
Sleep Disorders in Fragile X Syndrome

By Ann Reynolds, MD, Fragile X Treatment & Research Center, Children's Hospital, Denver

There are very few studies of sleep disorders in children with fragile X syndrome, but we know that such disorders are common in children with developmental disabilities. In fact, they occur in 30-80 percent of children with cognitive disorders, and they appear to be even more common in children who also have autism or psychiatric disorders such as anxiety, depression, ADHD, and mood lability (unstable moods). All these disorders are frequently seen in fragile X syndrome. Holloway, Hagerman and others at the Fragile X Research and Treatment Team in Denver evaluated 23 males under age 7 with fragile X syndrome, along with 14 age-matched controls without FXS. He found shorter sleep duration, greater variation in sleep duration, longer night waking episodes, and sleep timing problems in the group with FXS.

General information about sleep

Sleep is controlled by two different internal clocks. The first is the circadian rhythm, which refers to the daily physiological cycle of sleeping and waking. This internal biological clock runs on a 25-hour cycle. The second is the "ultradian" rhythm, which refers to the physiological cycles that occur multiple times per day. Individuals cycle through sleep stages multiple times per night.

Environmental, physiological and social cues are needed to entrain the sleep/wake cycle into a 24-hour cycle. The environmental cues are light/dark, ambient temperature, and noise. Physiological cues are hunger, pain, core body temperature, and hormone secretion. Social cues work by giving the message that a child won't get to play/interact with mom or dad during the night; therefore, you want to limit social interactions after bedtime. Sleep routines are especially important for children with autism in addition to fragile X syndrome because they are at even higher risk for sleep disorders. Such children can't make use of social cues to entrain their circadian rhythms.

While sleep/wake cycles occur daily, the stages during sleep itself cycle every 50 minutes in infants and every 90 minutes in adults. Sleep can be broken down into four

"non-REM" stages, encompassing light through deep sleep. Children who wake frequently during the night are often waking during the lighter stages of sleep (stages 1 and 2) and then can't get themselves back to sleep again. Stages 3 and 4 are the deepest, most restful sleep. REM sleep occurs next, and is characterized by an active mind, while the body is motionless except for the "rapid eye movements" from which the REM acronym is derived.

Sleep, like walking and talking, is a developmental phenomenon. Infants are not born with a sleep/wake cycle; in

Sleep routines are especially important for children with autism in addition to fragile X syndrome.

fact, it is not until 6 to 12 months of age that an infant's sleep electroencephalogram (EEG) can be read using adult criteria. Infants also do not make melatonin (a light-sensitive hormone that decreases core body temperature and appears to play a role in sleep onset and maintenance) until 9 to 12 weeks of age. From the basic

science literature, we can speculate that some difficulties with sleep in fragile X may be due to abnormal mechanisms for maintaining the circadian rhythm. For example, a study by Inoue and others from Japan found that fruit flies that are missing the "fmr1" gene (the gene responsible for fragile X syndrome) are dependent on light/dark cycles to maintain circadian rhythms, while typical fruit flies can maintain their circadian rhythm even in continuous darkness.

The only two studies of melatonin levels in children with fragile X demonstrate conflicting data, and both have small sample sizes. O'Hare and others (1986) did not find the expected increase in nighttime serum (blood) melatonin in three of five males with fragile X syndrome. Of the two remaining subjects, O'Hare found only a mild rise in one. Conversely, Gould and Hagerman (2000) found the expected increase in salivary melatonin at night in 13 boys with fragile X; in fact, it was higher than eight typical controls.

*We know that
children with
fragile X syndrome
have difficulty
with transitions,
and sleep is the
ultimate transition.*

Dyssomnias refer to problems with initiating and maintaining sleep, or to excessive sleepiness. These are the most common types of sleep disorders. Dyssomnias will be discussed in greater detail in the following paragraphs, since they have been reported in children with fragile X.

Parasomnias—sleep terrors, sleepwalking and nightmares—are abnormalities of arousal, partial arousal, and transitions between stages of sleep. These usually resolve without treatment. However, it is important to remember that many parasomnias worsen when a child is sleep-deprived, so avoiding overtiredness can be helpful.

