Seizures and Tremor in People with X & Y Chromosome Variations

Consensus-based recommendations from the

AXYS Clinic & Research Consortium

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Introduction

While data is limited, it seems that seizures are more common in people with Trisomy X and XXY than in the general population. Reports show that essential and kinetic tremors are very common in individuals with X & Y chromosome variations, including XXYY, XXY, and Trisomy X. This paper offers an overview of the existing literature on seizures and tremor in people with X & Y variations and presents standard, consensus-based treatment recommendations.

Section 1 of 2: Seizures

Definition

A seizure is a single event characterized by an abrupt change in behavior that starts when neurons in the brain cause a burst of electrical discharges and stops when the burst ends. This occurs either as primary excess electrical excitability in an otherwise normal brain or secondary to another disorder.

Potential causes

In people with X & Y chromosome variations, the excess electrical discharges that cause a seizure are most likely related to the genetic effect of the extra chromosome(s) on neuron activity. However, in diagnosing seizures in these individuals, providers must also consider other independent causes.

Causes of seizures not related to chromosome variation can include:

- Acute response to a new condition (such as trauma, infection, stroke, a toxin or drug, tumor, or metabolic problem)
- Delayed effect due to a recent condition (such as trauma, infection, or surgery)
- Permanent brain "scarring" from a past condition (such as stroke, prenatal/perinatal insult, tumor, or infection)

Classification

We classify seizures according to the International League Against Epilepsy's (ILAE) classification system. This system divides seizures into 3 broad types, with additional subtypes.

Seizure type 1: Focal onset seizures

Focal onset seizures are seizures that start on one side or in one area of the brain.

These include 2 seizures subtypes:

1. **Focal aware seizures**, in which the person is awake but experiences a localized seizure manifestation (like an arm twitching)
2. **Focal seizures with impaired awareness**, in which the person experiences an alteration of consciousness. These are also commonly referred to as complex partial seizures, or CPS.

A focal seizure can spread to the entire brain and "generalize," becoming a focal to bilateral seizure. Focal seizures may indicate a problem in a specific area of the brain, or they may occur as part of a genetic syndrome without a specific area of the brain being abnormal.

Seizure type 2: Generalized seizures

Generalized seizures involve both sides of the brain at the same time.

These include 2 main seizure subtypes:

- **Generalized motor seizures,** in which the person experiences an alteration of awareness or consciousness as well as some type of involuntary movement. These seizures can be tonic-clonic (stiffening followed by jerking), clonic (jerking), tonic (stiffening), myoclonic (single or clusters of jerks), or atonic (sudden loss of tone causing falls or head drops). Generalized tonic-clonic seizures (in the past called "grand mal") are the most well-known seizure type and occur instantly, sometimes associated with a loud cry at the onset. Typically, the person's eyes open and roll up. The person may also experience noisy breathing, jaw clenching, oral secretions pooling in the mouth, stiffening and/or jerking throughout the body, incontinence, and drowsiness after the seizure ends.
- **Generalized non-motor or absence seizures,** in which the individual experiences a brief period of altered awareness and symptoms such as staring or eye blinking.

Status epilepticus is a single or repeated seizure lasting more than 30 minutes. This may be associated with poor breathing effort (shallow breathing) as well as increased blood pressure, pulse, and temperature.

Febrile seizures are a specific kind of short generalized seizure occurring only with fever in children age 6 months to 5 years. They are very common, affecting 2 to 5% of typical children, and they go away by age 6. Because of their commonality, some children with X & Y variations will likely have febrile seizures. However, experts do not think there is an increased prevalence in children with X & Y variations.

Seizure type 3: Unknown onset seizures

When the beginning of a seizure is not known, we can still classify the seizure as motor, non-motor, or unclassified.

Evaluation

In the evaluation of seizures, providers must collect a detailed moment-by-moment history of the event. This includes:

- The individual's activity and body position
- The progression and duration of the seizure
- Any loss of sphincter tone
- Other symptoms such as tongue biting
- Any visual, auditory, or olfactory auras

This will help determine if the event was likely an epileptic seizure or whether it might be a non-epileptic spell like shuddering, breath-holding, benign nocturnal myoclonus (twitching when falling asleep), night terrors, migraine, panic attacks, fainting, hyperventilation, or heart arrhythmias.

