

An Interview with Jerome M. Siegel, PhD

Narcolepsy

INTRODUCTION

Jerome M. Siegel, PhD, is professor of psychiatry at the University of California, Los Angeles, former president of the Sleep Research Society, and the recipient of Merit and Javits awards from the National Institutes of Health and the Distinguished Scientist award from the Sleep Research Society. His laboratory has made discoveries concerning the role of hypocretin in human narcolepsy and Parkinson's disease. He has studied the phylogeny of sleep as a clue to sleep function, discovering that the primitive mammal platypus has rapid eye movement sleep and that marine mammals can go without extended periods of sleep for long periods without ill effects.

What is narcolepsy?

Narcolepsy is a disorder characterized by excessive sleepiness. The four classic symptoms of narcolepsy are excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. For diagnostic purposes, excessive daytime sleepiness is usually followed up with a multiple sleep latency test. That is, the patient is given repeated opportunities to go to sleep. Narcoleptics have very short latency to the onset of rapid eye movement (REM) sleep. In clinical practice, persistent sleepiness combined with short latency to the onset of REM sleep is sufficient to diagnose narcolepsy.

What is cataplexy?

Cataplexy is a sudden loss of muscle tone triggered by the sudden onset of strong emotion. The

most common trigger for cataplexy is laughter, but in some patients sudden anger and other rapid-onset emotions will trigger it as well. There is a spectrum of intensity of cataplexy. A person might fall to the floor for seconds or even minutes. More typically, there is weakness, such as the jaw or head dropping, which may be transient.

Most cases of narcolepsy with cataplexy are caused by a deficit in the peptide hypocretin (ie, orexin). In autopsy material, patients with narcolepsy with cataplexy showed a 90% loss of hypocretin cells on average. However, most patients with narcolepsy without cataplexy do not have a complete loss of hypocretin in the cerebrospinal fluid. This has led to the question of whether these two groups, in fact, have the same disease.

Is narcolepsy adequately diagnosed?

Narcolepsy occurs in ~1 in 2,000 people in the United States. It is underdiagnosed. It used to be that >15 years would pass between the onset of symptoms and a correct diagnosis. Though that lag has been reduced, I think many patients with excessive sleepiness are not correctly diagnosed and may just be told that they need to sleep more or that they should get more exercise. Thus, they are not adequately treated. The age of onset is typically in the teens or twenties. In many cases children will not be able to stay awake in school and may be ridiculed for these symptoms. It is very important that they get correctly diagnosed and treated so that their educational and social development are not impaired.

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Once narcolepsy manifests, do the intensity and frequency of symptoms change over time?

There is a progression during the year or two after the onset. Typically, the sleepiness presents first and cataplexy comes later. The onset of cataplexy can be delayed by up to 2 years or, in a few cases, more than that. Many patients with narcolepsy with cataplexy report that they have learned to reduce the cataplexy, mostly by avoiding situations that trigger it, such as anything which causes one to laugh. That in itself is quite sad.

However, I am not certain that this cognitive explanation is adequate, because in narcoleptic dogs we see the same progression. That is, the symptoms appear and then as the animal ages, the cataplexy in particular gets more and more infrequent. There is no reason to think that the dogs have any incentive to avoid cataplexy. They are not embarrassed, and the condition does not cause injury or "social" problems. Thus, it appears that with aging there may be some brain reorganization or some normal maturational change that may counter the effect of hypocretin loss on cataplexy. All in all, the general picture is that once the symptoms are established they do not continue to worsen.

Certainly, there is no generalized degeneration leading to other symptoms such as Parkinson's disease or Alzheimer's disease. However, a recent article¹ showed that Parkinson's disease patients do have a depletion of hypocretin cells. Though this depletion is not quite as extensive as in narcolepsy, it is still quite severe. This may account for the sleepiness that characterizes Parkinson's disease, which is quite similar to narcolepsy in many ways. However, it is clear from examining the brains of Parkinson's disease patients that the cause of the cell loss is not the same as in narcolepsy.

Is narcolepsy related to abnormalities in REM sleep?

In normal REM sleep, several groups of monoaminergic cells become silent. Norepinephrine-, serotonin-, and histamine-containing neurons are inhibited. This is partially responsible for the phenomena of REM sleep. In narcolepsy, these cells are no longer so well coordinated. That is, they do not all stop being active at the same time.

Norepinephrine cells become inactive during waking, which never happens in the normal animal. This loss of norepinephrine activity is responsible for the loss of muscle tone in cataplexy. This presumably occurs because of the loss of hypocretin. Normally, hypocretin, an excitatory peptide, keeps the norepinephrine cells active in waking. In the absence of hypocretin, which is the case in narcolepsy, these cell groups can fall silent in waking when strong emotions are triggered. That, then, causes cataplexy.

Have you been able to identify any genetic markers for narcolepsy?

