Seizures in Autism Spectrum Disorder

Symptoms, Assessment, and Treatment…

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Autism Spectrum Disorder (ASD) is associated with a high rate of seizures and epilepsy. Some estimates suggest that up to 45% of individuals with ASD are affected by seizures by the time they reach adulthood, and it is estimated that up to 60% have subclinical electrical discharge—many without any obvious clinical seizures. In this article, we review some of the more important basic facts about seizures and epilepsy as well as treatments in order to enhance the understanding of caretakers of individuals with ASD.

Seizures: What are they and Why are they Important?

The brain works by transmitting electrical impulses from nerve cell to nerve cell. When the brain is working correctly the local rhythm of one part of the brain is rather random since many different nerve cells are working with other nerve cells on different thoughts and sensations. There is also an electrical rhythm, known as the background rhythm, which orchestrates all of the overall higher brain's activity like a conductor.

When a seizure occurs, there is an abrupt change in the brain's electrical rhythm, such that the neurons in the brain become abnormally synchronized. When this happens, the nerve cells become enslaved to this abnormal rhythm preventing them from functioning normally. This disturbance in the electrical rhythm of the brain primarily affects the evolutionarily newer part of the brain known as the cerebral cortex (higher brain).

This abnormal brain activity typically shows up as abnormal rhythmic movements of the arms, legs and/

or face, which reflect this synchronous rhythm stimulating nerve cells responsible for controlling the limbs. Sometimes these movements are associated with a loss of consciousness since the nerve cells in the brain cannot function normally.

The most well known type of seizure is the generalized tonic-clonic seizure, one in which a person falls to the ground, transiently becomes stiff, looses consciousness and develops synchronous repetitive jerking of both arms and legs. During this type of seizure, the electrical rhythm of the whole brain is disrupted. Most generalized seizures only last a few minutes and will not result in long-term damage, but generalized seizures that go on for more than five minutes can be dangerous if they do not stop and require intervention with a rescue medication such as Diastat (rectal valium).

… in typically developing children, seizures tend to resolve within a year or two of starting medications while children with ASD tend to have seizures that are difficult to treat and do not resolve spontaneously after a few years. In addition, children with ASD and epilepsy tend to have more medical and behavioral problems.

Table 1 outlines some of the seizure types that are associated with ASD. It should be noted that the classification of seizure types has recently changed (see a good description of the new terminology from the Epilepsy Foundation),[1] so some people might use old terminology when describing seizures.

TABLE 1. Some Seizure Types. More Common Types are Listed First.

Generalized Seizures	Involves whole body shaking and electrical disturbances of the majority of the cerebral cortex
Focal Seizure	Involves electrical disturbance of one or more portions of the cerebral cortex. Can involve only jerking of one part of the body such as an arm, leg or one side of the face or head. Consciousness is not affected.
Secondary Generalized Seizures	Focal Seizure activity in the brain can spread to the whole brain resulting in a Generalized Seizure
Absence Seizures	Involves electrical disturbance of multiple parts of the brain or the whole brain, manifesting as subtle changes in consciousness such as staring episodes. Usually short (~5-20 sec) but can occur many times per day (sometimes up to 100).
Myoclonic Seizures	A type of generalized seizure that appears as quick short jerks of the arms, legs, body or head. They are usually associated with epileptic syndromes.
Epileptic Spasms	This type of seizure includes Infantile Spasms and involves brief repetitive spasms of the limbs and/or the body.
Atonic-tonic Seizures	A type of generalized seizure where an individual looses muscle tone and falls rapidly to the ground.
Electrographic Seizures	These occur when seizure activity occurs only in the brain without any obvious outward signs. These are not the same as subclinical electrical discharges described below. Subclinical electrical discharges occur in isolation (only one discharge) whereas seizure activity is rhythmic runs of discharges which is sustained for several seconds.
Landau-Kleffner Syndrome	A syndrome manifested by electrographic seizures in the language area of the brain that shows up as language regression after three years of age without other symptoms of autism. It is very rare.
Continuous spike waves during slow-wave sleep	A syndrome manifested by generalized electrographic seizures that only occurs during a certain portion of sleep. Children can have autistic symptoms but this syndrome is very rare.