When evaluating an initial seizure, consider the following standard methods:

- Laboratory tests such as glucose, electrolytes, and calcium. An elevated prolactin level can also verify a recent seizure.
- An MRI if the seizure appears to be a focal seizure
- A spinal tap to rule out infection if the person experiences a fever or an extended change in responsiveness beyond the seizure
- An EEG 2 weeks after the seizure to help diagnose the type of epilepsy, determine if episodes are actually seizures, identify epilepsy syndromes, and guide treatment decisions. We recommend waiting 2 weeks because there may be slowing of the brain activity and suppression of seizure foci for a time after a major seizure. Also consider ambulatory EEG (Neurotech, Digitrace) to monitor spells that may or may not be seizures to enable a correct diagnosis.

If any of the following are true, always refer the person to a neurologist:

- There is confusion over the cause of the seizures
- The person responds poorly to single drug treatment or has a complex mix of problems (such as behavioral issues, a learning disability, and seizures) that may require a specialized approach
- The treating provider is uncomfortable with seizure treatment
- The family is anxious about management options

Seizures in people with X & Y chromosome aneuploidies

There are a small number of papers in the literature that describe seizures in X & Y variation disorders.

One such study from the University of Siena collected all cases of X & Y variations from 1992 from 2002, involving a total of 43 people.

Results showed that:

- **In people with XXY,** 2 in 17 had partial complex seizures and the EEG was abnormal in an additional 4 in 17 with occipital or parietotemporal paroxysmal discharges.
- **In people with Trisomy X**, 5 in 7 had partial complex seizures, with all 5 having an abnormal EEG with paroxysmal activity in temporo-parieto-occipital areas in a characteristic pattern. Seizures were more likely in individuals with a subnormal IQ.
- **Clinically in people with all X & Y variation types,** seizures were easy to control and many of the individuals grew out of them over time.

Several other reports have focused on seizures in individuals with XXY.

A case series on 12 individuals from the USA, France, and Italy (9 of which had been previously published) including 2 mosaic individuals and 1 person with XXXY, reported multiple seizure types. The main seizure types among the groups were generalized tonic-clonic and complex partial seizures. There was also 1 person with febrile seizures, 3 with absence seizures, and 1 with atonic seizures. Five individuals had several seizure types. In addition, 10 of the 12 individuals had epileptic activity on EEG. These were mostly focal or multifocal spikes, but 3 individuals' EEGs showed generalized spike-wave patterns. Many of these individuals became seizure-free with anticonvulsant treatment.

Another report described 5 people with XXY referred to an epilepsy clinic. Of these, 4 had seizures (2 complex partial, 1 single GTC, 1 febrile), and 1 had an abnormal EEG but no seizures. EEGs showed occipital paroxysmal activity in 2 of the 5 individuals, suggesting perhaps a characteristic pattern. All of these individuals did well and grew out of their seizures with age, suggesting generally a good seizure outcome in XXY.

In a case series of individuals with XXYY, 15% of 93 affected individuals had non-febrile seizures at some point in their lives.

In a case series of individuals with XYY, 13% of the 55 diagnosed postnatally had seizures at some point in their lives vs. only 3% of the 35 diagnosed prenatally.

A recent national study of 74 individuals with Trisomy X recruited from 2005 to 2014 compared the incidence of seizures among those diagnosed prenatally vs. postnatally. In this study, 16.2% of the 74 individuals had seizures (2.3% of the 44 diagnosed prenatally

vs. 36.7% of the 30 diagnosed postnatally). Seizure types included both generalized tonic clonic and focal with impaired awareness, and 6 individuals had an abnormal EEG with paroxysmal discharges.

Although none of the studies presented in this section were epidemiological studies, it seems that taken all together, the literature indicates that seizures are increased in the XXY and Trisomy X populations relative to typical populations, but are not a severe or intractable problem in most individuals, and are relatively easily managed and often limited to childhood. The mechanism for this is not known. The EEG does not always predict seizures and thus is likely not warranted except to clarify diagnosis when there are episodes that might represent seizures or to evaluate an individual for seizure characteristics to help guide medication choice after a documented seizure.

Treatment

Immediate treatment

If a person has a seizure, follow standard seizure first aid procedures.

These include:

- Avoid panic.
- Put the person on their side.
- Check to make sure the person is breathing, and continue monitoring their breathing as the episode runs its course. If the person stops breathing or turns blue, call 911 right away.
- Do not put anything in the person's mouth or give them any food or drink.
- After the seizure ends, let the person sleep, if needed.

Additional considerations for length of seizure:

- If the seizure lasts more than **3 to 5 minutes**, administer Diastat or nasal midazolam, as prescribed and appropriate.
- If the seizure lasts more than **15 minutes** , call 911.
- If the seizure lasts more than **30 minutes** without the person becoming alert and responsive, this is defined as status epilepticus. In this case, the person should receive assessment and treatment in an emergency setting with airway management, metabolic studies on blood, and intravenous anticonvulsants. If the person's breathing is compromised, they may also need intubation and ventilation.

