Central neurogenic hyperventilation:
Pharmacologic intervention with morphine sulfate and correlative analysis of respiratory, sleep, and ocular motor dysfunction

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Article abstract—Central neurogenic hyperventilation (CNH), for which there is no effective therapy, can eventually result in respiratory fatigue and death. This report describes a patient with CNH due to a brainstem anaplastic astrocytoma who also exhibited disturbances of sleep and ocular motor function. The CNH responded clinically to morphine sulfate and methadone. Analysis of ventilatory response to CO_2 before and after morphine demonstrated a depression of ventilatory response (49 to 53% of baseline) and occlusion pressure response (35 to 50% of baseline) to CO_2, with a requirement for high doses of naloxone (10 mg IV) to reverse the effect. Polysomnography revealed sustained hyperventilation, elevated O_2 saturation, and low end-tidal CO_2 throughout all stages of non-rapid eye movement (NREM) sleep, and absence of rapid eye movement (REM) sleep. Ocular motor evaluation disclosed absence of horizontal and reflexive saccades with compensatory head thrusts. Correlation of the clinical and physiologic data with the MRI abnormalities suggested that the lesion responsible for CNH in this patient might reside in the medial tegmental parapontine reticular formation. Since recurrent episodes of hyperventilation responded in a sustained fashion to IV and oral opiates, this treatment may warrant consideration in other patients with CNH.

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Central neurogenic hyperventilation (CNH) is characterized by sustained tachypnea that persists despite an elevated arterial P_{O_2} and pH and a low arterial P_{CO_2}. By definition, CNH occurs in the absence of a respiratory stimulant and persists during sleep. Hepatic encephalopathy and brainstem tumors have been associated with this condition.[1,2] The mechanisms of production of CNH are unclear,[3] and there is no effective treatment. Persistent hyperventilation can eventually produce respiratory fatigue and death.[1]

This report describes the successful treatment of a patient with CNH with opiates. Ventilation was assessed quantitatively by documenting the response to CO_2 before and after administration of IV morphine and naloxone. Since this patient manifested disorders of extraocular movements and sleep, we also analyzed ocular motor function and performed polysomnography to search for clues that might lead to a better understanding of the pathophysiology of CNH.

Case report. A 32-year-old woman with neurofibromatosis had a 3-month history of diplopia, right-hand numbness, occipital and neck pain, intermittent twitching of the right eyelid and hand, and unsteady gait. Examination revealed poor pursuit, with absent horizontal volitional and spontaneous saccades but relative sparing of vertical eye movements. Full eye movements were obtained with vestibulo-ocular reflexes. She made typical head-thrusting movements along with blinks to change fixation. After the head thrust overshot the intended target, the eyes would fixate and a slower movement of the head would allow the eyes to resume their normal alignment. These movements were similar to those described in congenital ocular motor apraxia.[4] Electro-oculogram (EOG) revealed no volitional horizontal saccades. Optokinetic nystagmus was absent in the horizontal plane and present in the vertical plane. A decreased right corneal reflex, bilateral ptosis, right facial myokymia, truncal and gait ataxia, and mild right-sided appendicular ataxia were present. There was a mild right hemiparesis, hypertonia, hyperreflexia, and hemisensory deficit that equally affected the face, arm, and leg. Also noted were a hyperreflexic jaw jerk and bilateral Babinski signs. Multiple café-au-lait spots and subcutaneous nodules were present. MRI showed abnormal signal from the upper medulla to the pons, enveloping the 4th ventricle and distal aqueduct (figure 1, A and B). Stereotactic biopsy of the tumor in the pontine tegmentum revealed an anaplastic astrocytoma without necrosis. The patient received dexamethasone, 16 mg/d, and radiotherapy 5,500 cGy to the posterior fossa in 30 fractions over 44 days.

