Sleep Apnea in Olivopontocerebellar Degeneration: Treatment with Trazodone

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A 37-year-old man with a 19-year history of progressive autosomal-dominant olivopontocerebellar degeneration developed excessive daytime sleepiness and paroxysmal episodes that clinically resembled an ictal or postictal state. Polysomnography showed sleep apnea. Long-term therapy with trazodone resulted in resolution of the paroxysmal episodes, disappearance of daytime sleepiness, and gradual improvement of sleep architecture over several months.


Olivopontocerebellar degeneration (OPCD) is a heterogeneous clinicopathological entity characterized by atrophy of the cerebellum,pons, and medullary olives [1, 2]. In some subtypes of OPCD, the basal ganglia, cerebral cortex, lower cranial nerve nuclei, spinal cord, and peripheral nerves are also involved [1, 3-5]. Although OPCD can be separated into sporadic, recessive, dominant [2, 6], or X-linked types [7], the current classification is suboptimal because of the variability in clinical and pathological features that occur, even among members of the same pedigree [8].

OPCD has been associated with sleep disorders including hypersomnia [9], rapid-eye-movement (REM) sleep without characteristic atonia [10], and sleep apnea [9, 11-13]. We describe a patient with autosomal dominant OPCD and sleep apnea that produced episodes that resembled a seizure disorder; treatment of the sleep disturbance with trazodone was successful.

Case Report
At age 18, while in the army, the patient noticed dysarthria and gait ataxia. A neurological evaluation suggested a diagnosis of spinocerebellar degeneration. His mother, maternal uncle, and grandmother had also suffered from a similar disorder. At age 30, he stopped working because of severe gait ataxia and began to use a wheelchair intermittently. During the next seven years he developed cognitive impairment, more dysarthria, and limb ataxia. At age 35 he became confined to a wheelchair. At age 37 he became bedridden, developed excessive daytime sleepiness (EDS), and exhibited paroxysmal states of diminished responsiveness during which he appeared asleep. These episodes came on abruptly, lasted from several minutes to half an hour, and resembled ictal or postictal states. He was difficult to arouse during these episodes. There was no history of narcolepsy, cataplexy, or hypnagogic hallucinations. His mother, maternal uncle, and grandmother all suffered from EDS. An eight-lead electroencephalogram (EEG) was normal. A therapeutic trial of phentoin had no effect.

In August 1985 he was admitted to the University of Chicago Medical Center for further evaluation. On examination he was demented and had dysarthric speech that was only occasionally intelligible. Eye movements were markedly weak in all cardinal fields of gaze, and oculocephalic reflexes were diminished. The fundi were normal and cataracts were not seen. Hearing was unimpaired. Swallowing was labored, and voluntary and reflexive palatal movements were decreased. He had distal muscle wasting in the arms and intrinsic muscles of the hands, but less wasting in the feet and intrinsic muscles of the legs. Tone was decreased distally, and strength was graded 4+/5 (Medical Research Council scale). The reflexes were diminished in the arms and legs and absent in the ankles, with bilateral Babinski signs. There were occasional myoclonic jerks during wakefulness and severe limb and truncal ataxia. The sensory examination was unreliable.

Spinal fluid was normal. Computed tomography and magnetic resonance imaging (Figure) of the brain revealed cerebr al atrophy and severe cerebellar and brainstem atrophy. Nerve conduction velocities showed slowing of motor conduction velocities with normal compound muscle action potentials, and diminished or absent sensory nerve action potentials. Brainstem and somatosensory evoked potentials showed central conduction delays. Hexosaminidase A & B, aryl sulfatase A, and vitamin E levels and lipid profile were normal. Several all-night 16-channel EEGs failed to show any interictal epileptiform patterns.

Polysomnography included an eight-lead EEG, electrooculogram, chin electromyogram, and a modified V2 electrocorticogram. Respirations were measured with nasal and oral ther-
Computed tomograph (top) and magnetic resonance image (bottom) of the brain and brainstem showing marked brainstem and cerebellar atrophy.