Looks Can Be Deceiving

Although many types of seizures exist, children with ASD commonly can have abnormal movements such as tics and movement disorders that can look like seizures. Table 2 provides a brief description of other entities but, it is important for a medical professional to evaluate a child suspected of having seizures and carefully determine if the episodes are seizures or not since there can be very different ways of treating seizure and non-seizure events.

We commonly recommend a prolonged, typically overnight, recording of brain waves (known as an electroencephalogram) in order to capture the episodes and determine whether the events are seizures or not. An electroencephalogram is key to diagnosing seizures since seizures are defined by specific abnormal electrical rhythms of the brain.

TABLE 2. Things That Look Like Seizures But Are Not Seizures	
Stereotyped Movements	Repetitive complex movements that tend to be particular to an individual, usually worsened by excitement and/or anxiety.
Tic Disorder	Tics are sudden, usually simple, brief, involuntary movements of the face, eyes / eyelids, shoulder or arm (but can involve other parts of the body).
Movement Disorder	Complex involuntary "dance-like" movements of the arms and/or face that can involve the whole body. Can involve tightening of the muscles.
Behavioral Disorder	Complex, sometimes voluntary, sometimes involuntary, movements and behaviors, usually triggered by emotions.
Attentional Disorder	Staring episodes in which the individual seems unaware.

The Electroencephalogram (EEG): What Does it Mean?

To help diagnose and treat seizures, a test called an electroencephalogram (EEG) is commonly ordered. The EEG measures a person's brain waves. Table 3 provides some of the more common findings of an EEG.

Subclinical Electrical Discharges

Very often children with ASD have seizure-like activity on the EEG (epileptiform discharges) but do not have obvious seizures. It is possible that these abnormal electrical discharges may interfere with attention, cognition, and learning and may be associated with ASD symptoms.

However, many times these EEG abnormalities may be driven from underlying abnormalities in brain function, so the discharges themselves may be a marker of brain dysfunction. We usually recommend a trial of treatment if subclinical electrical discharges are found on electroencephalogram along with careful follow-up to determine if the treatment works.

TABLE 3. Common Findings on Electroencephalogram (EEG)	
Spikes, Sharps, Spike-Wave Discharges (epileptiform discharges)	These are brain waves that are considered epileptiform and are seen when a seizure occurs, but do not, by themselves, define a seizure. The presence of these findings suggests that there is an increased risk for seizures.
Seizure	A seizure occurs when epileptiform discharges successively occur in a rhythmic fashion for several seconds.
Generalized vs. Focal Discharges	Epileptiform discharges can occur only in one part of the brain (focal) as compared to being widespread throughout the brain (generalized). Sometimes this corresponds to the type of seizure.
How Often	During the EEG recording, epileptiform discharges can occur rarely (only a few times), occasionally, or frequently. If there is continuous seizure activity, it is known as Status Epilepticus.
Accompanied by Clinical Symptoms	Most of the times the findings on the EEG do not correspond to clinical symptoms. A correspondence between the clinical symptoms and activity on the EEG raises suspicion that the symptoms may be due to the EEG abnormalities.
Awake vs. Asleep	It is important to record brain waves during sleep since EEG abnormalities can be more obvious during sleep. In addition, there are specific epilepsy syndromes that are defined by abnormalities during deep sleep, so we routinely order an overnight EEG.
Hyperventilation	Hyperventilation can bring out specific types of seizures.
Photic Stimulation	Photic stimulation using a flashing light can evoke epileptiform discharges which can be helpful for determining a propensity of having seizures.
Background Rhythm	This is a rhythm that connects the entire brain. Abnormalities in the rhythm can suggest generalized dysfunction of the brain.
Focal Slowing	Slowing of the brain waves in one portion of the brain suggests dysfunction of the brain in a particular region. This can be seen after a seizure.
Generalized Slowing	Slowing of the entire brain suggests generalized dysfunction of the brain. This can be seen after a seizure or can be due to metabolic disturbances of the brain.
Hemispheric Asymmetries	Brainwaves should be similar in size and character on both sides of the brain. Asymmetries of the brain waves suggest that one side of the brain is dysfunctional.
Abnormal Sleep Architecture	Specific brainwaves occur during sleep and sleep is associated with a progression through specific sleep stages. Abnormalities affecting sleep brain waves can indicate abnormalities of brain function.

Epilepsy: What is it and Why is it Important?