Two weeks after a tapered discontinuation of the dexamethasone (3 months after biopsy; 5 weeks after completion of radiotherapy), the patient developed tachypnea, vomiting, diplopia, gait instability, slurred speech, and recurrent neck and head pain. Her husband reported that her tachypnea did not diminish during sleep, which he described as fitful. On admission, she was alert and oriented, but had a respiratory rate of 36 per minute with consistently deep breaths. Heart rate was 151 per minute, blood pressure 150/120 mm Hg,

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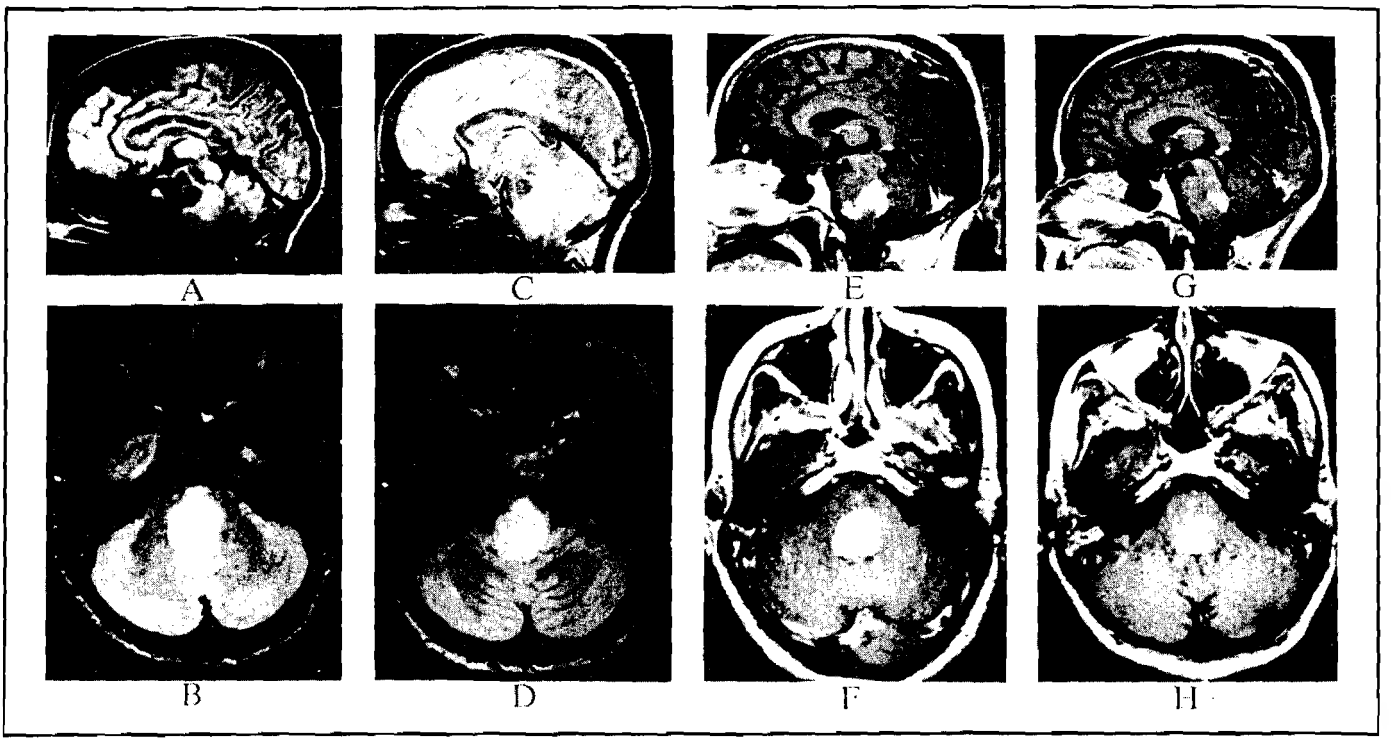

