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### Summary

The characteristic clinical features of FXS include moderate to severe mental retardation, dysmorphic facial features, joint laxity, postpubertal macro-orchidism and behavioral anomalies. Seizures are reported to occur in 10 to 20 percent of cases with a full mutation FXS and are typically of the complex partial type. Previous studies have identified marked similarities between seizures occurring in FXS and those found in benign epilepsy with centro-temporal spikes (BECTS). In this article, we describe the case of a child with FXS, which illustrate some of these aspects.

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**Key words:** Epilepsy, fragile-X, benign epilepsy with centro-temporal spikes

### Epilepsie bei Fragil-X-Syndrom : ein illustratives Fallbeispiel

Typische klinischen Merkmale eines Fragil-X-Syndroms sind eine mittlere bis schwere geistige Behinderung, Zeichen einer Dysmorphie und einer Hyperlaxität der Bänder, ein postpubertärer Makroorchidismus, sowie Verhaltensanomalien. Bei 10 bis 20% der Patienten mit vollständiger Mutation werden epileptische Anfälle, typischerweise von partiell komplexer Art beobachtet. Mehrere Studien haben Ähnlichkeiten belegt zwischen den bei einem Fragil-X-Syndrom auftretenden Anfällen und denjenigen einer benignen Epilepsie mit zentrotemporalen Spitzen. In diesem Artikel wird der Fall eines Kindes mit einem Fragil-X-Syndrom als illustratives Fallsbeispiel für einige der erwähnten Aspekte beschrieben.

**Schlüsselwörter:** Epilepsy, fragile-X, benign epilepsy with centro-temporal spikes

### Epilepsie dans le syndrome du X-fragile : un cas illustratif

Les caractéristiques cliniques typiques du syndrome de l’X-fragile incluent un retard mental modéré à sévère, des signes dysmorphiques, une hyperlaxité ligamentaire, un macro-orchidisme post-pubertaire et des

anomalies comportementales. Des crises épileptiques sont observées chez 10 à 20% des patients présentant une mutation complète, et sont typiquement du type partiel complexe. Plusieurs études ont mis en évidence les similarités entre les crises observées dans le syndrome de l’X-fragile et celles de l’épilepsie bénigne à pointes centro-temporales. Dans cet article, nous décrivons le cas d’un enfant atteint d’un syndrome de l’X fragile qui illustre certains de ces aspects.

**Mots clés :** Epilepsie, X-fragile, épilepsie bénigne à pointes centro-temporales

### Introduction

Fragile X Syndrome (FXS) is the most common cause of inherited mental retardation affecting approximately one in 4’000 males and one in 8’000 females [1]. The disorder results from the amplification of a trinucleotide repeat sequence (CGG) in the 5’ non coding region of the fragile X mental retardation 1 (FMR1) gene [2]. When this expansion mutation exceeds 200 repeats, referred to as a full mutation [3], the gene becomes transcriptionally silent resulting in decrease or loss of expression of the encoded fragile X mental retardation protein (FMRP). The absence of the FMRP is responsible for the syndrome’s clinical phenotype. The characteristic clinical features of FXS include moderate to severe mental retardation, dysmorphic facial features (macrocephaly, long face, prominent ears, high-arched palate), joint laxity, postpubertal macro-orchidism and behavioral anomalies (hyperactivity, aggression, timidity, autistic traits). Seizures are reported to occur in 10 to 20 percent of cases with a full mutation FXS [1] and are typically of the complex partial type [4]. Previous studies have identified marked similarities between seizures occurring in FXS and those found in benign epilepsy with centro-temporal spikes (BECTS). In this article, we present the clinical and EEG features of seizures occurring in a child with FXS.

### Case study

A 7 year-old boy diagnosed with FXS presented his first seizure at the age of 5 years, which consisted of loss of contact, eye revulsion, tonic posturing of the four limbs and clonic movements of the right upper



Figure 1: Asymmetric slow background activity predominant on the left side.



Figure 2: Bilateral posterior spike-waves, predominant on the left side.

limb. The seizure ceased upon administration of 10 mg rectal diazepam. The electroencephalogram performed two days later revealed a slow background activity (Figure 1), along with left fronto-central and bilateral occipital spikes occurring in sleep (Figure 2), of similar morphology to those found in BECTS (Figure 3). The cerebral MRI performed 3 weeks later revealed a mild hyper-intense signal in the left hippocampal region attributed

to transient post-ictal abnormalities. The following seizure arose seven months later and lasted approximately 2 hours. It consisted of eye and head deviation to the right, isolated hypertonia of the right upper limb with no clonic movements and intermittent phases of partial conscious activity during which he presented several episodes of vomiting. An EEG performed 48 hours later revealed a poorly modulated background activity





Figure 3: Benign epilepsy with central-temporal spikes, left frontal-temporal spike-waves, normal background activity.

in the alpha range during wakefulness, as well as predominantly left occipital and posterior temporal spikes and polyspikes that occasionally arose in small clusters. A third episode occurring a month later manifested as a partial loss of consciousness, with head deviation to the left and a fixed stare. Vegetative symptoms were present, and included pallor and vomiting. No tonic phase or clonic movements were noted. The seizure lasted for more than an hour and subsided upon administration of rectal diazepam. Anti-epileptic treatment with valproate was introduced at this stage and allowed good seizure control with only one seizure occurring in 9 months.

