Int. J. Devl Neuroscience 38 (2014) 155–160

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

journal homepage: www.elsevier.com/locate/ijdevneu

Short communication

EEG abnormalities and seizures in genetically diagnosed Fragile X syndrome

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ARTICLE INFO

Article history:
Received 24 January 2014
Received in revised form 21 June 2014
Accepted 1 July 2014
Available online 9 July 2014

Keywords:
Fragile X syndrome
EEG

ABSTRACT

We describe the seizure and EEG characteristics in a population of children with known Fragile X. The medical records of 135 genetically confirmed FXS patients receiving care in a Fragile X clinic and their available EEG reports were reviewed. The mean age was 5.94 years old including 18 males and 1 female. The mean age was 4–9 years old with an age range of 15 months to 13 years old. Twenty-two patients (16.3%) in the series had parent-reported behavior suspicious of seizures. Sixteen patients (14.1%, 1 female) had at least one EEG recorded for evaluation of clinical events suspicious for seizure, and three patients (2.2%) had an EEG in the context of a polysomnography for diagnosing sleep apnea. The mean age at EEG evaluation was 6.0 years (standard deviation 3.8 years). EEG findings included slowing of background rhythm ($n = 9$) and epileptiform discharges ($n = 7$). Four patients had normal EEGs ($n = 4$). Six patients (4.4% of the sample population) were diagnosed with epilepsy by both clinical seizure semiology and documented EEG abnormalities. Thirteen patients (68.4% of total) had episodes of staring and behavioral arrest with no EEG correlate, indicating non-epileptic events. Of the eight patients who underwent a repeat EEG, five patients had showed normalization in the posterior dominant rhythm over time, two patients had unchanged findings and one patient had worsening of his EEG. Our data warrant further prospective validation.

1. Introduction

Fragile X syndrome (FXS) is a genetic trinucleotide repeat syndrome associated with a variety of neurologic abnormalities, including intellectual disability, autism spectrum disorders, attention deficit hyperactivity disorder, hypotonia, and seizures (Terracciano et al., 2005). Reports suggest a prevalence of seizures among children with FXS of 10–20% in boys and 5–10% in girls (Berry-Kravis, 2002; Berry-Kravis et al., 2010; Musumeci et al., 1999).

Various studies over the years have investigated EEG abnormalities in the context of FXS. Patients with FXS have a higher prevalence of EEG abnormalities consistent with Benign Epilepsy with CentroTemporal Spikes (BECTS) and Benign Focal Epilepsy of Childhood (BFEC) (Berry-Kravis, 2002; Musumeci et al., 1999) and slowing of the background rhythm (Vieregge and Froster-Iskenius, 1989). These abnormal EEG findings, however, may not always manifest with seizures and a subsequent diagnosis of epilepsy. In this review, we investigate a series of children with FXS and clinical events concerning for seizures and who were evaluated by EEG in an attempt to better define the prevalence of epilepsy among patients with FXS.

2. Study design and methods

We reviewed charts of patients with FXS who received care in a specialized clinic in a tertiary care hospital. Patients were diagnosed with FXS on the basis of molecular genetic testing.

Charts were reviewed for EEGs ordered during the course of clinical evaluation. EEGs were reviewed to ascertain indication and type of EEG recorded (i.e. outpatient, inpatient video-EEG or sleep study). In patients with diagnosed epilepsy, data pertaining to seizure history, medications, and seizure control at last follow-up

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http://dx.doi.org/10.1016/j.ijdevneu.2014.07.002
0736-5748/

were documented. In patients who had undergone clinical neuroimaging, findings were documented.