Figure 1. Localization of the brainstem anaplastic astrocytoma by MRI. Sagittal (A, C, E, and G) and axial (B, D, F, and H) views. A through D were proton density images (gadolinium was not yet available), while E through H were T_1 images with gadolinium enhancement. (A and B) Prior to biopsy and therapy. Abnormal signal is present from the upper medulla to the pons, enveloping the 4th ventricle and distal aqueduct. (C and D) Scan 3 months later, at the time of initial development of CNH. Progressive caudal extension of the abnormal signal into the ventral medulla has occurred. (E and F) Gadolinium MRI 10 months after diagnosis, showing enhancement in the ventral rostral medulla, and pontine tegmentum and tectum. (G and H) At 30 months, after chemotherapy and off steroids, showing reduction in enhancing tissue.

temperature 37 °C. Arterial blood gases on room air were P_{O_2} 121 mm Hg, P_{CO_2} 7.6 mm Hg, pH 7.65, HCO_3^- 8.4 mEq/l, and base deficit −4.9 mEq/l. Unfortunately, CSF and serum lactate values were not obtained; urine pH was 6.5. An ECG showed sinus tachycardia, and chest x-ray was normal. A ventilation-perfusion scan was negative for pulmonary emboli. There was no history of cyanide or salicylate exposure, and the drug screen was negative. The ocular motor paresis with compensatory head thrusts persisted; vestibulo-ocular reflexes now identified mild bilateral abducens palsies and a mild left internuclear ophthalmoplegia. Additional new findings on examination included bilaterally increased tone, increased truncal ataxia, slurred speech, and decreased palatal elevation and gag reflex. MRI showed progressive caudal extension of the abnormal signal into the medulla (figure 1, C and D). The patient could not volitionally inhibit the respiratory drive for more than 3 seconds. CO_2 rebreathing augmented the patient's need to breathe and increased the respiratory rate. One hundred percent O_2 did not inhibit respirations despite changing the blood gases (P_{O_2} 259 mm Hg, P_{CO_2} 8.3 mm Hg, pH 7.66, HCO_3^- 9.3 mEq/l, base deficit −4.4 mEq/l). Midazolam, 5 mg IV, resulted in somnolence but no reduction in respiratory rate. Morphine sulfate, 5 mg IV over 5 minutes, immediately decreased the respiratory rate to 20 per minute without mental status depression. The patient was started on methadone, 5 mg q8h po, and respiratory rate remained at 20 to 28 per minute. Methadone, 10 mg q8h, further reduced respiratory rate to 18 per minute but caused confusion. After control of the respiratory rate was established, tachycardia and hypertension were treated with propranolol, 40 mg q6h, but within 24 hours, enalapril 10 mg q12h was required to control the hypertension. Dexamethasone, 10 mg q6h, was initiated 24 hours after the morphine sulfate. Over the next 5 days on methadone, her arterial blood gases on room air were P_{O_2} 85 to 93 mm Hg, P_{CO_2} 22 to 27 mm Hg, pH 7.52 to 7.60, HCO_3^- 17 to 22 mEq/l, and base deficit −2.4 to +2.4 mEq/l. On the 6th day, the methadone was discontinued but only a modest tachypnea (15 to 20 per minute) developed.

Chemotherapy was started with procarbazine, lomustine (CCNU), and vincristine (PCV) for presumed progression of her brainstem tumor. Repeat MRI 3 months later disclosed a slight reduction in tumor size (not shown). Over the next 9 months, during which time she received 5 courses of PCV, there were no episodes of symptomatic CNH, although mild tachypnea (15 to 20 per minute) persisted. The patient then developed severe tachypnea when her dexamethasone was tapered to 1 mg qod, which was accompanied by recurrent diplopia, dysphagia, gait instability, and neck ache. Examination revealed a blood pressure of 144/100 mm Hg, pulse 92 per minute, respirations 30 to 45 per minute, and temperature 35.2 °C. Neurologic examination showed worsening of right ptosis, bilateral facial weakness (R > L), and more severe left palatal weakness and ataxia. Her eye movement abnormalities persisted. Arterial blood gases on room air showed a P_{O_2} of 121 mm Hg, P_{CO_2} of 9 mm Hg, pH of 7.61, O_2 saturation (Sa_{O_2}) of 97%, HCO_3^- of 9 mEq/l, and base deficit of −7.1 mEq/l. Urine pH was 5.0. Gadolinium-enhanced MRI located the tumor in the posterior pontine tegmentum, without changes in the T_2-weighted abnormal signal as compared with the prior scan (figure 1, E and F). Polysomnography, EOG, and quantitative respiratory evaluation were performed (see below). In the 2 weeks prior to this evaluation, the patient's only medication was dexamethasone 1 mg po qod. After the evaluation, it was observed that single doses of morphine sulfate, 5 mg IV, produced a reduction in respiratory rate for 18 to 24 hours, whereas pupilloconstriction normalized at 8 to 12

