# Narcolepsy Following Cerebral Hypoxic Ischemia

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A 51-year-old man with non-HLA-DR2 histocompatibility developed classic signs and symptoms of the narcoleptic tetrad soon after recovering from an episode of cardiopulmonary insufficiency, which occurred during induction of surgical anesthesia. Symptoms included excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis, and cataplexy. The diagnosis was confirmed by repeated polysomnographic examinations in the sleep laboratory. Cerebral hemodynamic changes during the onset of sleep showed remarkable increases of cerebral blood flow during the onset of rapid-eyemovement sleep similar to those reported previously in patients with narcolepsy. Magnetic resonance imaging showed focal regions of abnormal spin-echo signals in the ventral pons.

> Rivera VM, Meyer JS, Hata T, Ishikawa Y, Imai A: Narcolepsy following cerebral hypoxic ischemia. Ann Neurol 19:505-508, 1986

Studies in animal models have shown that the brainstem and hypothalamus have a prominent role in neural mechanisms regulating sleep and wakefulness. However, there are few reports of narcolepsy following lesions of the brainstem in humans.

Narcolepsy is a disorder of sleep characterized by frequent occurrence of the onset of rapid-eyemovement (REM) sleep, as demonstrated by polysomnography. Sleep onset is usually associated with dreaming that is often described as vivid hallucinations. This type of sleep onset differs from the usual REM sleep onset, and has been attributed to a disorder of brainstem mechanisms regulating sleep [6, 7]. In the primary hereditary type of narcolepsy, genetic markers have been described by histocompatibility testing, but there are no reports of histocompatibility testing in the secondary types. As far as can be determined, there are no reported neuropathological studies of patients suffering idiopathic (or primary) narcolepsy during life; this is probably because the condition is not fatal. However, lesions of the brainstem have been reported in cases of secondary narcolepsy. These have included brain tumors [10], multiple sclerosis [1], and cerebrovascular disease [8].

The concept of secondary narcolepsy (i.e., narcolepsy resulting from identifiable disease of the brain) is not well established. A few reports are available of cases of narcolepsy secondary to brain tumors and multiple sclerosis involving the brainstem; these cases were confirmed by sleep polysomnography. In reviewing the reported cases of "secondary narcolepsy," those following brainstem infarction are extremely rare [1, 2, 8]. Several prospective studies of various types of sleep disorders secondary to cerebrovascular disease failed to mention any narcoleptic symptoms [5, 11].

This report describes a patient who developed signs and symptoms of the narcolepsy tetrad following an episode of cerebral hypoxic ischemia. Magnetic resonance (MR) scanning revealed several zones of abnormal spin-echo signals in the ventral pons near the midline, which were thought to indicate small cerebral infarctions.

### Case Report

A 51-year-old male engineer with no family history of narcolepsy was referred to the Cerebral Blood Flow Laboratory for further evaluation of a sleep disorder. He had been in excellent health without any sleep complaints until 1978.

In May 1978, surgical treatment was planned for a peptic gastric ulcer and hiatal hernia producing epigastric pain. Anesthesia was induced by intravenous injection of sodium pentobarbital. During intubation of the trachea his blood pressure fell rapidly and respiratory arrest and cardiocirculatory insufficiency occurred. Cardiopulmonary resuscitation was successful, but he remained in a coma for 5 days. Upon regaining consciousness, neurological examination yielded normal findings except for bilateral cerebellar incoordination.

