Neurologic and Medical Influences on Aggressive Behavior in Individuals with Angelman Syndrome

Learning Objectives

- Understand how an increase in seizure activity might result in an increase in aggression.
- Understand how an increase in seizure activity might result in a decrease in aggression.
- Describe the typical patterns of sleep problems in AS and management strategies.
- Describe the common gastrointestinal, orthopedic and mobility issues in AS.
- Understand how unrecognized pain may manifest as a direct or indirect change in behavior.

General information about seizures in AS

Epilepsy is very common in AS, affecting 80-95% of individuals. Neurologists work to optimize epilepsy treatment at all ages so as to minimize the detrimental impact of seizures. The treatment goal should always be seizure freedom with minimal medication side effects. The impact of epilepsy on the brain is poorly understood, but over time seizure activity does have the potential to impair learning and cognitive processing. Seizures also pose broader health risks to individuals with an increased incidence of injury due to falls, choking, and aspiration pneumonia. Furthermore, seizures can limit social opportunity and inclusion with peer groups. Finally, as you know, parents and caregivers often carry significant fear and anxiety about their child's seizure activity, often related to the inherently unpredictable nature of seizures. This reality often has negative implications for the quality of life of the family as a whole.

Seizure activity and behavior

The bottom line is that seizures have the potential to either exacerbate or suppress difficult behaviors depending on the individual, the seizure type, and the behavior. With an increase in epileptic activity in the brain, seizures can draw out more aggressive, hyperactive, and/or defiant behaviors. Our clinical experience has led us to believe that these changes may be related to discomfort, frustration, confusion, or fatigue in the setting of the seizures. Conversely, we have also seen many children with AS in whom a decrease in seizure activity parallels an increase in difficult behaviors. This type of change is more common when the baseline seizure activity is quite severe, with epileptic activity occurring almost continuously throughout the day and/or night. This kind of persistent epileptic activity can create a sort

of barrier between the individual and the outside world, and ultimately have a sedating effect. When this type of severe and persistent aberrant brain activity is suppressed with anticonvulsant medications or dietary therapy, challenging behaviors may in fact increase due to a heightened sensitivity and awareness of the outside world.

One way to think about this is to imagine wearing earplugs, dark sunglasses, and mittens for six months straight. Over time, your brain would acclimate to this decreased level of awareness and sensory input. Seizure activity can act like those earplugs, sunglasses, and mittens, blocking out some of the noise and intensity of the outside world. Then imagine the doctor finds the right medication or combination of treatments to quiet the seizure activity. With this change, suddenly the earplugs come out and the sunglasses and mittens come off. The brain now can perceive and process information from the outside world to a much greater degree. For the individual, this kind of change may feel overwhelming or frightening, and parents and caregivers may see a corresponding increase in aggressive, hyperactive, or defiant behaviors.

Keeping track of seizures

To further understand the relationship between an individual's behavior and his or her seizure activity, it may be important to learn more about the timing and frequency of both the epileptic events and the episodes of challenging behavior. To help determine if seizure activity may be exacerbating an individual's behavior, it is often helpful to gather data about when seizures are occurring during the day and/or night, and how the events relate to behavioral outbursts. For example, John's caregiver kept a log of both his seizure activity as well as his aggressive behavior over several weeks. Four mornings a week, just before breakfast John had a brief seizure. Over the course of two months, on average, at least three out of four of those mornings, less than two hours after the seizure John had a meltdown or displayed aggression towards his aide. In this case, the seizures themselves, or possibly how John felt after a seizure (his ‘post ictal' state) may have been driving the behavioral outbreaks. The more data we can gather about seizure timing and frequency, the more equipped you and your doctor will be to make informed treatment decisions, so as to optimize seizure control and potentially improve behavior.

https://www.seizuretracker.com/ is a helpful website for logging seizures over time.

Epilepsy management strategies

Seizures in AS can be quite challenging to treat, but it is very important for clinicians and parents to relentlessly pursue seizure control, because with time and sometimes multiple treatment trials, the majority of individuals will achieve a reduction in seizure frequency.