Oxygen saturation was measured by continuous ear oximetry. The first all-night polysomnogram showed an abnormal EEG without sleep spindles consisting of low to moderate voltage delta activity. REM sleep was absent. Analysis of respiration showed an apnea index (apneas/hour of sleep) of 26.1, with a predominance of central sleep apnea; oxygen saturation fell to a low of 80% (Table). Treatment with 50 mg trazodone per night resulted in a marked decrease in the episodes of EDS and disappearance of the episodes of altered consciousness. Subsequent polysomnograms at three-month intervals documented a slowly progressive improvement of sleep architecture (see Table); apnea indexes fell to 4.4, 2.4, and 0.8 over a period of seven months. After almost two years of treatment, the patient has remained free of further attacks, although his dysarthria and dementia have continued to progress.

Discussion
The patient reported here carries a diagnosis of autosomal dominant OPCD on the basis of clinical, electrophysiological, and neuroradiological (see Figure) findings. This case is remarkable in that paroxysmal episodes of EDS caused by sleep apnea mimicked an ictal or postictal state, causing considerable diagnostic confusion; these were successfully treated with trazodone. There was no evidence of a seizure disorder. In addition, narcolepsy was unlikely because narcoleptic symptoms were absent, and REM sleep was absent in the initial polysomnogram.

There is evidence that cerebellar lesions or degenerative cerebellar syndromes result in sleep dysfunction—in particular, sleep apnea. Bergonzzi and colleagues [9] found considerable sleep fragmentation and hyposomnia in serial recordings of 9 patients with cerebellar syndromes (1 had OPCD) when compared...
to normal subjects. Briskin and colleagues [14] reported 2 patients with multiple system atrophy, with prominent involvement of the cerebellum, who developed sleep apnea. Adelman and colleagues [12] described 2 cases of posterior fossa disease, 1 with syringobulbia and 1 with OPCD, with sleep apnea demonstrated on nocturnal polysomnography. In addition to detailing autonomic dysfunction in patients with OPCD, Chokroverty and colleagues [11] noted sleep apnea in daytime polysomnographic evaluations in 5 out of 10 patients with OPCD, 1 with dominant inheritance. Katayama and colleagues [13] evaluated 30 spinocerebellar degeneration (SCD) patients (6 with OPCD and 24 with cerebelloloxiaryl atrophy) by polysomnography. All SCD patients showed considerable fragmentation of sleep and disturbed progression of sleep stages, and a decreased number of sleep spindles (a finding present in our case [see Table]). Two patients with OPCD had central sleep apnea, whereas 1 with cerebelloloxiaryl atrophy had an obstructive sleep apnea.

Recently, Salva and Guilleminault [10] reported 2 patients with OPCD (1 sporadic and 1 familial) who had hyposomnia and lacked normal REM sleep atonia. They proposed that a lesion of the pontine tegmentum was responsible for the sleep disturbance, because lesions in this location in cats result in REM sleep without atonia [15]. Our patient did not display any clinical or polysomnographic features of such a sleep disorder.

Protriptyline is often used in the treatment of sleep apnea [16], but anticholinergic side effects are common and frequently result in discontinuation of therapy. We therefore selected trazodone because of the drug’s minimal anticholinergic effects. In our patient, trazodone produced a dramatic therapeutic response. The resultant clinical improvement was accompanied by an immediate reduction of the frequency of sleep apneic episodes and a gradual return toward normal of the sleep EEG, characterized by the appearance of distinct nonrapid eye movement sleep transitions, rapid eye movement sleep, and sleep spindles (see Table). Although trazodone is known to inhibit serotonin uptake, it is structurally and pharmacologically unlike other antidepressants [17, 18], and its effects may be mediated by a different mechanism than that proposed for protriptyline.

In summary, it is important to evaluate patients with OPCD for sleep apnea. In these patients, episodes of EDS may mimic seizures. There is a growing body of evidence, to which we add our case, that lesions or degeneration of the cerebellum or its connections may lead to the development of sleep apnea. Serotonin reuptake blockade with trazodone may be used successfully to treat sleep apnea. The drug’s effectiveness suggests that abnormal serotonin metabolism in the central nervous system may be etiologically important in the pathophysiology of sleep apnea of central origin.

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References

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