findings	
55, M	03.30.74	4/4/74	24.0	No REM; NREM 4.9 hours; S1– 26.4%, S2–73.6%; ill defined occasional spindles	Partially resolved spontaneous midpontine hemorrhage at autopsy
		8/28/74	6.0	No behavioral or EEG sleep	
		10/7/74	21.5	Same findings	
45, M	07.20.74	8/14/74	23.5	No behavioral or EEG sleep	-
		10/16/74	22.0	No REM; NREM 3.4 hours, essentially S1 and S2 sleep with occasional ill defined spindles	
60, M	08.03.74	8/7/74	23.5	12 midnight to 3 A.M. EEG became diffusely slow but no sleep spindles or REM	Midpontine infarction at autopsy
47, F	09.23.73	5/16/74	10.5	Total sleep time 5.67 hours including two REM periods; REM-10.8%, S1-12.2%, S2-73.2%, S3-3.8%	Tetraplegia and pseudobulbar palsy but intact facial and ocular motility
55, F	11.01.74	3/26/75	24.0	Total sleep time 6.03 hours including seven REM periods; REM-21.2%, S1-15.0%, S2-58.5%, S3-5.3%	Tetraplegia, pseudobulbar palsy, left 6th and left peripheral 7th palsies
65, F	06.01.75	6/11/75	24.0	No REM sleep; altered NREM sleep of 3.95 hours consisting of several periods of diffuse delta activity and occasional and ill defined vertex transients and spindles	Typical "locked-in" syndrome initially; during recovery, tetraplegia, pseudo- bulbar palsy, right MLF, right 6th and right peripheral 7th palsies
		7/7/75	24.0	Total sleep time 5.16 hours; no REM; S1-32.4%, S2-65.3%, S3-2.3%	periprier / III passes
S1, S2 and S3	3 = Non-REM slee	p stages 1, 2 and 3 r	espectively.		

Table. Polygraphic findings in seven patients with brain stem lesions

Within a month, she showed some improvement. Motor strength returned slightly in the arms and the legs so that she was able to grip and flex her elbows and knees. Severe lower motor neuron type of facial paralysis was now evident on the right and upper motor neuron paralysis on the left side. There was also a significant improvement in the horizontal eye movements. On right lateral gaze, slight restriction of abduction of the right eye was still present. On left lateral gaze, the right eye did not adduct and the left eye, which abducted almost completely, showed horizontal nystagmus. Clinically, she was thought to have a brain stem infarction at the midpontine level, involving the right tegmental region in addition to the basis pontis. Contrast studies were not done. She was discharged to a nursing home in September 1975.

Results. *EEG findings.* The EEG was either normal or only minimally altered in all patients. The basic rhythms of the tracings were in the alpha or high theta frequency range and were best developed in the occipital regions. Often the basic rhythms were more or less generalized. Significant delta activity was uncommon and was seen in only one patient in the early stages of his illness. Interestingly, changes in the frequency of the basic EEG

activity were seen on repeat studies, and these would often correlate with changes in responsiveness of the patient. Infections, metabolic derangements, and fever not only tended to depress alertness but also slowed the EEG activity. As would be expected, focal or lateralized slowing was not seen.

In contrast to patients deeply comatose because of extensive brain stem lesions who may also show a "normal" or "minimally altered" EEG, the patients with "locked-in" syndrome showed reactivity to various stimuli. Photic stimulation elicited driving response in all patients on one or more occasions.

Prolonged polygraphic recordings. The table summarizes the results of the prolonged polygraphic recordings on the seven patients.

