

Article ▶ Sleeping Beauty Gets an Eye Exam: A Case Report and Literature Review on Narcolepsy

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ABSTRACT

Background: Narcolepsy, a neurological sleep disorder that affects both adults and children, is caused by the inability of the brain to regulate sleep-wake cycles normally. The common tetrad of symptoms includes excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Ocular symptoms such as blurred vision, diplopia, ptosis, and ocular pain have been reported.

Case Report: A ten-year-old female who was diagnosed with narcolepsy at an early age presented for a comprehensive eye examination. She was taking Xyrem BID. Entering visual acuity was 20/30 OD, 20/70 OS, 20/25 OU at distance and 20/20 OD, OS, OU at near. Extraocular motilities, confrontation fields, and pupils were unremarkable with the exception of the patient continually falling asleep. A distance pair of glasses was issued: -0.50 DS, -1.25 DS.

Conclusions: Narcolepsy is a chronic disorder that can severely affect a patient's quality of life. Most control their symptoms with a wake-promoting drug. The disease itself, as well as its pharmacological treatment, can produce a range of ocular effects that optometrists should recognize and manage.

Keywords: amphetamines, cataplexy, hypnagogic hallucinations, modafinil, narcolepsy, sleepiness, sleep paralysis, sodium oxybate

Introduction

Narcolepsy is a condition characterized by chronic sleepiness and a marked disorganization of sleep-wake behavior. It usually begins in the teens and early twenties, although symptoms can begin in young childhood or after the age of 40 years. The exact cause remains unknown, but there is substantial evidence that a deficiency of the brain peptide hypocretin plays an integral role.¹ Hypocretin, which is derived from the dorsolateral hypothalamus, has been linked to multiple regulatory functions including sleep-wake cycles. Deficiency of hypocretin results in sleep fragmentation.¹

Due to the broad spectrum of symptomatology there is an average delay of a decade for a correct diagnosis. All narcoleptic subjects have chronic sleepiness, but the intensity varies across the day and between individuals. Younger populations report that excessive daytime sleepiness is the first symptom to appear, while older populations report that cataplexy is the most common initial symptom.¹ Generally speaking, narcoleptic subjects often have abnormal manifestations of rapid eye movement (REM) sleep that intrude into wakefulness, including cataplexy, hypnagogic hallucinations, and sleep paralysis.² While the literature investigating the ocular effects of narcolepsy is limited, reports of inattention, poor memory, blurry vision, diplopia, and automatic behaviors such as driving without awareness have been reported.^{3,4}

Case Report

A ten-year-old female reported for a comprehensive examination complaining of distance blur for the past few months. She was diagnosed with narcolepsy at an early age

and was taking Xyrem BID. Her mother noted that she is allowed to take frequent naps at school and the teacher wakes her to continue her work. She is doing well in school and is on the honor roll. Entering visual acuity was 20/30 OD, 20/70 OS, 20/25 OU at distance and 20/20 OD, OS, OU at near. Extraocular motilities, confrontation fields, and pupils were unremarkable with the exception of the patient continually falling asleep. A distance pair of glasses was issued: OD -0.50DS, 20/20; OS -1.25DS, 20/20. Negative relative accommodation/positive relative accommodation were balanced with this prescription, and the fused cross cylinder was +0.75 OD, OS. Near point of convergence was "to the nose," and accommodative amplitudes were 13D OD, OS. Intraocular pressure (13mmHg OU) was taken with the non-contact tonometer as we were afraid the patient would fall asleep and injure herself during Goldmann tonometry. The anterior and posterior segment evaluation was normal.