Epilepsy is defined by having two unprovoked seizures of any type. Unprovoked indicates that the seizures were not caused by a fever, trauma, infection, or metabolic illness. To many parents, epilepsy is a scary diagnosis but it is actually relatively common even in typically developing children. However, in typically developing children, seizures tend to resolve within a year or two of starting medications while children with ASD tend to have seizures that are difficult to treat and do not resolve spontaneously after a few years. In addition, children with ASD and epilepsy tend to have more medical and behavioral problems.

Epilepsy and Autism

Autism is associated with an increased risk of epilepsy and almost every type of seizure has been described in autism. Several years ago, we held a series of "Elias Tembenis Seizure Think Tanks" (named in honor of a boy with autism who died as a result of seizures at the age of seven) that included practitioners who treat children with ASD and seizure disorders and a wide variety of scientists and clinicians with expertise in ASD and seizures. Table 4 represents some of the summary points of the Think Tanks, which are based on the most valid, evidence-based information available at the time.

TABLE 4. Consensus Statements from the Elias Tembenis Seizure Think Tanks

1. Seizures and epilepsy are very prevalent in autism spectrum disorder.
2. Subclinical electrical discharges are very prevalent in autism spectrum disorder.
3. The reason for a high prevalence of seizures is not well understood.
4. Children with autism deserve an overnight electroencephalogram .
5. Children with autism and seizures deserve a comprehensive medical workup to identify the underlying cause of the seizures.
6. Treatments for seizures in children with autism have not been well studied.
7. Treatment of subclinical electrical discharges should be strongly considered in children with autism.
8. Given the lack of research of the effectiveness of alternative and complementary medicine treatments in controlling seizures, such treatments should only be used as add-on therapy to traditional treatments.
9. There is a significant need for research in seizures and epilepsy in autism.

Causes of Epilepsy in Autism

The close association between autism and seizures suggests that there might be common causes that result in both disorders. Many genetic disorders associated with ASD also have seizures as a common feature. However, we are starting to understand that we must look beyond simple errors in the genetic code as causes for ASD toward environmental factors as well as abnormalities in the body's metabolic process (see our recent blog in the Huffington Post).[2] Our recent article in Epilepsy and Behavior[3] outlines many of the metabolic diseases that are associated with both ASD and epilepsy. In addition, we are learning that the bacteria in our gut known as the enteric microbiome can change metabolism in the body and potentially result in seizures and epilepsy (See our Special Issue on the Microbiome in ASD).[4]

Seizure Treatments for Children with ASD

Treatments for seizure and epilepsy for children with ASD have not been well studied. Children with ASD sometimes are more sensitive than other children to the adverse effects of antiepileptic drugs (AEDs). To gather information about the effectiveness and tolerability of treatment for seizures and epilepsy in children with ASD, several years ago we surveyed caretakers of individuals with ASD to determine which treatments were found by caretakers to work best with the fewest side effects (Read our paper published in BMC Pediatrics).[5] We also systematically reviewed the scientific literature as well as discussed potential novel treatments with experts in the field of ASD (Read our Review Paper in Frontiers in Public Health).[6]

Table 5 outlines some of the traditional AEDs and non-AED treatments as well as novel treatments that appear to be helpful for children with ASD. In general, treatment is often a trial-and-error process. Often medications will reduce but not eliminate seizures or may have adverse effects, resulting in additional medications and treatments.

Many times diets, such as the Ketogenic Diet, can be effective for both controlling hard-to-control seizures and improving autism symptoms. Often, the Ketogenic diet may be difficult to implement, leading to the use of the modified Atkin's diet which seems to have similar benefits and is easier to implement. Still, many times addressing underlying immune and/or metabolic abnormalities can be helpful for seizure control.

TABLE 5. Selected Treatments for Seizure in Children with Autism.

Traditional Treatments		Non-Traditional Treatments
Anti-Epileptic Drugs	Non Anti-Epileptic Drugs	
Depakote (Valproate)	Ketogenic / Atkin's Diet	GFCF Diet
Lamictal (Lamotrigine)	Intravenous Immunoglobulin	Mg / B6
Keppra (Levetiracetam)	Mitochondrial Cocktail	Omega 3 Fatty Acids
Zarontin (Ethosuximide)	Folinic Acid	Antioxidants
Trileptal (Oxcarbazepine)	Pyridoxine	N-acetylcysteine

Improving Seizure Control

Factors that affect general health can also worsen seizures, so improving these factors can improve seizure control. (See Table 6)

TABLE 6. General Health Factors That Can Affect Seizure Control

1. **Sleep**, both duration and quality, can have a profound effect on seizures.
2. **Illness and fever** can trigger seizures or worsen the frequency of seizures.
3. **Psychological stress** can worsen seizures.
4. **Dehydration** can worsen seizures.
5. **Dietary factors.** It is important to be nutritionally balanced to minimize seizures.
6. **Other medical conditions,** such as allergies, when not controlled well, can be associated with increased seizures.