There were two patients who could be studied only during the acute stage of their illness and both had polygraphic studies within less than a month of the onset of the brain stem insult. One had no evidence whatsoever of either REM or NREM sleep states in two different studies done after 2 and 3 weeks of the onset of symptoms. The other patient had no REM sleep but probably had

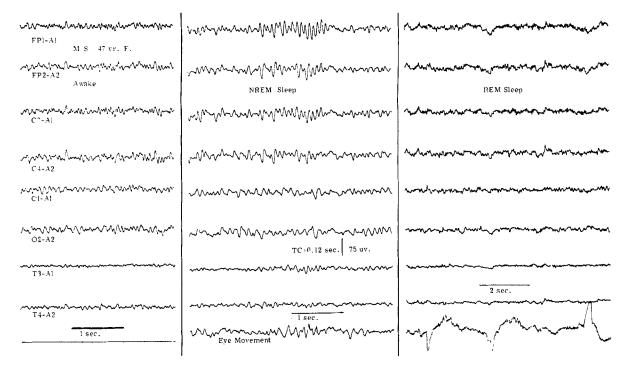


Figure 2. The EEG activity of a 47-year-old patient with "locked-in" syndrome during awake, NREM, and REM stages of sleep.

severely altered NREM sleep. His EEG became diffusely very slow between midnight and 3:00 A.M. but showed no activity resembling sleep spindles, vertex sharp waves, or K complexes. Behaviorally, the patient was relaxed and quiet during this time. Photic stimulation during the period of slow EEG activity did not elicit any driving response, though stronger stimuli promptly made the patient alert.

The remaining five patients could be studied by prolonged polygraphic recordings after 1 month to several months of the brain stem insult when they were clinically stable. The results were as follows: (1) Both REM and NREM sleep states were identified in two patients. One of them had an essentially normal sleep pattern, except for a minimal decrease in the total sleep time. Twenty-four hours of continuous recording in this patient showed a total of 6.03 hours of sleep. There were seven REM periods. The time spent in different sleep stages was as follows: REM-21.2 percent, stage I-15 percent, stage II-58.5 percent, and stage III-5.3 percent. In the second patient there was similar reduction in the total sleep time but the REM stage was more significantly reduced. Continuous 10.5 hours all-night recordings showed a total sleep time of 5.6 hours and two REM periods (figure 2). The percentage time spent in different sleep states was as follows: REM-10.8 percent, stage I-12.2 percent, stage II-73.2 percent, and stage III-3.8 percent. (2) The remaining three patients showed an entire absence of REM sleep and variable alterations of NREM sleep.

One patient who showed long periods of EEG slowing associated with ill-defined occasional sleep spindles in the polygraphic recordings done within 1 week of pontine hemorrhage (figure 3), showed neither this period nor any clinical evidence of sleep activity in the two studies done 5 and 6 months after the cerebrovascular accident. However, a year after the original brain stem insult, a routine EEG done after giving the patient 500 mg of chloral hydrate did show similar periods of EEG slowing with a few ill-defined sleep spindles.

Similarly, another patient who had no evidence of sleep activity in the polygraphic study done 3 weeks after the brain stem infarction, showed only short periods of EEG slowing in a second study 2 months later. However, vertex sharp waves, sleep spindles, and K complexes did not occur. He appeared to be more relaxed and quiet during these periods of EEG slowing.

The above two patients remained hospitalized for several months in the Veterans Administration Hospital. The relatives and the nurses attending them noted marked diminution to entire lack of behavioral sleep in both of the patients. They had variable periods during which the eyes would be closed and the patient would seem to be relaxing, but on minimal stimulation the eyes would open and they would be alert again.

One patient showed no REM sleep but had normal duration of NREM sleep in a polygraphic study more than a month after the brain stem infarction. However, during the acute stage (10 days after the onset), not only was the REM state absent but the total sleep time was reduced to less than 4 hours.

Discussion. There have been only a few sleep studies reported in the literature in patients with brain stem lesions. In a comatose 63-year-old man who had extensive pontine infarction involving both the basal and the

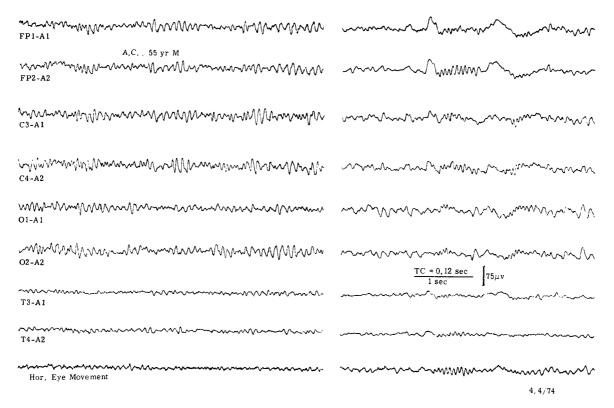


Figure 3. Prolonged polygraphic study of a 55-year-old patient with "locked-in" syndrome showing EEG activity during awake and NREM sleep. Sleep spindles were only rarely seen and were usually ill defined.