hours. The patient was restarted on methadone, 5 mg q8h, which reduced the respiratory rate to 15 to 20 per minute; dexamethasone, 1 mg qod, and PCV chemotherapy were continued. Repeat MRIs 4 and 11 months later showed reduction in enhancement and abnormal T_2 signal (figure 1, G and H). Dexamethasone was stopped without subsequent tachypnea; at follow-up 30 months after tumor diagnosis and 27 months following her 1st episode of CNH, she remains neurologically stable, without tachypnea, on methadone, 2.5 mg at bedtime.

Methods. *Respiratory evaluation.* Details of the CO_2 rebreathing technique and apparatus (modified after Read) have been previously published.[5] Briefly, the subject wore nose clips and breathed through a tight-fitting mouthpiece attached to a low-resistance circuit and a 7.0 l neoprene bag, which was primed with 100% O_2 to a volume of 1.0 l greater than vital capacity. End-tidal CO_2 was measured at the mouth with an infrared CO_2 analyzer (Beckman LB-2). The signal from a Fleisch pneumotachograph was electronically integrated to measure ventilation. Occlusion of the airway was achieved by a microcomputer-controlled solenoid valve, and the occlusion pressure at 100 msec after the onset of inspiration ($P_{0.1}$) was measured by a pressure transducer. Subjecting the patient to a CO_2 challenge to assess brainstem respiratory drive presented difficulties that are not normally encountered. The usual priming of the rebreathing apparatus (approximately 7% CO_2 in O_2) would present this patient, whose normal end-tidal CO_2 ranged from 8 to 12 mm Hg, with a sudden and stressful CO_2 level. In addition, priming the rebreathing apparatus with 7% CO_2 would not allow a gradual linear rise in CO_2 and ventilatory response, which were necessary for a meaningful interpretation of results. Instead, the apparatus was primed with 100% O_2 in an attempt to avoid this problem. The patient was informed that these increases in CO_2 and ventilatory drive might prove difficult to tolerate. She was, however, a highly motivated patient who tolerated a 10-mm Hg rise in end-tidal CO_2 before stopping the test. After baseline evaluation, the patient received morphine sulfate, 10 mg IV, and CO_2 challenge was performed as above. Thirty minutes later, naloxone 0.8 mg was administered, followed by another CO_2 challenge. The same protocol was repeated 48 hours later, except that naloxone 10 mg was used instead of 0.8 mg. No opiates were administered between these evaluations.