When seizures are refractory to standard treatments and general health has been optimized, there are several factors that must be considered that can prevent adequate seizure control (See Table 7 on next page).

◂ **DIETARY INTERVENTIONS**—Ketogenic and modified Atkin's diets are sometimes effective in seizure treatment.

▲ **CANNABIS CONNECTION**— While more study is needed, marijuana may be helpful in treating some seizures.

Cutting Edge Treatments

The use of cannabis has become of particular interest for treating epilepsy and/or ASD. It is important to understand that cannabis contains hundreds of phytocannabinoids, some of which may have medicinal properties. Two of the most researched compounds are tetrahydrocannabinol (THC), a compound that gives marijuana its psychoactive properties, and cannabidiol (CBD), a non-psychoactive compound that appears to have therapeutic effects in animal models of epilepsy.

The effectiveness of CBD in epilepsy is a promising and active area of research throughout the world. It is important to realize that CBDs do not have to be derived from marijuana and that by having a higher THC content, marijuana may have

TABLE 7. Factors Associated with Poor Seizure Control

1. **Unrealistic Treatment Plan.** Many times patients will not be able to tolerate treatments or cannot implement the treatment as prescribed. For example, compliance with a 3x/day medication is much lower than a 1x/day medication, even in the best patients. When the number of medications prescribed increases, the ability to implement the treatments is decreased. Many times patients are reluctant to tell their doctors if they are having trouble implementing the treatment and doctors tend to assume that the treatment is going as planned if the patient does not say anything. Finding a treatment regimen that the family can implement is important to controlling seizures.
2. **Generic Medications.** Some generic medications are not absorbed as well as name brands. If seizures increase after changing the brand of medication, it is important to recheck blood levels of medications to make sure they are being absorbed adequately.
3. **Gastrointestinal Disorders.** Since medications are absorbed through the gut, many gastrointestinal disorders can interfere with the absorption of medications. Optimizing gut health can improve seizure control, presumably by improving the consistency of medication absorption.
4. **Undiagnosed Metabolic Disorder.** Many metabolic disorders associated with autism are associated with seizures. Identifying and treating such metabolic abnormalities can improve seizure control.
5. **Undiagnosed Immune Disorder.** Immune disorders and autoantibodies sometimes found in children with autism can be associated with seizures. Identifying and treating abnormalities of the immune system can improve seizure control.

a higher incidence of adverse effects. Because the formulation and/or dosing of CBDs that may be effective is unknown, we recommend that caretakers interested in this treatment highly consider entering a clinical trial where their child's health can be carefully monitored and they can contribute to our understanding of the effectiveness of CBDs (See Clinical Trials on Cannabidiols and Epilepsy).[7] ◄

Resources

1. http://www.epilepsy.com/learn/types-seizures/new-terms-and-concepts-seizures-and-epilepsy
2. Frye RE, Slattery J, Kahler SG. Autism: From Biology to Behavior. Huffington Post; 2014. http://www.huffingtonpost.com/richard-e-frye/autism-from-behavior-to-biology_b_7882420.html
3. Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. Epilepsy Behav. 2015; 47:147-57.
4. Frye RE, Slattery J. Introduction. Microb Ecol Health Dis. 2015 May 7;26:28168.
5. Frye RE, Sreenivasula S, Adams JB. Traditional and non-traditional treatments for autism spectrum disorder with seizures: an on-line survey. BMC Pediatr. 2011; 11:37.
6. Frye RE, Rossignol D, Casanova MF, Brown GL, Martin V, Edelson S, Coben R, Lewine J, Slattery JC, Lau C, Hardy P, Fatemi SH, Folsom TD, Macfabe D, Adams JB. A review of traditional and novel treatments for seizures in autism spectrum disorder: findings from a systematic review and expert panel. Front Public Health. 2013; 1:31.
7. https://www.clinicaltrials.gov/ct2/results?term=epilepsy+CBD&Search=Search