Discussion

Clinical Presentation

The first symptom of narcolepsy is usually excessive daytime sleepiness and is present in all patients suffering from the disease. It manifests as sudden and brief attacks of irresistible sleep, or it can be much more subtle. Historical data shows that sudden, abrupt sleep is not the usual symptom, but a sustained drowsiness is more commonly seen.³ Daytime naps, which are normal in younger children, can compound the difficulty in recognizing this excessive sleepiness in the pediatric population. However, normal naps should cease by age three to four, and the presence of daytime naps becomes

Table 1: Drugs marketed in the US that have narcolepsy as a clinical indication

Trade name	Generic name	Common side effects	Ocular side effects
Sleepiness			
Adderall tablets Dexedrine capsules DextroStat tablets	Amphetamine (d and l)	Insomnia, weight loss, headache, jitteriness	Visual disturbances, blurred vision, mydriasis
Metadate ER tablets Methylin ER tablets Ritalin hydrochloride tablets	Methylphenidate	Irritability, headaches, insomnia, dry mouth	Visual disturbances, blurred vision, abnormal accommodation
Provigil tablets	Modafinil	Headaches, nausea, rhinitis, insomnia	None reported
Cataplexy			
Effexor	Venlafaxine	Weight loss, decreased appetite, nausea, dizziness	Blurred vision, mydriasis, abnormal accommodation ⁸
Prozac	Fluoxetine	Dry mouth, nervousness, headache, fatigue	Acute angle closure glaucoma (rare), abnormal vision, blurred vision, mydriasis, keratitis sicca, diplopia, ptosis
Vivactil	Protriptyline	Anxiety, disturbed nighttime sleep	Blurred vision, mydriasis, ⁹ photosensitivity ¹⁰
Xyrem	Sodium oxybate	Sedation, nausea, dizziness, urinary incontinence, headaches, sleep walking	None reported

significant.^{4,5} Other complaints that may be elicited from narcoleptic patients are mental dullness, forgetfulness, irritability, declining performance in school, or inattentiveness. In children, hyperactivity and inattentiveness instead of sleepiness may present.⁴

Another feature of narcolepsy is cataplexy, a transient loss of muscle tone. Cataplexy represents the appearance of REM atonia during wakefulness.⁴ While narcolepsy can occur without cataplexy, cataplexy occurs in 60-90% of patients with narcolepsy.⁴ Typically, the onset of cataplexy follows the onset of daytime sleepiness by months to years, which often brings attention to the child's condition for the first time.^{4,5} Consciousness is usually unaffected, and respiratory movements and ocular motility are not compromised. Most attacks subside within a minute, and recovery is quick without any confusion after the event. Cataplexy can take various forms. At its most subtle, muscle weakness can cause the child to feel unsteady, or slight observable weakness of the limbs, face, head, or neck can be seen.⁴ Positive and negative emotions such as laughter and fear can trigger a cataplexy attack, as well as general emotional stress. Cataplexy is often misdiagnosed as clumsiness, syncope, attention-seeking behavior, malingering, or atonic seizures, the latter being the most common misdiagnosis for children under five years old.⁴

Hypnagogic hallucinations occur in approximately 60% of narcoleptic patients.⁴ These hallucinations consist of vivid dreams that usually are frightening, but can also be visual, auditory, or out-of-body experiences.⁴ They are most often confused with sleep terrors, nightmares, or panic attacks and often occur with any disorder in which there is significant sleep disruption. Hallucinations are often under-reported due to the perceived psychiatric implication, as well as poor insight into the unreal nature of the hallucinations.⁶ While the causes of various visual hallucinations are exhaustive, optometrists

should be familiar with hypnagogic hallucinations associated with narcolepsy in order to reassure the patient and minimize associated anguish.

Sleep paralysis is the inability to move, usually upon awakening. No disruption in breathing or eye movements occurs, but the person is unable to move their head or limbs. Sleep paralysis seems to occur due to the persistence of REM atonia after awakening.⁴ The paralysis can last seconds to minutes and end spontaneously, typically when the person is touched or talked to.