Polysomnography. The polygraphic sleep study was performed in the patient's private room on the neurology ward according to standard clinical guidelines[6] and interpreted by one of the authors (C.R.J.), who is certified by the American Sleep Disorders Association as an Accredited Clinical Polysomnographer. EEG channels necessary to stage sleep (C_3-A_2, and O_1-A_2), 2 channels of horizontal EOG, submental EMG, ECG, rib cage and abdominal breathing movements (Respitrace breathing monitor) were recorded at 10 mm/sec paper speed on a 12-channel Nihon-Kohden polygraph machine. SaO_2 was continuously recorded from a Nellcor model N-200 pulse oximeter (fast-response mode) on a multichannel, slow-speed Linseis strip chart recorder. The patient tolerated a full (nose and mouth) face mask with a dead space of approximately 50 cc without additional dyspnea, perhaps because of her large tidal volumes (1,000 cc). Essentially all the exhaled tidal volume passed through the wide-bore sampling port of a Novametrix model 1260 end-tidal CO_2 monitor attached to the face mask. The monitor was calibrated using 0% and 5% CO_2 gas mixtures. Waking values of end-tidal CO_2 obtained with this method just prior to the sleep study were consistently 12 to 14 mm Hg. A waking arterial P_{CO_2} was 9 mm Hg prior to the sleep study, which we considered to reflect a comparable degree of hyperventilation for the purposes of this study. The Novametrix sampling port has been used routinely for continuous in-line CO_2 monitoring of intubated patients and does not contribute clinically significant airway resistance. The polygraphic recording was visually scored for sleep stages by 30-second epochs according to the criteria of Rechtschaffen and Kales.[7] The digital readout of the end-tidal CO_2 monitor was manually recorded in real time on the appropriate polygraph page. The corresponding simultaneous respiratory rate was obtained from the respiratory polygraph channels by averaging over 1 minute. The above values were plotted on the same time scale as the strip chart recording of SaO_2 and heart rate to produce a summary sleep graph (hypnogram).

Results. *Respiratory evaluation.* Pulmonary function tests, including spirometry and lung volumes, were normal. Corrected DL_{CO} (diffusion capacity) was reduced to 62% of predicted; however, chest radiograph, clinical examination, and arterial blood gases showed no evidence of interstitial disease. The CO_2 challenges were considered successful in that (1) a rapid equilibrium between rebreathing circuit and alveolar CO_2 was established, as demonstrated by the small differences between inspired and expired CO_2 tensions; (2) a linear increase occurred in the ventilatory and occlusion pressure response that was parallel to linear increase in the end-tidal CO_2; and (3) the patient's baseline responses to CO_2 were well within the range of normal. Morphine, 10 mg IV, depressed the ventilatory response to CO_2 to 49 to 53% of baseline and the occlusion pressure response to 35 to 50% (figure 2). Similar doses (0.21 mg/kg) had previously produced virtually identical depression of the ventilatory and occlusion pressure responses (57% and 47%, respectively) in normal young adults[8]. Naloxone, 0.8 mg IV, produced no significant reversal of respiratory morphine-induced depression of the ventilatory and occlusion pressure response to CO_2, while naloxone, 10 mg, restored these responses to baseline (figure 2).

Polysomnography. The polysomnographic testing revealed fragmented sleep, with frequent, unexplained awakenings, although the patient reported a relatively normal night of sleep (figure 3). Slow-wave (delta) sleep constituted 12.7% of total sleep time and was confined primarily to the first ⅓ of the night. Careful inspection of the entire polygraph showed no EEG, EOG, or EMG evidence (either singly or in combination) for rapid eye movement (REM) sleep, and the patient reported no dreams. Respiratory monitoring showed a rate of 25 to 30 per minute throughout the night. The SaO_2 was also abnormally high (98 to 100%), especially for the altitude of the University of Utah (1,500 m above sea level, barometric pressure 630 to 640 mm Hg). Essentially all apparent O_2 desaturation events shown in figure 3 represented movement artifacts, correlating with visual observations of interrupted sleep. End-tidal CO_2 values remained <15 mm Hg for almost the entire night, consistent with sustained hyperventilation during all stages of non-rapid eye movement (NREM) sleep. Finally, the polygraphic morphology of inspiratory rib cage and abdominal breathing movements provided further qualitative evidence for increased respiratory drive throughout sleep.