Long-term treatment

After a person's first seizure, begin testing to determine the underlying cause.

After 2 seizures, consider treatment with anticonvulsants. If there is a long period of time between the first and second seizure, treatment may be delayed until a third seizure occurs.

Total epilepsy care should include medication for seizure control, with adjustments for side effects.

Treatment should also include added support as needed, including:

- Psychosocial support
- Educational recommendations and accommodations
- Behavioral management
- Vocational counseling

In some cases of difficult-to-control seizures, additional treatment options may include:

- A ketogenic diet
- A Vagal Nerve Stimulator (VNS) device
- Surgery

We will discuss these additional treatment options on the following pages.

Considerations when selecting seizure medication

Effectiveness

Effectiveness is typically the key consideration of dosing. When selecting a medication, consider the person's characteristics and select a single drug regimen with the lowest effective dose. Use the person's EEG results to help determine which drug to use as well as dosage and length of treatment.

Side effects and blood levels

Next, consider side effects and blood levels. Anticonvulsants with good side effect profiles that are commonly used initially for seizures include Keppra (levetiracetam) and Trileptal (oxcarbazepine). If these are not effective or result in side effects for the individual, consider other medications.

Read the table below for a summary of available anticonvulsants along with the seizure types for which they are used and their primary potential side effects.

Anticonvulsants for treating seizures		
Anticonvulsant	**Main seizure type(s) used in**	**Primary potential side effects**
Phenobarbital	All	Sedation Cognitive depression **Note:** Not used frequently due to side effects.
Phenytoin	All	Gingival hypertrophy Cerebellar effects Facial coarsening **Note:** Not a firstline choice due to side effects.
Carbamazepine	All (particularly partial)	Marrow suppression Liver toxicity
Valproic acid	All	Weight gain Hair loss Low platelets Liver toxicity
Felbamate	Partial	Marrow toxicity Liver toxicity
Oxcarbazepine	All (particularly focal)	
Levetiracetam	All	**Note:** Low rate of side effects and interaction with other drugs. May aggravate behavior, but co-treatment with vitamin B6 can protect against this.
Lamotrigine	Focal Myoclonic Absence **Note:** May be used first for generalized seizures instead of valproic acid.	**Note:** Recommend slow titration to avoid rash.

Gabapentin	Focal **Note:** Easy add-on drug	
Vigabatrin	Focal	Infantile spasms **Note:** Watch vision.
Tiagabine	Focal	
Topiramate	Focal	Weight loss Language impairment Kidney stones
Zonisamide	Focal	
Lacosamide	Focal	**Note:** Good side effect profile.
Rufinamide	Generalized	
Perampanel	All	Psychiatric side effects (psychosis) Sedation
Fosphenytoin	Status epilepticus **Note:** Given intravenously.	**Note:** Less toxic than phenytoin and phenytoin prodrug.
Brivaracetam	Focal	**Note:** May have less behavior side effects than levetiracetam.
Cannabidiol	Lennox-Gastaut syndrome (Epidiolex)	

Considerations for adjusting medication to mitigate breakthrough seizures

Even while on an active treatment regimen, a person may have breakthrough seizures. These may be associated with medication noncompliance, lack of sleep, illness, or fever. They may also be related to stress, or may occur for no known reason.

When a person has ongoing seizures with no obvious cause (such as missed medication doses), consider increasing or changing medication, including adding another medication to the person's treatment regimen. If seizures recur frequently over a prolonged period of time or in clusters, consider prescribing rectal Diastat (valium) or nasal midazolam to stop seizures and avoid frequent emergency room visits.

Considerations for stopping medication

Consider stopping medication after the person is 2 years seizure free. As part of this decision, reevaluate epileptic activity using an EEG:

- If the EEG is normal, consider stopping medications.
- If the EEG still shows strong epileptic activity, or if the person has an underlying condition associated with significant seizure risk, consider continuing treatment for a longer period.

If a patient is on multiple medications, consider weaning medications 1 at a time after the patient is seizure free for 1 to 2 years.

Recurrence

There is always some risk of recurrence no matter how long weaning is delayed past 2 years seizure-free, but the risk does not change significantly after 2 years. If seizures recur after weaning, consider restarting medication.

Additional treatment options for difficult-to-control seizures

The ketogenic diet

The classic diet is a strict calorie-restricted, high fat, low protein, low-carbohydrate diet in which 90% of calories come from fat. The diet causes ketosis, which is associated with seizure control. It offers approximately 20% of patients with intractable seizures good control rates and is typically used when multiple anticonvulsants fail or when there are problems with anticonvulsant side effects.