Individuals with AS, in most cases, should be routinely followed by a neurologist and/or epilepsy specialist who can work to optimize treatments as well as monitor for medication side effects and toxicities. Levetiracetam (Keppra), lamotrigine (Lamictal), and clobazam (Onfi) are three antiepileptic medications that we commonly use to treat epilepsy in the AS population; however, every person is different and treatments must always be uniquely tailored to the individual. Additionally, we have had wonderful success with the treatment of AS-related seizures using dietary therapy. Specifically, high fat,

low carbohydrate treatments, including the ketogenic diet and the low glycemic index treatment, have proven effective in AS.

Antiepileptic treatments

Essentially, any anticonvulsant medication has the potential to affect an individual's behavior. This is not the kind of thing we want to say, and it certainly is not the kind of thing you want to hear. Anticonvulsant medications can impact behavior directly or indirectly. It is therefore very important when a new medication is started, or a new behavior is observed, that doctors and caregivers act as detectives thinking about the new behavior and then backtracking to consider what the individual with AS might be feeling, physiologically or emotionally, to precipitate the behavior.

For some medications, behavioral changes can be a direct side effect. For example, a subset of the individuals who are prescribed levetiracetam (Keppra), shortly after starting the medication will experience an increase in irritability. This crankiness can be a direct side effect of the medication. Fortunately, we only see this side effect in only approximately 20% of people who take the medication. Additionally, some medications may have side effects that cause discomfort for the individual such as abdominal pain or nausea, headache or dizziness. These discomforts may indirectly exacerbate challenging behaviors. Imagine an individual with AS starts a new antiepileptic medication. For him, this medication has a side effect of periodic, low-grade headaches. He may respond to this new unpredictable discomfort with aggression towards others or self-injury. Unfortunately, there is no way for your neurologist to truly predict either the level of efficacy or the behavioral side effects of any given medication prior to actually starting the new therapy. Therefore, we must be vigilant in monitoring for secondary behavior changes, possibly resulting from an unidentified medication side effect. These changes are typically seen within the first two weeks of starting a new therapy. In our clinical experience, the medications that have shown the potential to negatively impact behavior in AS most frequently are levetiracetam (Keppra), valproate (Depakote), and Phenobarbital.

Sleep

The majority of individuals with AS at some point in their lives have difficulty with sleep. These problems are often particularly severe for infants and young children. Difficulties may include trouble falling asleep, reduced total sleep time, frequent night wakings, and irregular sleep-wake cycles. Fortunately, sleep problems tend to improve with age. Clinically, we most frequently work with patients and families on problems of sleep latency - when the individual has difficulty falling asleep. Additionally, increased night wakings are not uncommon. In the case of increased night wakings, it is important to investigate if the individual may be waking up at night due to an increase in his or her nocturnal seizure activity. In such cases, individuals should follow up with a neurologist for further evaluation of his or her sleep patterns. An EEG or a polysomnogram might be recommended for further diagnostic information in such cases. The results of insufficient sleep, both fatigue and daytime sleepiness, may have a significant impact on an individual's behavior, again with the potential to either increase or decrease levels of aggression.

There are many sleep treatment strategies such as improving an individual's sleep hygiene, external

sleep factors like bedtime routines and minimization of distractions in the sleep environment (sound, light, toys). Also, many families describe increased exercise, and/or dietary modifications such as limiting sugar intake can improve sleep patterns in AS. Finally, in many cases, medications have proven very helpful for sleep. Two such medications that may be worth discussing with your neurologist include melatonin and gabapentin (Neurontin).

Orthopedic health and mobility

Many individuals with AS have orthopedic health issues, especially as they get older. These may include scoliosis, tight heel cords, osteoporosis, muscle weakness or poor coordination. As a consequence, independent mobility is often limited to varying degrees for a large proportion of the AS population. An individual's ability to walk independently may be limited by pain, endurance, or balance and stability. To help individuals both achieve and maintain as much independence as possible, physical therapy, occupational therapy, and routine exercise, both with endurance and muscle strengthening, are essential for all individuals with AS regardless of age. Additionally as is true for almost everyone, routine exercise can significantly improve an individual's baseline mood, energy, and sleep.