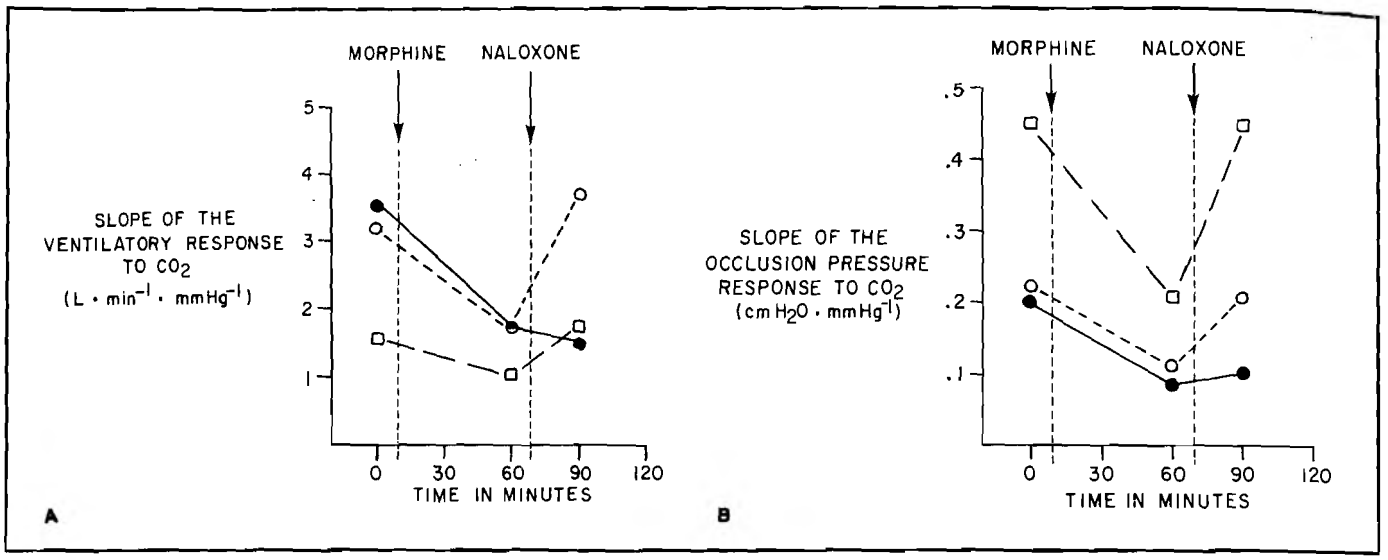

Figure 2. Ventilatory and occlusion pressure response to CO_2. (A) Changes in the slope of the ventilatory response to CO_2 in the CNH patient before and after morphine, 10 mg IV, and after antagonism with naloxone, 0.8 mg (●—●) and 10.0 mg (○--○). Data modified from Bailey et al[2] for the responses (mean) in 12 healthy young adults, before and after morphine, 0.21 mg/kg, and after antagonism with naloxone, 0.014 mg/kg (□——□). (B) Changes in the slope of the occlusion pressure response to CO_2 in the CNH patient before and after morphine, 10 mg IV, and after antagonism with naloxone 0.8 mg (●—●) and 10 mg (○--○). Data modified from Bailey et al[2] for the responses (mean) in 12 healthy young adults before and after morphine, 0.21 mg/kg, and after antagonism with naloxone, 0.014 mg/kg (□——□).

Discussion. By definition, CNH persists despite a normal or high P_{O_2}, a low P_{CO_2}, and an elevated arterial pH.[3] Unlike psychogenic tachypnea, CNH persists during sleep and must not be due to ingestion of respiratory stimulants such as salicylates or cyanide.[3] The syndrome is rare, with only 10 prior tumor-associated cases reported and in only 4 of which the patient has been alert.[1-3,10-15] Except for the 2 patients with hepatic encephalopathy described by Plum,[3] all patients have had brainstem astrocytomas or CNS lymphomas as associated conditions.[10-15] The clinical features of CNH have been elaborated upon elsewhere.[2,3]