3. Results

3.1. Population demographics

One-hundred-and-thirty-five patients had genetically confirmed FXS. Of these, nineteen (14%, 18 males and 1 female) underwent EEG to evaluate either a discrete recurring clinical event concerning for seizure (e.g. staring spells, repetitive behaviors, etc.), or a sleep study with EEG for suspected sleep apnea. Mean age at EEG evaluation was 6.0 years (standard deviation, 3.8 years). The mean age was 5.94 years old (range; 15 months–13 year). Fourteen patients in the series underwent routine EEGs, two patients underwent long term monitoring with video-EEG, and three patients had an EEG in the context of a sleep study. Six parents presented with concerns for seizure-like behavior which did not warrant an EEG by the patient's neurologist. Details regarding all 19 patients with EEG data are provided in Table 1.

3.2. Indications for EEG (Table 1)

Indications for obtaining EEG included evaluation for staring spells ($n = 6$), suspected motor seizures versus stereotypies ($n = 4$), developmental delay and behavioral changes (i.e. aggressiveness, arrest in activity) ($n = 2$), recurrent loss of tone ($n = 1$), episodes of eye rolling ($n = 1$), atypical febrile seizures ($n = 1$) and follow-up for known epilepsy ($n = 1$). Three EEGs were obtained via a sleep study during their evaluation of obstructive sleep apnea due to complaints of excessive snoring.

3.3. EEG findings

Abnormal EEGs were documented in 14/19 (74%) patients (Table 1). Nine (47%) exhibited slowing of the posterior dominant rhythm (PDR) for age. Six had focal spikes on their EEG from various anatomic regions, including the temporal ($n = 3$), frontal ($n = 3$) parietal ($n = 2$), and occipital regions ($n = 1$). Seizures were well localized to the temporal lobe in one patient. Other observed EEG findings included pseudo-rhythmic slow theta activity in the bi-occipital area and increased generalized theta rhythm bilaterally.

3.4. Repeat EEG findings

Eight patients required one or more EEGs either to evaluate new events concerning for seizures or to evaluate for an EEG change after initiation of antiepileptics. Six patients continued to have an abnormal EEG with a slow background. One patient had 2 normal EEGs, and one patient had a worsening of the EEG with focal seizures. Five patients (Patients 7, 11, 12, 13, 16) showed normalization of EEG background after 8 years of age.

3.5. Epilepsy diagnoses and treatment

Epilepsy was diagnosed by the pediatric neurologist in these cases. Epilepsy was diagnosed if patients had 2 discrete unprovoked seizures or if there was a single unprovoked seizure with an abnormal epileptiform EEG. Epilepsy was diagnosed in 6 FXS patients, based on clinical and EEG findings, with an overall incidence of 4.4% in our Fragile X population. The mean age of seizure onset in the FXS group was 8 years (range 4–11 years).

All 6 FXS patients with epilepsy either had taken or were currently taking antiepileptic drugs (AEDs) at last follow-up. There was one patient that had a diagnosis of epilepsy but who did not take medication due to parental preference. His initially occurring clinical events dissipated and his EEG normalized. Three of the six patients were on AED monotherapy and were seizure free at last follow-up. Three patients were off AEDs. One patient had an improvement in seizures on monotherapy but continued to have occasional seizures. One patient, after recurrent episodes of prolonged status epilepticus, developed mesial temporal sclerosis with refractory epilepsy and underwent epilepsy surgery. Status epilepticus can lead to the development of mesial temporal sclerosis in 3% of the population (D'Hulst et al., 2006). Thirteen patients (68.4% of total) had episodes of staring and behavioral arrest without an EEG correlate.

3.6. Imaging

MRI imaging was available for ten patients. Imaging was normal in the majority of cases. A single patient had mesial temporal sclerosis with refractory seizures due to recurrent prolonged episodes of status epilepticus.

4. Discussion

This series further supports the known literature that EEG abnormalities in FXS may exist even in the absence of clinical seizures and a diagnosis of epilepsy (Musumeci et al., 1999). Musumeci et al. has mentioned the common EEG abnormalities in the Fragile X population. This includes frontotemporal seizures and age-related paroxysmal EEG patterns. Specifically, Musumeci has identified Benign Epilepsy with CentroTemporal spikes as a common EEG abnormality among children with FXS (Musumeci et al., 1999, 1988).