tegmental regions, Lundervold, Hauge, and Loken¹⁰ reported a few hours of ordinary sleep pattern, including sleep spindles, in a single, continuous day and night recording. However, the EEG pattern failed to show any reactivity to strong pain and sound stimuli, and the tracing shown in the paper did not show convincing sleep spindles. It is therefore difficult to evaluate the presence or absence of sleep in this patient. Friedlander¹¹ reported normal NREM sleep in routine clinical EEGs in three of his 31 patients with brain stem vascular lesions. These patients, however, had either unilateral or very restricted lesions in the brain stem. Chase, Moretti, and Prensky,¹² on the other hand, found no evidence of behavioral and EEG sleep in two patients with extensive brain stem infarctions, but the recordings were not prolonged enough for the findings to be conclusive. Only a few reports^{4-7,13} in the literature, each comprised of a single patient with a brain stem lesion studied by prolonged polygraphic recording, have the specific aim of determining abnormalities of sleep states. In a patient with traumatic basilar artery occlusion and clinical features typical of "lockedin" syndrome, Feldman⁴ observed a modest decrease in the total sleep time to 4 to 6 hours in all-night recording, but a marked decrease was noted in the REM state that accounted for just 3 to 4 percent of the total sleep time. Similarly, a 5-hour nocturnal EEG recording by Wilkus and associates¹³ on a comatose patient with extensive pontine infarct revealed only 11/2 hours of NREM sleep and no REM state. On the other hand, the sleep studies by Guilleminault, Cathala, and Castaigne⁵ in a patient with traumatic brain stem damage and that of Freemon, Salinas-Garcia, and Ward⁶ in a patient with brain stem infarct showed somewhat different sleep abnormality. Both patients showed moderate to marked decrease in the total sleep time, but the percentage time spent in REM sleep was normal. Barros-Ferreira and co-workers⁷ observed selective disorganization of REM sleep but a normal duration of both NREM and REM sleep states in a child with pontine glioma. This patient apparently had clinical features suggestive of a unilateral pontine involvement. Because of the variable extent and severity of the brain stem lesions, the results of these studies are not uniform, though they do suggest prominent alteration in sleep patterns caused by extensive brain stem lesions. All showed a significant decrease in the total sleep time with or without selective reduction in the percentage time spent in the REM state.

The findings of the present study are unique in that five of the seven patients, including three studied in the chronic stage, showed entire absence of REM sleep. Variable alterations of NREM sleep also were observed in these patients, ranging from absence to almost normal NREM sleep. Most patients, however, showed marked disorganization of NREM sleep, including decrease in the total NREM time and poorly developed and less frequent vertex sharp waves and sleep spindles. It is interesting that all of the five patients who showed severe abnormalities in the sleep pattern had lesions at the midpontine level that not only interrupted the corticospinal and corticobulbar fibers bilaterally but also resulted in severe horizontal gaze paralysis. The only motor activity that remained intact was the vertical eye movements. One may argue that the entire absence of REM sleep in this group of patients was simply due to the severe paralysis of horizontal gaze that made the recognition of REM sleep difficult. It is true that REMs are absent during sleep in patients with gaze palsies, but these subjects do show change of the EEG activity to a low voltage fast pattern characteristic of REM sleep.¹⁴ It may be further added that the eye movements during REM sleep are more commonly oblique or vertical rather than horizontal.¹⁵ Because the above-mentioned patients had intact vertical eye movements, REMs would have been obvious had REM sleep occurred.

Both REM and NREM sleep states were recorded in the present study in only two patients. One had a lesion presumably below the midpontine level while the other had bilateral basis-pontis lesions with extension into the tegmentum only on the left side. Both patients had a slight decrease in the total sleep time, but the former patient had in addition a significant decrease in the percentage time spent in the REM state.