The diet works best for children under the age of 4, and the family and child must be motivated to strictly follow the diet. The diet works best for atonic (drop) and absence seizures, but can work for all seizure types.

Vagal nerve stimulator (VNS)

The VNS is a small device implanted by surgery at the base of the neck on the vagus nerve. It is then set to stimulate the nerve at a certain frequency, with adjustments to give the best seizure control.

The VNS achieves a substantial improvement in seizure control in about 10% of patients with difficult-to-control seizures. It works best when the patient has an aura and can activate the device to abort a full seizure. Risks of VNS placement include hoarseness after surgery and infection around the device.

Surgery

Epilepsy surgery is an option for patients with very difficult-to-control focal seizures coming from one part of the brain. It can sometimes be used in a disorder affecting the entire brain if the seizures are uncontrolled and there is one area from which most seizures seem to arise.

Section 2 of 2: Tremor

Definition

Tremor is a rhythmic, sinusoidal, oscillation of a body part composed of alternating contractions of opposing muscle groups.

Types of tremor include:

- **Rest tremor** that occurs when the body is at rest and not moving (typically seen in Parkinson's disease)
- **Action tremors** that occur during movement of a limb. Action tremors include these cerebellar or "intention" tremor when a person can't point directly to things and there is a shakiness as the finger gets closer to its target, myoclonic tremor with jerky movements and twitches as a person moves, kinetic tremor which is brought out by movement, and postural or "essential" which involves shaking when holding a posture.
- **Essential tremor**, which is the most common type of tremor, and in many cases is benign and does not interfere much with functioning. This type of tremor tends to be more prominent in the morning, after caffeine, and when a person is stressed. Essential tremor looks much like enhanced physiological tremor, which is an amplification of the expected tremulousness seen with adrenaline release (such as with intense fear) and can be a side effect of medications. However, essential tremor appears without a trigger. In some cases, essential tremor can become gradually worse with age and interfere with function, such as writing and activities of daily living. If this happens, the tremor requires treatment.

Tremor in X & Y chromosome aneuploidies

There are many case reports of tremor and some case series in the literature regarding individuals with XXY. A case-control questionnaire study was conducted at University of Iowa in which all people in the hospital database were recruited and 44 individuals with XXY and 94 controls were recruited. Of these, 63% of the XXY group reported tremor, as compared to 13% of controls, while 10% of the XXY group reported being previously diagnosed with essential tremor versus 0% of controls. Tremor began at an earlier age in the XXY group. The XXY reported gait/balance problems more often than controls but the nature of this problem was not further studied. Most tremor reported in XXY was characteristic of essential tremor and cases of XXY with both alcohol-sensitive and -insensitive essential or kinetic tremor have been described.

Essential and kinetic tremors have been reported as very common in individuals with XXYY as well, observed in all 10 individuals examined in one report, and in 8% of 32 people age <10, 60% of 38 individuals age 10-18, and 70% of 22 individuals age 20+ in a larger series. In a case series of XYY individuals, tremor was observed in about 40% of 90 cases diagnosed either prenatally or postnatally. A few case reports describe tremor in XXX syndrome. In an XXX national study 23.6% of 72 individuals had tremor on examination which was classified as either intention or essential tremor in different people. By report of the XXX individuals, 16.8% of 74 had tremor, 11.4% of 44 individuals diagnosed prenatally, and 22.3% of 30 with postnatal diagnosis.

Treatment

Consider treatment of essential tremor when the person's function is impaired. Self-medication with alcohol makes this type of tremor much less severe. Therefore, be sure to ask about alcohol history during diagnosis. Medications for essential tremor include propranolol as well as other beta-blockers and primidone. Less proven treatments include gabapentin, levetiracetam, clonazepam and other benzodiazepines, topiramate, and nimodipine. Botox and deep brain stimulation (DBS) have also shown success in some cases. Treatment of X aneuploidy-associated tremor is essentially the same as tremor treatment in the general population. A few cases of DBS in X-aneuploidy disorders have been reported with both positive and negative results.

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Note: *This guideline was authored by Elizabeth Berry Kravis, MD, PhD and has been approved by and represents the current consensus of the members of the AXYS Clinical & Research Consortium.*

The AXYS Clinical & Research Consortium was founded in 2015 and exists to:

- **Make life easier for those seeking evaluation and treatment.**
- **Bring consistency to treatment that is consensus and/or evidence-based.**
- **Advance the overall X&Y variation field through coordinated efforts including research.**
- **Bring clinical excellence to the field of X&Y variations.**

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