The most common indications for EEG included staring spells and unusual motor movements. Motor movements suspicious for seizures were ultimately identified as behavioral or stereotypies in 69%. Nonepileptiform abnormalities (10%) were more common than actual epileptiform abnormalities (4%). We found a 14% incidence of abnormal EEGs in FXS. Epileptiform discharges, seizures and slowing of the EEG background were observed. Berry-Kravis (2002) highlighted benign epileptiform discharges as benign focal epilepsy of childhood in a previously described EEG abnormalities. The slowing of the EEG background was previously reported as a frequent EEG abnormality in FXS by Vieregge and Froster-Iskenius (1989).

In our series, a relatively high number (2/19) of FXS patient presented with status epilepticus. Additionally, one of these patients (Patient 14) has successfully completed epilepsy surgery with a temporal lobectomy, demonstrating that appropriate patients with genetic epilepsy diagnoses can be candidates for epilepsy surgery.

4.1. Prevalence of epilepsy in FXS

Our series revealed that the prevalence of epilepsy in the Fragile X population was 4.4%, significantly lower than the currently accepted 10–20% prevalence of epilepsy previously described in this population (Berry-Kravis, 2002; Berry-Kravis et al., 2010; Musumeci et al., 1999). Part of this difference may be accounted to age-specific differences in seizures among patients with FXS. In an evaluation of the natural history of seizures in patients with FXS, Musumeci et al. (1999) demonstrated that seizures did not occur before age 2. Thus the incidence of epilepsy may vary with the age of the child. Additionally, since this study was done in a Fragile X clinic that was headed by a geneticist instead of a neurologist or epileptologist, our clinic may have a decreased emphasis on neurological co-morbidities, including epilepsy. This may have led to a sample that is potentially more representative of the population of individuals with FXS than may have produced from a panel of

Table 1
Demographic, clinical, EEG and MRI findings in 19 patients with Fragile X syndrome.

Patient	Age/sex	Indication for EEG	EEG study	EEG findings	Repeat EEG findings	Imaging findings	Epilepsy diagnosis	Medications
1	2y/M	Minimal developmental progress over 6 months	Routine EEG	Slowing of posterior dominant rhythm for age	None. Repeat EEG not warranted	Not available	–	–
2	5y/M	Staring spells	Routine EEG	Left central parietal sharp wave discharges, potentiated in sleep	None. Repeat EEG not warranted	Not available	–	–
3	6y/M	Staring spells	Routine EEG	Normal	None. Repeat EEG not warranted	Not available	–	–
4	11y/M	Disrupted sleep, episodes of whole-body shaking and staring episodes	Long term monitoring video-EEG	Increased generalized theta bilaterally, lack of posterior dominant rhythm	None. Repeat EEG not warranted	Not available	–	–
5	21m/M	Episodes of whole body shaking	Routine EEG	Rare right frontal and midline spikes and sharp waves in sleep	None. Repeat EEG not warranted	Mild thinning the corpus callosum suggests a small reduction in white matter volume. Otherwise normal brain MRI	–	–
6	17m/M	Episodes of loss of tone	Routine EEG	Normal	None. Repeat EEG not warranted	Normal brain imaging	–	–
7	5y/M	Two tonic-clonic in the setting of fever	Routine EEG	Slow background with focal slowing in the left posterior quadrant. Multifocal spikes in left midtemporal, left frontal, left parietal areas during sleep	Normal. Improvement in PDR	Normal brain imaging	Complex partial seizures with secondary generalization	Oxcarbazepine
8	7y/M	Episodes of whole body shuddering	Routine EEG	Rare right frontal and midline spikes and sharp waves in sleep	None. Repeat EEG not warranted	Increase in T2 signal involving the left amygdala and hippocampal head	Generalized tonic-clonic seizures, complex partial seizures	Keppra
9	15m/F	Staring episodes	Routine EEG	Slow background for age	None. Repeat EEG not warranted	Hyperintensity in the periatrial region on the right side	–	–
10	20m/M	Eye rolling and nystagmus	Routine EEG	Normal	Normal	Mild prominence of the Sylvian fissures	–	–
11	7y/M	Episodes of twitching of the limbs and eyes	Routine EEG	Diffuse slow activity that appears to be more prominent on the left hemisphere. Poorly formed background rhythm	Normal. Improved PDR	Not available	2 episodes of status epilepticus, complex partial seizures	Lamictal