The pathophysiologic mechanism involved in the production of CNH is unclear. Originally, dysfunction of the reticular formation of the midbrain and upper pons was thought to be correlated with this syndrome.[2] However, destructive midbrain and pontine lesions in animals did not produce CNH.[3,9] Plum originally suggested[3] that local production of lactic acid by tumor cells in the brainstem results in an increase in hydrogen ion concentration, which stimulates chemosensitive respiratory neurons. This concept is supported by the finding of elevated CSF lactate and low CSF pH in CNH patients.[3,11] However, the absence of CNH in other patients with brainstem tumors, in which local medullary lactate concentration would presumably also be elevated, suggests that other unknown factors might be involved. In addition, CNH is rare in patients with meningitis (carcinomatous or infectious), in which CSF lactate is commonly elevated. In contrast, Arnold et al[16] have identified relatively normal pH within experimental gliomas with alkalosis of the surrounding tumor microenvironment. It is clear that the role of local brainstem pH in the pathogenesis of CNH has yet to be defined.

One might assume that the medullary respiratory center must be intact for production of this syndrome, with disruption of descending inhibitory neurons from the pons, mesencephalon or cerebral cortex. Nevertheless, many of the described patients have extensive infiltration of the medulla as well.[3,12,13] Cohn et al[11] described a case in which tumor involved only the right brainstem; since rostral brainstem respiratory regulatory effects are bilaterally represented,[9] disinhibition was unlikely to be responsible for CNH in their patient. Another problem is posed by the case described by Bateman et al,[14] in which the brainstem below the superior colliculus was free of lymphoma, except for meningeal metastases. It is possible that the CNH was produced by undetermined indirect effects of meningeal tumor in these cases without definite brainstem involvement. Our patient had an extensive lesion involving tegmentum and tectum of the upper medulla and dorsal pons. By MRI, the abnormal signal progressed into the medulla when CNH initially occurred; however, it would only be speculative to suggest that the medullary extension was responsible for the CNH.

In our patient, morphine sulfate resulted in a rapid reduction of the respiratory rate, which was sustained with oral methadone. The patient of Rodriquez et al[12] responded transiently to morphine sulfate. Neurons containing both mu and delta opiate receptors are present in feline brainstem respiratory-related neurons, located in the nucleus solitarius, nucleus ambiguus, and reticular formation, which exert direct control on central transmission of rhythmic signals related to respiration.[17] Experimental evidence suggests that opiates binding to both mu and delta receptors will decrease respiratory rate, rhythmicity, and pattern, as well as responsivity to CO_2.[18,19] However, little information is available regarding opiate binding to respiratory neurons in humans.

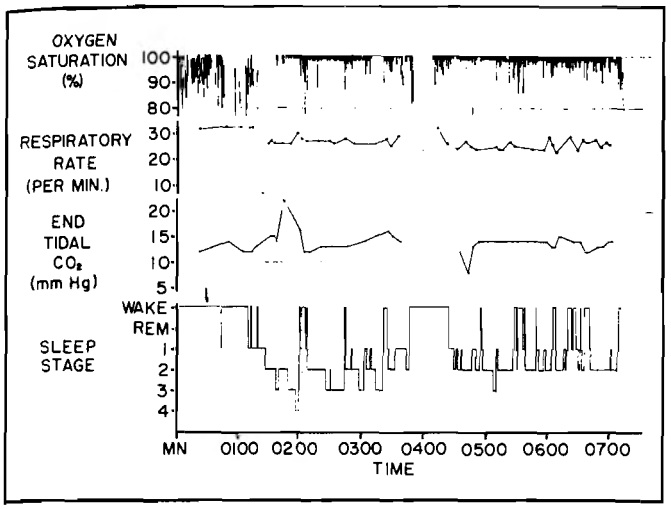

Figure 3. Sleep study summary graph. Summary of polysomnographic results showing sleep stages and simultaneous respiratory determinations across the night. Percent O_2 saturation was measured with a pulse oximeter. Respiratory rate/minute was calculated from the continuous recording of breathing movements. End-tidal CO_2 (mm Hg) is the partial pressure of carbon dioxide measured at the mouth. Sleep stages are shown for wakefulness (wake), rapid eye movement sleep (REM) and stages 1 through 4 non-rapid eye movement sleep (1, 2, 3, 4). Arrow near the beginning of the sleep period indicates the time the room lights were turned off. Certain oscillations in O_2 saturation (especially between midnight and 1:15 AM) were actually movement artifacts.