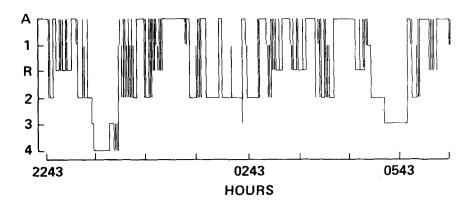
Three weeks after discharge from the hospital he began to complain of episodes of cataplexy during which he would become unable to move his extremities or to speak for 1 to 3 minutes. During these attacks, which occurred without warning, he would fall to the floor or slump in his chair. They increased in frequency and appeared to be precipitated by coughing or emotional stress. He also complained of attacks of irresistible sleepiness during the day. These sleep attacks occurred at any time and made driving hazardous. During each attack he would fall asleep for a few seconds or minutes; his wife reported that on a number of occasions he awoke during the night stating that he was unable to move. He also reported vivid dreams or hallucinations immediately after falling asleep; in these he recalled seeing people and hearing voices and participating in activities going on around him, despite the fact that he was asleep.

In March 1981, he was admitted to The Methodist Hospital in Houston; narcolepsy was confirmed by sleep polysomnography. Tricylic antidepressants and methylphenidate were prescribed without symptomatic improvement. He was readmitted to the hospital in 1983 and 1985, and during each

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Received June 17, 1985, and in revised form Sept 16. Accepted for publication Sept 23, 1985.

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admission narcolepsy was confirmed by sleep polysomnography. Results of physical examination were normal except for mild incoordination of all four extremities, generalized hypotonia, depressed reflexes, and extensor plantar responses. The results of examinations of the cranial nerves, motor systems, and sensory system were normal. Examinations during several cataplexic attacks revealed dysarthria, bilateral ptosis, worsening of the generalized hypotonia, and irregular saccadic ocular movements in both lateral and vertical directions.

Results of urinalysis, complete blood counts, blood chemistries, and endocrinological studies were within normal limits. Histocompatibility testing showed that his HLA types were HLA-A11, A24, B35, B39, and Cw4. Neuropsychological examination revealed cognitive and memory performance to be within the superior normal range (Wechsler Adult Intelligence Scale, 146; Wechsler memory quotient, 140). Results of other neuropsychological tests, including cognitive capacity screening examinations, were also normal. Sleep polysomnography was performed during three separate hospital admissions (6/24/81, 8/8/83, and 1/22/85), and results were similar on each occasion. Nocturnal sleep was characterized by low total sleep time and frequent awakenings. Sleep stages were poorly defined with relative suppression of REM stages 3 and 4. As shown in Figure 1, there were numerous episodes of sleep-onset-stage REM during the nocturnal period, and similar events were observed during daytime recovery sessions. Episodes of sleep apnea, reductions in arterial oxygen saturation, electrocardiographic abnormalities, and nocturnal myoclonus were absent. The patient was noted to fall asleep at inappropriate times such as prior to assigned nocturnal sleep intervals, during routine electroencephalographic recording, and during neurological examinations. Several episodes of sleep paralysis were observed.\*

Conventional computerized tomographic (CT) scans of the brain and four-vessel aortocerebral angiography were normal. MR scans were made on two occasions in 1985 and showed multiple small regions of abnormal spin-echo signals, which were decreased on  $T_1$  scans and increased on  $T_2$  scans.<sup>†</sup> These abnormal regions were located in the ventral portions of the mid and inferior pons and were thought to

<sup>†</sup>Interpreted by Michael L. Lewis, MD, PhD, of the Houston Imaging Center and confirmed by Anthony Bledin, MD, of Fondren Imaging Center.

Fig 1. Polysomnographic records made in 1985 during nocturnal sleep in a 51-year-old man. Records were obtained seven years after an episode of cardiopulmonary insufficiency that preceded the onset of narcolepsy. Stages of sleep are indicated on the Y axis: A = awake; 1 = stage 1, non-rapid eye movement (REM) sleep; R = REM sleep; 2 = stage 2 sleep; 3 = stage 3sleep; and 4 = stage 4 sleep. Similar results were obtained 3 years and 5 years after the episode of cerebral anoxic ischemia. Numerous episodes of sleep-onset-stage REM were recorded.