While the tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations is the hallmark of narcolepsy, not all symptoms need to be present. Some symptoms may present in isolation even if the patient has experienced the whole tetrad. Secondary (symptomatic) narcolepsy can also result as a consequence of a focal nervous system lesion, most commonly in the posterior hypothalamus.⁷ Other etiologies of secondary narcolepsy can be found in Table 1.^{1,4,5} There is much debate as to whether symptomatic narcolepsy in such conditions should be classified as narcolepsy because some of the aforementioned conditions lack the characteristic clinical features of disease.⁵

Other symptoms that are important in the identification and treatment of narcolepsy that are not included in the classic tetrad include automatic behaviors, or semi-purposeful behavior without awareness or recall. For example, adults may complain of driving to a location without memory of doing so.⁴ In children, it can manifest as sloppy handwriting or completing household tasks without recollection.⁴ Moreover, excessive sleepiness may be considered as normal daytime naps in children younger than five. Children also may have difficulty expressing their symptoms and may use words pertaining more to their cognitive or emotional state, such as bored, cranky, or sad.¹¹ While care must be taken to avoid misdiagnosis,

Table 2: Secondary etiologies of narcolepsy

Hypothalamic lesion
Stroke
Tumor
Prader-Willi syndrome
Traumatic brain injury
Neimann-Pick disease Type C
Myotonic dystrophy
Encephalomyelitis
Multiple sclerosis

interestingly enough, epidemiologic studies have linked excessive daytime sleepiness to psychiatric disorders including atypical depression, seasonal affective disorder, and bipolar disorder.¹ Thus, it is important to evaluate the complaint of excessive daytime sleepiness in great detail since it is observed in numerous disorders.

Ocular effects noted in narcolepsy include blurred vision, ptosis, ocular pain, and headaches.⁴ These complaints may be related to the level of tiredness. Difficulty with concentration and memory may also be reported.¹ Diplopia may also be an early manifestation, but it is commonly overlooked.³ Diplopia and loss of focus have also been reported specifically during cataplexy attacks.¹² There may also be twitching of the facial muscles or limbs which can lead to a misdiagnosis of epilepsy.¹ An isolated case of central serous chorioretinopathy associated with untreated narcolepsy has also been reported. The proposed mechanism is that chronically disrupted sleep can potentially amplify sympathetic activity and the release of cortisol and catecholamines, thus increasing the risk for central serous chorioretinopathy.³

Unfortunately, the presence or absence of symptoms often varies during the course of the illness, making a diagnosis difficult. One study noted that children had three referrals before the diagnosis of narcolepsy was made.⁴ Such misdiagnosis can result in a significant delay in treatment, with some children being referred for psychiatric or educational services. The implications of such misdiagnosis can leave children suffering from narcolepsy becoming fearful, embarrassed, distressed, and helpless about their situation. Furthermore, the effect of daytime sleepiness can cause poor school progress and have an effect on the child's concentration, memory, and other aspects of cognitive function.⁵

Treatment and Side Effects

The most effective non-pharmacologic treatment for daytime sleepiness in narcoleptic patients is brief naps.⁴ While such naps are effective, they seldom suffice as stand-alone therapy and are impractical in older, school-age children. Dietary modifications can also be helpful in maintaining wakefulness by reducing the amount of refined sugars and carbohydrates that tend to produce daytime sleepiness.⁴

Pharmacologic therapy is typically the first line treatment for narcolepsy to manage daytime sleepiness (Table 2). A commonly prescribed drug is methylphenidate, a stimulant that is a dopamine and catecholamine reuptake inhibitor. Many formulations of methylphenidate are available, such as Ritalin, Methylin, and Concerta. Another enantiomer of methylphenidate, dexmethylphenidate, is available as Focalin. Side effects of methylphenidate and its derivatives include insomnia, weight loss, decreased appetite, stomach ache, and dry mouth. There are cardiovascular risks in children with known cardiac disease. Ocular side effects include visual disturbance, blurred vision, and abnormal accommodation.¹⁴ Any side effects encountered can usually be avoided with a dose reduction.