Table 1 (*Continued*)

Patient	Age/sex	Indication for EEG	EEG study	EEG findings	Repeat EEG findings	Imaging findings	Epilepsy diagnosis	Medications
12	8y/M	Staring episodes	Routine EEG	Asymmetric pseudorhythmic slow theta activity in the bioccipital area in excess for age	Normal. Improved PDR	Not available	–	–
13	12y/M	Behavioral change suggestive of seizures	Routine EEG	Frequent intermittent bursts of generalized slowing, bursts of high amplitude slowing, mild background slowing	Normal. Improved PDR	Not available	–	–
14	13y/M	Follow-up EEG for known epilepsy	Long term monitoring video-EEG	Three electroclinical seizures with the onset in the left temporal region. Occasional spikes in the left temporal region	Repeat worse with focal seizures consistent for epilepsy surgery	Mesial temporal sclerosis, generalized parenchymal volume loss, dysmorphic right hippocampus	Generalized seizures, auras	Keppra
15	6y/M	Staring spells	Routine EEG	Slow background for age, generalized burst of spike and wave activity	Stable PDR	Not available	Generalized seizures, history of status epilepticus	Trials of clonazepam, valproate, lacosamide
16	5y/M	Staring spells	Routine EEG	Slow background for age, sharp waves over left temporal, frontal and parietal areas, spikes over occipital area	Normal. Improved PDR	Normal brain imaging	Complex partial seizures	None
17	12y/M	Excessive snoring	Polysomnogram	Normal study	None. Repeat EEG not warranted	Normal brain imaging	–	–
18	4y/M	Excessive snoring	Polysomnogram	Normal study	None. Repeat EEG not warranted	Normal brain imaging	–	–
19	4y/M	Excessive snoring and thrashing in sleep	Polysomnogram	Decreased EEG amplitude in right hemisphere	None. Repeat EEG not warranted	Normal brain imaging	–	–

patients from a neurology-run clinic. Notably, in this study a fraction of children with seizure-like symptoms, such as staring spells and nystagmoid-like movements did not have an electrographic correlate. However, while the present study demonstrates a higher prevalence of epilepsy in patients with FXS in comparison to the general population, the incidence of seizures in these patients may be lower than has been previously described.

4.2. EEG findings in FXS

A retrospective review of 35 Fragile X patients with EEG abnormalities (13 with seizures and 22 without seizures) found a high incidence of centrotemporal spikes (Berry-Kravis, 2002). A study of 6 patients with epilepsy and FXS found that EEG abnormalities included spike-wave discharges in centro-parietal and centro-temporal regions. These EEG findings are consistent with benign epilepsies of childhood that remit by adulthood (Incorpora et al., 2002). We found a slightly increased prevalence of background slowing (47%) similar to previously published reports, which normalized with age in some of the patients. This suggests that FXS patients may have intrinsically different EEG characteristics that normalize in a delayed fashion.

4.3. Clinical seizures in FXS

The age of onset of epilepsy in our series was 4–11 years, similar to previously published data (Berry-Kravis et al., 2010). Patients had either complex partial or generalized epilepsies. The predominance of complex partial seizures in the FXS population over generalized epilepsies has been previously documented (Berry-Kravis, 2002; Berry-Kravis et al., 2010; Musumeci et al., 1999).