Genetic mutations can cause narcolepsy but that is extremely rare. There are only one or two human cases identified in which there is a mutation in genes synthesizing hypocretin or its receptors. Most narcoleptics do not have such mutations and do not have first-order relatives with narcolepsy. In addition, 87% of identical twins are discordant for narcolepsy, even many years after onset. One identical twin may have narcolepsy but 30 years later the other twin will still be symptom free. However, in the case of some animal models, it is entirely genetic. Two narcoleptic dogs with a mutation that inactivates a hypocretin receptor produce only narcoleptic offspring.

However, there is a genetic risk factor in human narcolepsy, namely, a particular human leukocyte antigen (HLA) subtype called DQB-10602. The HLA system is related to the immune system and mediates tissue compatibility. Most HLA-linked disorders are autoimmune in nature. Ninety-five percent of Caucasian narcoleptics have this particular HLA subtype, whereas in the general population only 20% to 30% have it. Certainly, the HLA subtype by itself is not sufficient to produce the disease. The HLA correlation suggests that narcolepsy may be an autoimmune disease. There is some direct evidence in the postmortem brains of narcoleptics of gliosis in the region of cell loss, which is an indication of prior inflammation. This suggests that something happened at symptom onset that caused these particular cells to be destroyed. In fact, adjacent cells are left untouched. This points to an immune mechanism that would recognize particular cell types, rather than just the destruction of a particular area of the brain as the cause of most human narcolepsy.

Are there any characteristic psychiatric symptoms associated with narcolepsy?

There appears to be a greater incidence of depression in narcolepsy. Although this has not been very well documented or quantified, it has been reported in an anecdotal manner. However, now that we understand that the hypocretin system is the key to this disorder, and we can work with narcoleptic animals, we notice behavioral signs that seem to be similar to depression. For example, it has long been known that narcoleptics tend not to get addicted to various drugs. They very seldom abuse drugs of treatment, such as amphetamines and γ -hydroxybutyrate. It has also been documented that mice without hypocretin do not get addicted to agents that produce addiction in normal mice. We know that the hypocretin system connects very strongly to the dopamine system, which has been implicated in addictive behavior and in pleasure. Therefore, the loss of hypocretin may cause depression. This may also be the case of Parkinson's disease, which has a similar loss of hypocretin cells and similar symptoms of depression.

Should a practitioner who suspects someone might have narcolepsy start treating it or first send the patient to a sleep lab?

I think it is always desirable to go to a sleep lab. The drugs that are prescribed are potential drugs of abuse so it is certainly highly desirable to get objective evidence that the patient has the symptoms that are diagnostic for narcolepsy before prescribing these drugs. Typically, patients will take these drugs for the rest of their lives. In the sleep center, narcolepsy with cataplexy is easily diagnosed. For narcolepsy without cataplexy it is certainly desirable to have the full electroencephalographic workup that can document that the patient has sleep-onset REM periods. Of course, excessive daytime sleepiness is quite common, and other potential causes, particularly sleep apnea, must be ruled out. Another

disease category which can look like narcolepsy is idiopathic hypersomnia, where people are just sleepy all the time but do not have cataplexy or REM sleep near sleep onset.

What are the treatments for narcolepsy?

Sleepiness in narcolepsy has traditionally been treated by dextroamphetamine and methamphetamine. Methylphenidate and modafinil are also used. Tricyclic antidepressants are used if cataplexy is a major complaint. More recently, selective serotonin reuptake inhibitors such as fluoxetine have been used. Antidepressants, such as venlafaxine, protriptyline, and imipramine are also commonly used to treat cataplexy. Typically, a narcoleptic will be treated with both anticataplectic drugs and stimulants.

A relatively new drug being used is sodium oxybate (ie, γ -hydroxybutyrate). Its mode of action is not well understood but it seems to help both the sleepiness and the cataplexy. It is taken in liquid form, in very large doses of up to approximately 8 grams per night. The patient has to wake up in the middle of the night to take the second half of the dose. It is inconvenient to use but it can be uniquely effective on both symptoms.

The hope is that hypocretin itself or hypocretin agonists will be used as a treatment since that is the underlying deficit. We have shown that hypocretin given to narcoleptic dogs can reverse symptoms. Deadwyler and colleagues² showed that hypocretin can be administered by nasal inhalation to monkeys that were sleepy. It reversed the sleep deficits very effectively. Potentially, that would be a very useful treatment, but to my knowledge it has not been tested in human narcoleptics. **CNS**

REFERENCES

1. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. *Brain*. 2007;130(Pt 6):1586-1595.
2. Deadwyler SA, Porrino L, Siegel JM, Hampson RE. Systemic and nasal delivery of orexin-A (Hypocretin-1) reduces the effects of sleep deprivation on cognitive performance in nonhuman primates. *J Neurosci*. 2007;27(52):14239-14247.