One may speculate that the changes in the sleep pattern seen with brain stem lesions may be related to immobility associated with tetraplegia. This does not appear to be so, because EEG sleep patterns in patients with severe quadriplegia secondary to high cervical cord lesions show only a slight reduction in total sleep time, though the percentage of time spent in REM sleep is significantly reduced.¹⁶ At least two patients of the present series who had severe lack of both NREM and REM sleep had less severe tetraplegia (and could move limbs and trunk to some extent) than the two who had preservation of both NREM and REM sleeps. It is obvious, therefore, that it is not the mere presence of quadriplegia in "locked-in" syndrome but is instead destruction of some neural structure located in the brain stem that results in alteration of sleep patterns.

Much experimental evidence implicates brain stem structures in both REM and NREM states of sleep. In cats precollicular (or high cerveau isole) or postcollicular (or prepontine preparation or low cerveau isole) transections produce radical modification of sleep and wakefulness.^{17,18} The EEG is characterized by spindles, and there are many behavioral signs of sleep. On the other hand, midpontine pretrigeminal transection results in an entirely different behavioral and EEG pattern.¹⁹ Low voltage fast activity characterizes the EEG of such cats for 65 to 90 percent of the recording time, and the ocular behavior strongly suggests constant alertness or vigilance. Four of the seven patients reported in the present study had somewhat similar EEG and behavioral findings. The elegant pharmacologic and ablative studies of Jouvet^{2,3} in cats have further defined the role of different brain stem systems in sleep. The midline raphe nuclei of the brain stem, where the majority of the serotonin (5 HT)containing neurons are located, seem to be essential for the initiation of NREM sleep. Their destruction in cats produces hyposomnia to total insomnia, depending on the extent of the lesion. Inhibition of the synthesis of serotonin by p-chlorophenylalanine leads to reversible insomnia; 5-hydroxytryptophane effects return to normal sleep. REM sleep, on the other hand, has been shown to be dependent on "priming" serotonergic mechanisms located in the caudal raphe system and on "triggering" mechanisms located in the catecholamine-containing neuronal systems in lateral brain stem, particularly in the region of the locus ceruleus. Destruction of these nuclei in animals leads to the suppression of REM sleep without alteration of NREM sleep.

The present study suggests that, as in animals, bilateral extensive brain stem lesions in human beings are associated with entire absence of REM sleep and some reduction or alterations in the NREM sleep. Though the exact delineation of the structures essential for sleep states in humans is not possible in this study, several conclusions can be drawn:

1. Bilateral extensive lesions in the midpontine region are likely to be associated with severe sleep abnormalities that consist of absence of REM sleep and severe reduction or alterations of NREM sleep.

2. It probably is not the involvement of the corticospinal or corticobulbar tracts in the midpons but more likely the associated involvement of the pontine tegmentum that results in sleep abnormalities.

3. The fact that sleep was markedly affected in those patients who had severe bilateral horizontal gaze palsy would further suggest that the neural mechanisms concerned with sleep are located close to the paramedian pontine reticular formation, which mediates conjugate horizontal eye movements.²⁰ This area would roughly correspond to that of the midline raphe nuclei, which has been incriminated in animals not only in NREM sleep but also in "priming" REM sleep. The importance of the pontine reticular formation near the midline in human sleep is supported by the autopsy findings in two patients of this series and one patient of Freemon, Salinas-Garcia, and Ward⁶ who had bilateral tegmental lesions including involvement of the caudal midline raphe nuclei.

4. Lesions of brain stem below the midpontine level or those in which the pontine tegmentum is involved unilaterally may be associated with minimal alterations in the sleep pattern. Changes may consist of slight reduction of total sleep time and/or selective reduction of REM sleep.

It cannot be overemphasized that the above conclusions are only tentative. Further polygraphic recordings are needed on patients with brain stem lesions, particularly studies with pathologic confirmation of the site and extent of the lesion, before all types of sleep abnormalities and their correlation with lesions of particular neuronal system can be clearly defined in man.

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