represent small infarcts (Fig 2). The remainder of the brain appeared normal except for moderate enlargement of the ventricles and slight cortical atrophy. Xenon 133 inhalation cerebral blood flow measurements were made in the awake stage and during the onset of sleep. Awake values were reduced for the patient's age, probably resulting from effects of ischemic anoxic encephalopathy. During sleep onset there was typical REM activity according to sleep polysomnography. This was associated with generalized increases of gray matter blood flow (Fig 3). Normal flow increases in the gray

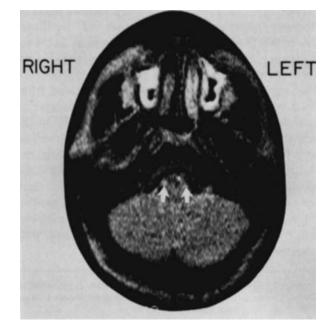
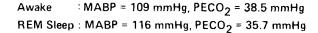
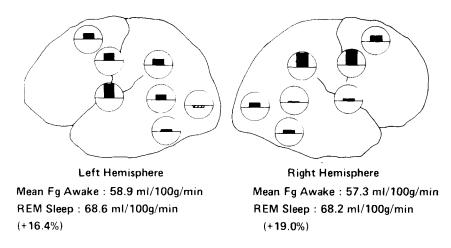


Fig 2. Magnetic resonance (MR) scan of the cerebellum and brainstem. There are loci of increased spin-echo signals  $(T_2)$  appearing as white regions in the ventral portions of the pons (arrows). These abnormal signals remained unchanged when MR scans were repeated 4 weeks later.

<sup>\*</sup>Interpreted by James D. Frost, Jr, MD, of the Sleep Laboratory of Methodist Hospital, Houston, TX.





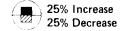


Fig 3. Cerebral blood flow values in the gray matter recorded during rapid eye movement (REM)-onset sleep immediately after recording of awake values. During REM sleep there were marked increases of gray matter blood flow. These are similar to those reported in patients with spontaneously occurring, hereditary narcolepsy {7}. (MABP = mean arterial blood pressure; PECO<sub>2</sub> = end-tidal carbon dioxide partial pressure.)

matter were maximal in the right parietooccipital regions. These were similar to those reported from this laboratory during onset of REM sleep associated with vivid dreaming and hypnagogic hallucination among patients with spontaneously occurring narcolepsy. This type of REM sleep onset with increased cerebral blood flow has never occurred in agematched normal controls during sleep onset [7, 9].

### Discussion

Excessive daytime sleepiness, sleep paralysis, cataplexy, and hypnagogic hallucinations, as observed in our patient, are considered to comprise the classic tetrad of narcolepsy. Laboratory examinations, including sleep polysomnography and sleep cerebral hemodynamics, confirmed this diagnosis. The sleep-wake disturbances began after an episode of cerebral hypoxic ischemia in 1978, when the patient was 44 years of age. Three weeks after regaining consciousness the narcoleptic attacks began, increased in frequency and severity, and failed to respond to standard pharmacological treatment. In patients with idiopathic narcolepsy the symptoms begin in childhood or adolescence. In addition, there is usually a family history of the disorder. Onset of narcolepsy after age 40 is rare [2]. Furthermore, this patient did not have the HLA antigens that have been shown to have strong associations with idiopathic narcolepsy-Cw7, B7, and DR2 [4].

MR imaging of the brain in our patient revealed small lesions, which appeared to represent multiple small infarctions involving ventral portions of the basis pontis and the raphe nuclei in these locations. Based on studies in animal models these lesions might explain the patient's neurological signs as well as the sleep disorder [6, 7]. Neurophysiological studies in animal models suggest that there are two major systems within the pons that regulate sleep, one involving the pontine raphe nuclei and the other the locus ceruleus. The brainstem is usually more resistant to hypoxic ischemia than is the cerebral cortex [3]; however, this region is supplied by the paramedian branches of the basilar artery and it is possible that this was a region of reduced perfusion possibly related to some congenital abnormality.