Two features of our patient's response to opiates and the antagonist naloxone are notable. First, morphine and methadone produced clinical effects (therapeutic relief of dyspnea and tachypnea) that far outlasted their predicted duration from the known pharmacokinetics of these agents. Second, a dose of naloxone (0.8 mg), which usually restores CO_2 responsiveness to baseline in adults who have received similar doses of morphine,[5] failed to produce reversal of morphine-induced respiratory depression in our patient. Supramaximal doses of naloxone (10 mg) were necessary to achieve this effect. The reason for the prolonged response to morphine and the requirement for an extremely high naloxone dose for reversal of effect is unclear. One unproven hypothesis is that morphine was capable of initiating an alteration of the set point of medullary respiratory neuronal drive, and once altered, maintenance of the new respiratory rate was not further influenced by conventional doses of opiate agonist or antagonist.

The polygraphic sleep study documented the persistence of hyperventilation throughout all stages of NREM sleep, thereby eliminating psychogenic hyperventilation as a possibility. The patient's hyperventilation was presumably driven by medullary inspiratory- and expiratory-related neuronal groups near the nucleus retroambiguus and nucleus tractus solitarius,[20,21] which may have been spared from tumor involvement.

On the other hand, sleep stage abnormalities in the polysomnogram suggested dysfunction of certain brainstem tegmental structures. The most striking finding was the total absence of REM sleep. Although it is not uncommon during the 1st night's recording to observe a missed REM period or prolonged REM latency,[22] the total absence of REM sleep suggests pontine tegmental injury.[23] By stimulation and lesion studies, Seigel[23] demonstrated that the lateral rostral pontine reticular formation ventral to the locus ceruleus is critical for REM sleep in the cat. In our patient, it is possible that diffusely infiltrative tumor may have extended from this area to the adjacent parapontine reticular formation (PPRF), with resultant impairment of horizontal saccades in both REM sleep and the awake state. The authors are well aware of the shortcomings of a single night's polysomnographic recording, and that conclusions based on these results have limitations. However, the association of a medial pontine tegmental lesion with absent REM sleep is consistent with the report of Autret et al,[24] who described reduction in REM and NREM sleep with lateral gaze paralysis and internuclear ophthalmoplegia in 4 cases of brainstem stroke in which the common pathologic lesions were localized in the medial pontine tegmentum.

In our patient, the lack of volitional horizontal saccades with compensatory head thrusts is reminiscent of congenital ocular motor apraxia. However, since spontaneous, random (ie, reflexive) horizontal saccades were also absent, the findings do not fit strict criteria for a true apraxia.[25] Loss of horizontal volitional and reflexive saccades, with preservation of the vestibular ocular reflex and vertical saccades, is consistent with dysfunction of the PPRF. Our patient developed bilateral abducens palsies with mild internuclear ophthalmoplegia and CNH simultaneously; these abnormalities suggest dysfunction of areas quite proximal to the PPRF. It is unclear why the CNH, but not the ocular motor dysfunction, improved. It is possible that reversible physiologic factors (eg, edema, pH, opiate receptor binding) were involved in CNH production, whereas permanent structural alterations due to tumor affected ocular motor function.

In summary, the clinical findings in our patient implicate a medial tegmental pontine lesion, possibly affecting the PPRF bilaterally. These data would be consistent with a model of CNH that is based on the disinhibition of pontine inhibitory influence on medullary respiratory neurons, but by no means is this mechanism clearly responsible in our patient. The sustained response of this patient's hyperventilation to opiates warrants consideration of this treatment in other patients with CNH.

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