Another type of sleep disorder is obstructive sleep apnea (OSA), also known as “sleep disordered breathing.” It is characterized by obstruction of the airway, either at the level of the nasal passages due to allergies, or in the back of the throat due to a narrow palate, large tonsils and adenoids and/or low tone in the throat. Two studies of OSA have been done in children with fragile X. One study by Tirosh and Borochowitz from Israel found that four of seven had OSA, while another study by Ferri and Musumeci from Italy used seven children with fragile X as controls in a study of OSA in Down’s syndrome and found that none had OSA.

Facial structure and low tone in the mouth may both have a role in individuals with fragile X syndrome who also demonstrate OSA. Typical treatments involve removing tonsils and/or adenoids, treating allergies, and using continuous positive airway pressure (CPAP). CPAP involves wearing equipment on the face at night, which is difficult to get used to, but, Tirosh and others in Israel (1995) reported successful use of CPAP in an 8-year-old with fragile X, leading to improvement in sleep and some improvement in behavior.

Risk factors for Obstructive Sleep Apnea

- Snoring
- Breathing pauses during sleep*
- Difficulty breathing, chest wall moves in instead of out when inhaling *
- Mouth breathing during the day
- Noisy breathing
- Restless sleep
- Sweating during sleep
- Morning headaches
- Difficulty waking in the morning
- Nasal voice
- Daytime sleepiness
- Daytime irritability
- ADHD symptoms

*Starred symptoms are very specific for OSA and definitely require evaluation by a physician; the other symptoms may indicate OSA but are not specific.

Impact on children and families

Sleep disorders cause significant distress for families. Parents report more stress—fatigue and difficulty implementing daytime behavioral strategies—if their children have sleep disorders. There is also evidence that sleep disorders may worsen daytime behavior in people with develop-

mental disabilities. For example, inattention and hyperactivity have been associated with OSA. This association is demonstrated by improvement in ADHD symptoms after treatment of OSA. In addition, the role of sleep in learning and memory is yet to be fully understood. There is evidence that REM sleep is important in memory consolidation in rats, but the evidence in humans is less clear. Children with cognitive disorders have been noted to have less REM sleep. In a small case series of seven children, Elia and others in Italy found decreased REM sleep in children with fragile X syndrome.

Practical strategies

When your child has trouble getting to sleep and staying asleep, there are several strategic interventions you can pursue. We know that children with fragile X syndrome have difficulty with transitions, and sleep is the ultimate transition. It is therefore very important to prepare your child for the transition to sleep just as you would for the transition from any other activity to the next.

Bedtime should be part of your child’s visual schedule, if you have one. (A visual schedule is made up of pictures of daily activities. It can be very helpful when dealing with all kinds of transitions. Consult your therapists or teachers on whether one would be helpful for your child.) It is critical to create a routine—at the same time each day—that helps prepare your child for sleep. Children with fragile X syndrome are usually overly sensitive to many types of environmental stimuli, and they may have particular difficulty settling down for bed. An occupational therapist can usually suggest calming techniques that are helpful if done regularly. Always remember that behaviors are often worse for a short time after you begin any behavior management strategy.

The bedtime routine should start shortly after dinner with calming activities. These activities can be different for

continued →

every child, so it is important to speak with your O.T. or psychologist about what might be appropriate if you are not sure. Activities might range from a family walk to watching a movie. A movie, however, can actually work against you if it gets your child excited or causes a tantrum when you have to turn it off. Children also shouldn't fall asleep in front of the television, because they may need it to get back to sleep if they wake up in the middle of the night.

Bath time is very calming for some children but may not be for others, especially if there is a big battle to get in the tub

and another one to get out.

If you struggle with your child over this matter, consider giving the bath in the morning or earlier in the afternoon or evening.

Most children will sleep better if they have been physically active during the day. Obviously, long naps late in the day can become a problem at bedtime because

the child just isn't sleepy. Nonetheless, naps are important, and many families report more night waking when their child has missed his or her nap because the daily rhythm is disrupted. Routines are just as important for naptime as for bedtime. Both should be at the same time each day, which can be difficult when you are running around to appointments and activities, but it can really pay off to stick to a routine.

It is very important to do the same thing each evening, giving the child a non-verbal message that bedtime is coming soon. It also helps to create the proper atmosphere throughout the house as you start the bedtime routine: use lamps or dim overhead lights. Turning on a 60-watt light bulb for one minute can cause melatonin levels to go back down to daytime levels for 40 minutes. Therefore, try not to turn overhead lights on when your child wakes up during the night; rather, use a 4-watt night light or a small flashlight if possible.

