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Case report

Severe hypersomnolence associated with periodic limb movements and central sleep apnea in a cocaine addicted HIV patient

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Abstract

Drugs such as cocaine and amphetamines potentiate the effect of epinephrine and norepinephrine on the brain and act as stimulants. Here, we report a case of paradoxical severe hypersomnolence from cocaine use in an HIV cocaine-addicted patient. We describe a possible pathomechanism for cocaine depletion at the synapse, causing decreased synaptic activation and leading to sleepiness. © 2005 Elsevier B.V. All rights reserved.

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1. Introduction

An estimated one in eight adults have excessive somnolence severe enough to affect daytime activities. Cocaine abuse is associated with a variety of neurological complications, including strokes, migraines, and seizures. Cocaine potentiates the effect of dopamine and norepinephrine on the brain and acts as a stimulant drug [1]. Although poorly understood, cocaine cerebrovasculitis and neutrophilic meningitis have been reported [2]. However, severe hypersomnia from cocaine use is distinctly uncommon [3]. Here, we report a case of severe hypersomnolence in an HIV patient who was also a cocaine addict and discuss possible pathophysiologic mechanisms for this.

2. Case

A 49-year-old homosexual male with HIV was referred for evaluation of 11-month history of hypersomnolence. He was on highly active anti-retroviral therapy (HAART) since 1998 and had undetectable viral load with CD4 count $> 500/\mu$ l. He had no history of opportunistic infections.

2.1. Sleep history

This patient claimed to fall asleep around 11:30 p.m. daily with immediate sleep onset when his symptoms first began. Initially, he had excessive daytime somnolence and reported episodes of sleep attacks at work lasting up to 30 min. He had progressively developed difficulty rising from sleep and maintaining wakeful state since January 2004. His sleep requirements increased gradually, causing him to sleep for days without waking. By December 2004, he slept continuously for 3-4 days and still woke up tired. Although he was not sure about sleepwalking episodes, he found his furniture having been rearranged upon awakening, and dishes cleaned, on three different occasions without his knowledge. His relatives noticed snoring and jerky body movements. There was no history of head trauma, childhood sleep disturbances, or cataplexy. He denied current or past substance abuse.

On physical exam he appeared disheveled. Weighing 132 lb, he was 67 in. tall, with body mass index (BMI) 21 and neck size of 14 in. He was oriented to person, time, and place, but he fell asleep easily even with a 30-s 'break' during history intake or physical exam. The remainder of his

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physical exam was unremarkable. His Epworth Sleepiness Score was 24.

His complete blood count, basic metabolic panel thyroid-stimulating hormone (TSH), liver enzymes, erythrocyte sedimentation rate (ESR), C3 and C4 levels were within normal limits. Cerebrospinal fluid (CSF) analysis was normal and was negative for herpes simplex virus (HSV), cytomegalovirus (CMV), arboviral panel, JC virus, cryptococcus antigen, bacterial and fungal culture. CSF orexin level was 226 pg/ml (normal is more than 200 pg/ml). His urine drug screen was positive for cocaine on three successive days and no other substance. This was confirmed by gas chromatography and mass spectrophotometry for benzylecgogine level to be 1100 ng/ml on the fourth day.

Sleep study (Sandman, Nellcor Puritan Bennett, Inc., Kanata, ON, Canada): Sleep was scored as per standard criteria. He slept for a total of 348 min for a sleep efficiency of 90%. This included 1% stage 1, 60% stage 2, 17% stages 3 and 4 and 22% REM sleep. Respiratory events and periodic limb movements were scored according to the criteria by the American Academy of Sleep Medicine. The respiratory channels recorded 75 central and 41 obstructive hypopneas for a total index of 20. Mean awake O₂ saturation was 95%; minimal O₂ desaturation associated with respiratory events was 89% in REM sleep and 76% in NREM sleep. However, he spent <1% of sleep with O₂ saturation of <90%. The leg channel recorded a total of 243 events for an overall periodic limb movement index of 42. There were 56 arousals related to periodic limb movements for a periodic limb movement arousal index of 10.

2.1.1. MSLT

The patient fell asleep on all five nap opportunities for a mean latency to sleep onset of 2.5 min. There were no sleep onset REMs.

Digital 72-h video electroencephalogram (EEG) monitoring was performed during his hospital admission. In the awake state there was well-developed posterior dominant 9–10 Hz activity which attenuated with eyes opening symmetrically. The patient was asleep for most of the recording and stages 1–4 were seen. There were no epileptiform discharges or bursts of delta activity.