4.4. Response to treatment

Epilepsy in FXS is generally amenable to treatment. A case series demonstrated that 14 out of 16 patients with FXS and epilepsy had adequate seizure control (Berry-Kravis, 2002). In a larger study, 75% of treated FXS patients reported adequate seizure control on medication (Berry-Kravis et al., 2010). Our study showed that 4/6 patients (66%) achieved seizure control, which parallels previously published results. One patient, progressed to have mesial temporal sclerosis, as visualized on MRI. This change likely occurred due to multiple events of febrile and prolonged episodes of status epilepticus. The risk of mesial temporal sclerosis developing from childhood complex febrile seizures is estimated to be 3% (Chungath and Shorvon, 2008).

4.5. Genetic factors in epilepsy and FXS

Recent research has shed more light on the pathophysiology of FXS and seizures. FXS-induced seizures may also occur due to down regulation (D'Hulst et al., 2006) or altered metabolism (D'Hulst et al., 2009) of gamma amino butyric acid. Prevailing explanations lay in the activity of the group I metabotropic glutamate receptor (mGluR) pathway. FMR1 inactivation has been found to lead to excessive AMPA receptor internalization and increased glutamate receptor-induced long term depression (Brooks-Kayal, 2011). Though this leads to an overall decreased excitability in neurons, the cascading effect of dysregulated noncoding mRNA and the absence of BC1 mRNA specifically may be sufficient to lead to convulsive seizures (Zhong et al., 2009). Increased mGluR activity may occur via overexpression of the *App* gene, leading to excess formation of amyloid β-protein precursor (Westmark and Malter, 2007). In mouse-models of FXS, deletion of the *App* allele resulted in normalization of audiogenic seizures, anxiety symptoms, and ratios of mature versus immature dendritic spines. Alternative evidence has suggested that mGluR dysregulation may lead to a hyperxcitable state. Using brain slices prepared from *Fmr1* knockout mice and stimulated with mGluR agonists, investigators were able to demonstrate a reducted activation of somatostatin-expressing low-threshold-spiking (LTS) interneurons, leading to decreased synaptic inhibition (Paluszkiewicz et al., 2011). This subsequent decrease in LTS activity may predispose toward epileptiform activity.

4.6. Limitations

Data may be subject to information limitation and selection bias. We lacked sufficient numbers to provide statistically significant correlations between epileptiform abnormalities and seizure semiology. We were unable to compare the findings between males and females with FXS due to the low number of females with this condition. EEGs are not routinely performed in our center for FXS patients unless deemed necessary by the referring physician. As Autism Spectrum Disorder and other genetic neurodevelopmental syndromes (including Down syndrome and Angelman syndrome) were not available in our chart review, we were unable to include these comorbidities into our analysis. A possible aspect of further research would be complete a large prospective study on Fragile X patients in which all patient receives an EEG irrespective of their presentation and to correlate the subjective clinical suspicion of behavioral changes.

5. Conclusion

A slowed background EEG rhythm and multifocal epileptiform discharges were common series of FXS patients. Overall, EEG abnormalities were noted in patients irrespective of the presence of diagnosed epilepsy. While a larger number of patients had behavior suspicious of epilepsy, only 4% met the clinical criteria for the diagnosis of epilepsy. Our series suggests that the prevalence of epilepsy in the FXS population may be less than previously established rates. A larger fraction of patients in our series had behavior concerning for seizure without a diagnosis of epilepsy.

Conflict of interest

Sriram Ramgopal, Takijah Heard, and Sharyn Lincoln have nothing to disclose. Jonathan Picker is on the Roche Data safety monitoring committee for the R 04917523 fragile X drug study and is a co-PI for the Novartis AFQ056 phase 2 fragile X study. Dr. Kothare is funded by the following grants: National Institutes of Health: 1 RC1 HL099749-01 (R21), and RFA-HL-09-001, and Investigator Initiated Grant from Eisai Pharma, Inc., to assess safety and efficacy of rufinamide in children, and the Harvard Catalyst to assess cardiorespiratory abnormalities during seizures in children.

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