In an excellent review of narcolepsy, Bonduelle and Degos concluded that secondary narcolepsy is extremely rare but does occur [1]. Only one previous case of fully documented narcolepsy secondary to brainstem ischemia has been reported [8].

Supported by the Veterans Administration, Washington, DC, and by grants from Mr and Mrs Harry K. Smith, Mr Albert K. Smith, Tenneco Inc, Entex Inc, and the J. S. Abercrombie Foundation, Houston, TX.

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# Edrophonium: An Aid in the Diagnosis of Acute Organophosphate Poisoning

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Unsuspected accidental cutaneous exposure to an organophosphate insecticide caused flaccid paralysis in a 10-year-old girl. Electromyogram demonstrated repetitive compound muscle action potentials in response to a single stimulus of nerve; decremental response, more prominent at higher rates of stimulation; worsening of decremental response after edrophonium injection; and normal nerve conduction velocities. Electromyogram with repetitive nerve stimulation and an edrophonium test may provide a simple and rapid method for diagnosis of acute organophosphate poisoning.

> Maselli R, Jacobsen JH, Spire J-P: Edrophonium: an aid in the diagnosis of acute organophosphate poisoning. Ann Neurol 19:508-510, 1986

The immediate effects of acute organophosphate poisoning are primarily due to the inhibition of acetyl-

From the Department of Neurology and the Brain Research Institute, The University of Chicago, Chicago, IL. cholinesterase. This acute effect is distinct from the delayed polyneuropathy associated with some organophosphates, which depends on inhibition of neurotoxic esterase [13]. We report here a case in which an unusual electromyographic pattern led to the diagnosis of acute organophosphate poisoning.

## **Case Report**

A 10-year-old girl developed postprandial nausea, vomiting, and abdominal pains followed by rapidly progressive muscular weakness. She was transferred from another hospital 72 hours after the onset of symptoms with a presumptive diagnosis of botulism. On admission the patient was awake and alert, with generalized muscle weakness. Her heart rate was 120, blood pressure 110/80 mm Hg, and respiratory rate 50. Auscultation revealed coarse rales and rhonchi. An endotracheal tube was inserted and mechanically assisted respirations started. Both pupils were 3.5 mm in diameter and reacted to light. There was bilateral lid ptosis with occasional twitches of the eyelids, generalized hypotonia, and only minimal voluntary movement of fingers and toes. Fasciculations were not seen. The muscle-stretch reflexes were absent to an initial single percussion but facilitated to hyperreflexia on repeated percussion. Plantar reflexes were absent. Results of complete blood count, serum electrolytes, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and creatine phosphokinase tests were normal. Serum glucose, alkaline phosphatase, and lactic dehydrogenase concentrations were 141 mg/dl, 209 IU (n = 10-85 IU), and 355 IU (n = 56-194 IU), respectively.

## Hospital Course

Electrophysiological studies were performed 24 hours after admission. Nerve conduction velocities were normal. In muscles of all extremities, repetitive compound muscle action potentials (CMAPs) of slightly reduced amplitude occurred in response to single nerve stimulation (Fig 1). The needle electromyogram showed fibrillation potentials, positive sharp waves, and fasciculations. Recruitment of motor units was minimal. Repetitive stimulation of the right ulnar nerve at 2 Hz, with recording from the abductor digitorum brevis, revealed an initial repetitive CMAP amplitude of 7.6 mV and a decrement of 22% that was maximal between the first and second CMAPs (Fig 2A). This decrement was more

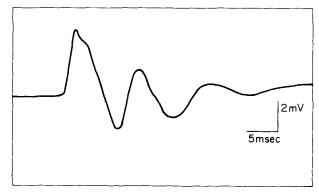


Fig 1. Repetitive compound muscle action potential recorded from the right thenar muscles in response to a single stimulation of the median nerve at the elbow.

Received Apr 1, 1985, and in revised form Aug 8. Accepted for publication Sept 27, 1985.

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