FRAGILE X INFO SERIES:
SEIZURES IN FRAGILE X SYNDROME

NATIONAL **FRAGILE X** FOUNDATION

Overview

Fragile X is a group of conditions associated with changes in the Fragile X gene – called FMR1 and located on the X chromosome. The FMR1 gene can undergo changes when inherited, which affects a pattern of DNA called CGG repeats. Typically, the FMR1 gene has up to 54 CGG repeats, though the range between 45 – 54 repeats, is called the intermediate or gray zone. A premutation carrier has 55–200 CGG repeats, and someone with a full mutation has more than 200 CGG repeats.

When a premutation or full mutation is present, it can result in a Fragile X-associated Disorder (FXD). These include:

- Fragile X syndrome (FXS): A condition that can affect intellectual, behavioral, and social development. It occurs in both males and females who have a full mutation of the FMR1 gene.
- Fragile X-associated tremor/ataxia syndrome (FXTAS): An adult onset (over 50 years of age) neurological condition, seen in males and females, but more common and more severe in some male premutation carriers. It can cause tremors, memory, and balance issues.
- Fragile X-associated primary ovarian insufficiency (FXPOI): A condition affecting ovarian function that can lead to infertility and early menopause in some female premutation carriers.
- Other issues may be present in premutation carriers, and this is an ongoing area of study for researchers.

What is a Seizure?

- A seizure is a single event characterized by an abrupt change in behavior (e.g., staring without response, dropping to the ground, or twitching a part or all of the body).
- What you don't see is that the behavior is accompanied by a burst of electrical discharges that comes from neurons in the brain, i.e., the behavior appears in association with the burst and then goes away when the burst is over.
- A seizure occurs either as primary excess electrical excitability in an otherwise normal brain or secondary to another disorder.
- In fragile X syndrome (FXS)the excess electrical excitability is most likely related to the effects of the genetic change in the fragile X gene (FMR1) and the resultant loss or reduction of the fragile X protein (FMRP) on activity in neurons.
- Other causes of seizures have to be considered in a person with FXS as there could be another diagnosis in addition to the FMR1 gene mutation.

Classification of Seizures

Seizures are classified according to the International League Against Epilepsy (ILAE). There are Focal Seizures (also known as Partial Seizures), Generalized Seizures, Status Epilepticus Seizures, and Febrile Seizures.

Evaluation of Seizures

- In the evaluation of seizures, it is important to collect a detailed moment by moment history of the event (activity, body position, progression, duration, loss of sphincter tone resulting in urination or a bowel movement, tongue biting, visual/auditory/olfactory auras).
- This will help determine if the event was likely an epileptic seizure versus a non-epileptic spell that might include things like shuddering, breath-holding, benign nocturnal myoclonus (twitching when falling asleep), night terrors, migraine, panic attack, fainting, hyperventilation or heart arrhythmia.

Typically, patients would be referred to neurology to manage seizures although in uncomplicated cases the primary care physician may handle the problem.

Use of EEG

- The EEG is used in people with seizures to diagnose the type of epilepsy, determine if episodes are actually seizures, identify epilepsy syndromes, and to help guide treatment decisions.
- After a major seizure there may be slowing of the brain activity and suppression of seizure foci so the EEG may miss seizure activity, and it is better to get the EEG 2 weeks after a major seizure.

It is important to recognize that while a routine EEG is indicated to help guide treatment for a person suspected of seizure disorder, it may not be diagnostic and then one has to rely on clinical judgement.

Frequency of Seizures in FXS

Recently the largest and most definitive study yet published on seizures in FXS was completed using the Fragile X Online Registry with Accessible Research Database (FORWARD. In this study the overall chance of having at least one seizure was 12% overall in FXS, 13.7% in males and 6.2% in females.

Age of Onset and Resolution of Seizures in FXS

- In the group with seizures, the average age of the first seizure was 6.4 years of age with the great majority (86.7% of males and 81.8% of females) having the first seizure before age 10 years.
- The age of the last seizure followed a similar age dependence to age of first seizure, with 70.9% of seizures in males and 63.6% of seizures in females resolving by age 10 years.

Types of Seizures in FXS

Partial (focal) seizures were reported in 25% and generalized seizures in 31% of those with seizures, with febrile seizures in 8% and the remainder of seizures being of unknown type. Males and females did not show a different distribution of seizure types.

Association of Seizures with Other FXS Characteristics

As compared to individuals with FXS without seizures in FORWARD, those with seizures were more likely to have more severe intellectual disability, current sleep apnea, delayed acquisition of expressive language, autism spectrum disorder (ASD), hyperactivity, irritability, and stereotyped movements.

Treatment of Seizures in FXS

Treatment and management of seizures in FXS is similar to seizure treatment in other conditions associated with seizures. There is no FXS-specific medication or approach to treating seizures.

Medications for use in FXS

A person with seizures is usually treated with medications, known as anticonvulsants, after two (or sometimes more if there is a long time between seizures) seizures.

Conclusion

In summary, based on the FORWARD data, 12% of people with FXS have seizures. Treatment and management of seizures in FXS is similar to seizure treatment in other conditions associated with seizures. There is no FXS-specific medication or approach to treating seizures, but the approach is to try to use the medications expected to have the least side effects first and those not requiring blood monitoring. In general seizures are easily controlled in FXS and most patients grow out of their seizures before their twenties, although infrequently seizures can be a more challenging problem.

About the NFXF

The National Fragile X Foundation (NFXF) was founded in 1984 to support individuals with Fragile X syndrome (FXS), their families, and the professionals who work with them. Today, it is a comprehensive resource not only for FXS, but also for the conditions of Fragile X-associated tremor/ataxia syndrome (FXTAS), Fragile X-associated primary ovarian insufficiency (FXPOI), and other premutation carrier issues. The organization offers help for today and hope for tomorrow with personalized support, community, education, awareness, advocacy, and research. Get your free Fragile X 101 e-book, Welcome Packet, connect with your local chapter, learn about the upcoming conference, and more at https://fragilex.org/welcome.

If you have specific questions about what to expect, treatments, clinics, well, just about anything, please email **treatment@fragilex.org** or call **(800) 688-8765**.

For more information: Seizures in Fragile X Syndrome
https://fragilex.org/wp-content/uploads/seizures-fxs-treatment-recommendations.pdf