Decreasing the temperature in the house may also help trigger the rise in melatonin. The goal is to entrain the circadian rhythm.

When beginning any treatment for sleep disorders, it is important to keep a diary for two to three weeks. Try to record the following: the time when the bedtime routine


begins, the time for "lights out," the time the child actually falls asleep, the number of times the child wakes up during the night, the length of time the child is awake with each night waking, the things that help the child get back to sleep, and the time the child wakes up in the morning. It is also important to keep track of whether the child is sleepy during the day, whether he or she takes a nap (and if so, for how long and when), the level of activity, and what the child eats in the hours before bedtime. Writing things down often helps parents see patterns; for example, your child might sleep better on the days when he or she went swimming. The diary is also helpful for monitoring treatment.

If all else fails, you can try "fading"—putting your child down at the time he or she usually falls asleep, even if it is late—with the assumption that sleep will come quickly. The hope is that the child will develop the habit of falling asleep soon after lights-out. Once you have established this pattern, you can make bedtime earlier by 15 minutes every couple of days, until your child is going to bed at a time that seems appropriate.

Always make sure that you have picked a reasonable bedtime. Seven o'clock may be unreasonable for some children, especially if it is still light outside and there is activity around the house. On the other hand, you don't want to begin the bedtime routine when your child is over-tired—and completely unreasonable! In addition, anecdotal evidence suggests that many individuals with fragile X are early risers and therefore need to go to bed early. This is probably due to sensitivity to light. They wake up with the sun, so they need to go to bed with it as well.

Waking during the night is normal and an expected part of the sleep stages. Many of us wake briefly during the night but don't remember it. Getting back to sleep is the issue. That is why it is important for children to be able to get themselves to sleep initially. Then when they wake up at 2 a.m., they'll have the tools to get themselves back to sleep.

Behavioral interventions should always be part of treatment for sleep disorders, but sometimes medications are necessary as well. Clonidine, which is used to treat ADHD, is often helpful for getting to sleep. Trazadone, which is an antidepressant that is very sedating, can be helpful for children who have trouble staying asleep. All medications used for sleep in children do not have FDA approval specifically for them, so you should go over risks and benefits carefully with

your physician. A sedating antihistamine such as benadryl can sometimes be used short term to “reset” the circadian clock. Some people use melatonin for help getting to sleep. It is not regulated by the FDA, so different brands may vary in effectiveness. There have been some studies of melatonin for sleep disorders in children with disabilities. It shows the most promise for children who are blind. 

Dr. Reynolds works with the Fragile X Treatment and Research Team at The Children’s Hospital in Denver, Colorado. Team members include Dr. Jennifer Epstein and

Dr. Rebecca Wilson, psychologists with expertise in FXS, Claire Summers, an occupational therapist who has treated many children with FXS, and Lisa Nobel, a speech and language pathologist with expertise in augmentative communication/computer technology use in children and adults with FXS. Dr. Reynolds is currently studying sleep and gastrointestinal disorders in children with FXS. She also collaborates with Dr. Maureen Leehey and Dr. Jim Grigsby on studies of the Fragile X Tremor Ataxia Syndrome, and with Dr. Susan Hepburn on the longitudinal study of autism in children with FXS.

Eleven Tips for a Good Night’s Sleep

1.

Routine, Routine, Routine!

2.

Dim lights at least 40 minutes before bedtime.

3.

Transitional objects can be helpful, such as a knotted up t-shirt with mom’s scent on it.

4.

Limit high fat foods in the evening. They slow down digestion and may make gastroesophageal reflux symptoms worse.

5.

Make sure your child is physically active during the day.

6.

Avoid caffeine in drinks and in foods like chocolate—they can disrupt sleep patterns during the night even if falling asleep is not a problem.

7.

Do calming activities before bed.

8.

Avoid long naps late in the day. But if your child really needs a nap, don’t cut them out altogether, because a missed nap sometimes leads to problems with sleep at night.

9.

Reinforce good bedtime behavior.

10.

Try to keep the bed and, if possible, the bedroom, only for sleeping. This way your child will associate the bed with sleeping and not with playing.

11.

Expect sleep disruptions with changes in the daytime routine. Vacation, new teacher, parent out of town—all these can disrupt sleep at night. A consistent daytime routine helps synchronize the sleep/wake cycle.