2.1.2. Radiograms

MRI of the brain showed no parenchymal or meningeal abnormal enhancements. There was no focal lesion, acute infarct or intracerebral hemorrhage. Ventricles and cisterns appeared normal. There was evidence of maxillary sinus surgeries bilaterally. A single photon emission computed tomography (SPECT) study of the brain showed diffuse heterogeneity of tracer distribution throughout the cerebral cortex, suggestive of diffuse vasculitis or inflammation.

3. Discussion

This patient is interesting for several reasons. First and foremost he had severe hypersomnia which was enough to incapacitate him from activities of daily living. We found cocaine still in his system during this state of sleepiness, despite his denial of having used it. This is unusual since cocaine being a stimulant should have had the very opposite effect on his sleep pattern.

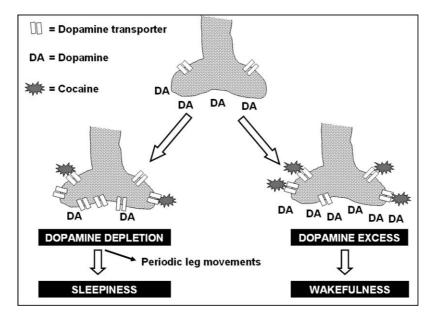


Fig. 1. Dopamine transporter (DAT) clears dopamine (DA) from the extracellular space. Cocaine acts as a competitive inhibitor for DA at the DAT but also upregulates surface expression of DAT. When the inhibition by cocaine is lesser than the up-regulation, the net effect is a DA depletion causing decreased activation and hence sleepiness.

Determinants of sleep disruption in cocaine users seem to be complex. In a retrospective study of cocaine withdrawal [4], a variety of sleep disturbances were reported, beginning with insomnia followed by hypersomnolence during the earliest phase of withdrawal (9 h to 4 days) and normalization of sleep after a week of cocaine abstinence. Weddington et al. [5], in their controlled laboratory evaluation of cocaine abstinence, found that cocaine abusers reported difficulty falling asleep. In the first study to record polysomnographic changes after controlled administration of cocaine, it was seen that sleep architecture was different from controls even after two weeks of abstinence indicating some residual permanent change [6].

Hypersonnolence in an HIV patient could occur due to meningoencephalitis as a part of change in mentation. Although there have been isolated reports of obstructive sleep apnea in patients with HIV [7], there have been no reports of central sleep apnea. There have been reports, however, of central apneas in infants of substance-abusing mothers [8] and in multisystem atrophy [9]. Periodic limb movement is a phenomenon in sleep that can distort sleep architecture and has been reported along with central apnea in idiopathic Parkinson's disease, where there is a depletion of dopamine in the basal ganglia [10]. Although the severity of sleepiness could be accounted for by the central apneas and periodic limb movements, the SPECT study pointed towards a more global pathology, suggestive of an inflammation or vasculitis. In our patient, we ruled out meningitis, encephalitis, hypothyroidism, opportunistic infections and significant iron deficiency. Could the neurochemistry of cocaine itself cause such effects of excessive sleep? Looking at the dynamic regulation of dopamine at the synaptic junction in the central nervous system, it seems likely there could be a possible functional depletion of dopamine (DA) at the synapse [10].

It is understood that the firing of nucleus accumbens (NAc) neurons (which are involved in the 'drug-seeking' pathway) is closely related to the state of arousal [11]. In the NAc when postsynaptic D1 and D2 receptors are stimulated by DA, GABAergic output is reduced, resulting in activation. Depending on the net effect of cocaine on dopamine transporter (DATs) at the NAc, firing can go up or down because of synaptic DA increase or decrease, resulting in arousal or sleepiness, respectively. With normal orexin level in CSF, it is unlikely that the hypocretin pathway could be significantly affected. A proposed mechanism is outlined in Fig. 1.

Although a cause and effect cannot be proven, we believe that in the patient described above there was a net effect of functional DA depletion at the synaptic junction. His sleepiness did improve when he was given carbidopa suggesting a possible exhaustion of DA at the synapse. For residual sleepiness he was prescribed modafinil under supervision. He was advised to use continuous positive airway pressure (CPAP) which he uses intermittently. During his follow-up, his urine was free of cocaine with marked improvement in daytime functioning. He has since returned to work.

We report this first case of such severe hypersomnia associated with central sleep apnea and periodic limb movements in a cocaine-addicted HIV patient. Further studies are needed to explore the relationship of cocaine use, dopamine regulation and sleep.

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