Another commonly used drug class for the treatment of daytime sleepiness in narcoleptics is amphetamines, which also treat cataplexy due to their sympathomimetic effects. Dextroamphetamine is used clinically, as well as other formulations such as Dexedrine, Adderall, and Vyvanse. Side effects of this class of medications are similar to those seen with methylphenidate and include insomnia, weight loss, stomach ache, headache, jitteriness, increased blood pressure, and irregular heart rhythm.^{4,5} Noted ocular effects include blurred vision, mydriasis, and visual disturbance.¹⁵ While amphetamines produce objective improvement in 65-85% of patients with narcolepsy, many physicians prefer more recently developed drugs with less abuse potential such as methylphenidate and modafinil.¹⁶

Modafinil, marketed as Provigil, is another wakefulness promoting agent used in treating narcolepsy, and is Federal Drug Administration (FDA) approved for excessive daytime sleepiness associated with narcolepsy. In addition to its waking effect, modafinil is also known for its mood-brightening and memory-enhancing effects.¹⁷ The mechanism of action of modafinil is not currently understood; many theories have been proposed. Little data is available for use in children. Side effects are generally mild and include headache, nausea, nervousness, and rhinitis.⁴ Headaches associated with modafinil use are often transient and typically resolve after three days of treatment.¹⁸ Rare but more serious side effects include Stevens-Johnson syndrome, elevated liver enzymes, suicidal tendency, and psychosis.⁴ There have been no reports of ocular side effects associated with modafinil.

Lastly, sodium oxybate, marketed as Xyrem, is an endogenous neurotransmitter which improves daytime sleepiness and cataplexy. It is the only FDA-approved medication for the treatment of cataplexy but has been reported to be effective on all symptoms of the tetrad, as well as disturbed nocturnal sleep.¹⁹ Side effects observed in adults include nausea, sleep walking, confusion upon waking, nocturia, elevation in blood pressure, dizziness, and headaches.¹⁴ Other common side effects include nasopharyngitis and vomiting.¹ Studies are lacking in the pediatric population, but side effects noted in children include suicidal thoughts, terminal

insomnia, dissociative feelings, and constipation.⁴ There are no ocular side effects reported with sodium oxybate other than visual disturbance upon drug withdrawal.²⁰ Sodium oxybate has also been shown to reduce the frequency of hypnagogic hallucinations.

Other drugs used to treat cataplexy include antidepressants. Initially, tricyclic antidepressants were used, but due to their long list of side effects, selective serotonin reuptake inhibitors (SSRIs) have been used to treat narcolepsy-associated cataplexy.⁴ Fluoxetine, an SSRI antidepressant marketed as Prozac, may cause nervousness, headache, fatigue, anxiety, and tremors.⁴ In addition, hyperkinesia, personality changes, and epistaxis can occur in children.⁴ Ocular effects of Prozac include abnormal vision, blurred vision, mydriasis, keratitis sicca, diplopia, and ptosis.²¹ Because of their anticholinergic activity, antidepressants also tend to suppress hypnagogic hallucinations and sleep paralysis.⁴

Conclusion

Narcolepsy is a chronic disorder that can severely affect a patient's quality of life. Understanding the signs and symptoms can decrease the chance of misdiagnosis. The clinical picture in children is often quite different than the fully developed narcoleptic syndrome in adults, which makes the narcolepsy diagnosis at risk for being overlooked. Some narcoleptics can manage their symptoms with several daytime naps; however, most patients require treatment with a wake-promoting drug. None of these drugs completely eliminates sleepiness, but these medications usually reduce sleepiness enough for substantial improvements in performance and quality of life. Optometrists should be aware of the condition, treatments available, and side effects of medications used.

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Liechty J. Sleeping Beauty Gets an Eye Exam: A Case Report and Literature Review on Narcolepsy. *Optom Vis Perf* 2014;2(3):126-9.

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