In much the same way that communication limitations may generate feelings of frustration, mobility restrictions have the potential to similarly contribute to an individual's loss of independence or autonomy. In some cases, the most natural response to these feelings of frustration may in fact be challenging behaviors. For example, in a busy store, John feels overwhelmed/bored/tired - wants to leave. Problem: for a variety of reasons, some of which may include mobility limitations, simply leaving isn't an option for him. He may have very limited control over an increasingly uncomfortable situation and therefore may feel frustrated. Solution: he screams. In the past, screaming around people he doesn't know has frequently resulted in him being taken out of the given situation. The behavior has facilitated movement.

What can we do to address these mobility-related behaviors? Again, unfortunately, there is no simple solution. Regardless of an individual's baseline mobility, whether they routinely need to use a wheelchair in the community or if they walk and run independently, we have found that, to the extent that is possible, it can be profoundly helpful to focus on an individual's autonomy. Many of the principles addressed in the communication module overlap with challenging mobility-related behaviors. To address these behaviors we again need to consistently work with teachers and caregivers to maximize opportunities for independence - focusing on communication as well as incorporating choice and self-reliance.

Gastrointestinal health

As you know, gastrointestinal issues are very common in Angelman syndrome and constipation specifically is almost universal among this group. The negative impact can be quite insidious and in some cases very severe. Constipation is stressful to the system and the body as a whole. The stress of constipation can in some individuals, trigger an increase in seizure frequency in much the same way that lack of sleep can. As an epileptologist working with individuals with AS, sometimes seizure treatment boils down to getting constipation under better control; in some cases, we see a direct decrease in seizure

frequency simply with a corresponding increase in the number of bowel movements the individual has per week.

In addition to causing stress on the body, constipation may also contribute more directly to an individual's behavior. The episodic low to high-grade discomfort that we see with constipation can sometimes be hard to recognize in non-verbal patients. For some individuals with AS, the intermittent pain of constipation may manifest as intermittent erratic behavior. This is the type of behavior where caregivers often describe, "she's fine one minute and then next she's having a major meltdown for no apparent reason." When behavior follows this pattern, it's important to consider gastrointestinal causes. Additionally, for reasons we don't fully understand, GI discomfort is often associated with self-injurious behaviors such as self-biting or head banging.

To treat constipation in Angelman syndrome, we always first recommend activity. The more we move, the more our GI track moves - swimming, walking, tummy time, whatever we can do to move and stretch, the better. We also always recommend trying to get as much fiber into the diet as possible - lots of fruits, lots of vegetables. However, probably the most important factor contributing to constipation is hydration, so it's really important to push the fluids as much as possible when working to improve a constipation problem. For individuals with AS, we have also had a great deal of success with polyethylene glycol (Miralax). It's an over-the-counter medication that comes as a powder and can be mixed water/juice/milk. It can be taken daily or on an as needed basis to help keep bowel movements regular.

So, how often is often enough? The truth is, we're not sure but we often recommend to parents and caregivers that the goal should really be as close to one stool per day as possible. This frequency seems to help ensure that when an individual does have a bowel movement, it's less likely to be painful. With large painful stools, individuals with AS can get into a pattern of avoiding the pain and holding their stool - setting up a cycle that can be difficult to break. These same behavioral issues can also be evident with GI reflux (heartburn) and individuals with AS and reflux can often exhibit behaviors such as head banging and self-injury.

Identification and management of pain

In much the same way that constipation can drive behavior, other sources of unrecognized pain have the potential to similarly trigger a change in behavior in AS. With an abrupt increase in aggressive behavior, or alternatively with a sudden decrease in baseline behaviors in which an individual with AS may become more withdrawn, an unrecognized source of pain may need to be investigated. Migraine headaches, fractures, blisters or poorly fitting ankle-foot orthotics (AFOs), seasonal allergies, ear or sinus infections, pneumonia, or swallowed foreign objects are some medical situations that can present with very subtle clinical signs. For an individual with AS, a behavioral change may be the first and/or only clue to caregivers that the individual is in pain. Parents, friends, and teachers are much more equipped to identify and describe these behavioral deviations than doctors, and therefore communication among all members of the care team is essential in these cases. Putting together a timeline of when and where the behavioral changes were first seen, as well as how they progressed over time is often essential for making the diagnosis of the cause of the pain and facilitating appropriate and timely medical management.