## Discussion

Epilepsy in FXS has been described as significantly related to BECTS. One cohort study evaluating seizure type and frequency in individuals with FXS showed that central-temporal spikes were the most common form of EEG findings in these individuals [1]. In this case study we present a child with FXS displaying similar epileptogenic clinical and EEG characteristics. This child also notably exhibits less typical clinical characteristics, such as to present with status epilepticus as his initial seizure. Moreover, vegetative symptoms were predominant in two of his seizures, a clinical feature more

suggestive of Panayiotopoulos syndrome (PS), another focal idiopathic epilepsy syndrome of childhood. PS is characterized by rare but prolonged seizures, appearing at school-age in normal children. Seizures manifest by predominant vegetative symptoms, such as nausea, vomiting, and pallor, and ocular motor manifestations, such as eye deviation may also occur. Interictal EEG findings include posterior “functional” spikes, but centro-temporal or frontal spikes, as well as global slowing may also be present [5]. The “atypical” findings in our patient have been described in a manuscript in print elsewhere [6].

BECTS is an idiopathic age and localization related epileptic syndrome. It is usually characterized by brief, simple partial and hemifacial motor seizures frequently occurring upon awakening. Interictal EEG shows unilateral or bilateral spike discharges in the central or central-temporal region. The spikes are usually slow, of high voltage, diphasic and typically activated by drowsiness and sleep. Other characteristics of BECTS include spontaneous remission achieved in almost all patients by adolescence.

As previously stated, the EEG pattern most often described in young patients with FXS comprises paroxysmal discharges of spikes prevalently localized in the central or centro-temporal regions [1]. Spikes were shown to be more frequent on EEG sleep recordings [4]. In correlation to these findings, our patient presented

biphasic spikes in the left fronto-central, bi-occipital and posterior temporal regions that were activated by sleep. One variation from the typical EEG pattern of BECTS found in patients with Fragile X syndrome is the presence of a slow background activity [4], which we also found in our case.

Physical features in FXS can be sufficiently discreet and variable, mental retardation being occasionally the only apparent symptom, thereby making diagnosis difficult. We believe that those patients with mental retardation of unknown origin may benefit from an EEG, even in the absence of seizures. The recurrence of a typical EEG pattern in patients with FXS, resembling that of BECTS, suggests that it could be seen as a distinctive marker used for the diagnosis. Individuals, namely adults, presenting with mental retardation along with EEG findings of central or central-temporal spikes and slow diffuse background activity should be considered as potentially affected with FXS. In such situations, clinicians may be attentive to other characteristic morphological traits of the syndrome, and molecular genetic testing of the FMR1 gene could be undertaken.

However using EEG findings as an initial diagnostic marker of FXS does have some limitations. Several studies have identified that EEG phenomena as well as clinical presentation of epilepsy are partially age dependant. One such study observed the typical EEG patterns during sleep only in boys between the ages of 4 to 8 years, although the number of patients over the age of 11 years included in this study was limited to three [3]. One study following a group of FXS male patients showed that 25% continued to have seizures in adulthood but that there was a tendency for spontaneous resolution of focal spikes. Moreover, EEG recordings in several adult patients revealed nonspecific paroxysmal abnormalities [4]. However, such studies also outlined the heterogeneous outcome of epilepsy in FXS, namely in regards to therapeutic response and the recurrence of seizures upon drug discontinuation. These findings suggest a higher percentage of characteristic EEG readings in younger patients but a need to identify the clinical and EEG particularities of FXS at any age.

Epilepsy is a frequent manifestation in patients with FXS. Pathophysiological insights into the mechanisms of neuronal dysfunction underlying epileptiform susceptibility have been proposed. Evidence suggests that dysregulation of the metabolic glutamate receptor arising from the absence of FMRP, results in the activation of a voltage-gated inward current with a net increase in the excitability of neuronal circuits [2]. In addition, downregulation of GABA receptor subunits and altered expression of enzymes implicated in the metabolism of GABA contribute to neuronal hyperexcitability [7]. Similarities between FXS and BECTS at a molecular level have not been substantially investigated and remain an important aspect of future investigation.

Despite such variants in the clinical presentation and EEG patterns of epilepsy in FXS, we believe in the

potential usefulness of performing an EEG in all patients affected with developmental delay of unknown cause. This seems particularly important in adults, some of which may not have had extensive genetic testing in their previous diagnostic work-up.

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