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BRIEF COMMUNICATION

Status epilepticus in fragile X syndrome

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Summary

Epilepsy is frequent in fragile X syndrome (FXS), the most common cause of inherited mental retardation. Status epilepticus (SE), however, seems exceptional in FXS, particularly as an initial epileptic manifestation. To our knowledge, SE was reported in only four FXS patients. We report the clinical features and electroencephalography (EEG) findings of five children with FXS, who presented with SE as their initial seizure.

KEY WORDS: Status epilepticus, Fragile X syndrome, Panayiotopoulos syndrome.

Fragile X syndrome (FXS) is the most common cause of inherited mental retardation, affecting approximately one in 4,000 male and one in 8,000 female individuals (Visootsak et al., 2005). The genetic mutation involved in FXS is a triplet repeat (CGG) expansion and hypermethylation involving the fragile X mental retardation one (*FMR1*) gene. The clinical spectrum of FXS is wide. Common findings include characteristic morphologic signs (macrocephaly, large head, long face, prominent forehead and chin, protruding ears, joint laxity, and macroorchidism), behavioral peculiarities (hyperactivity, anxiety, tactile defensiveness, gaze avoidance, socialization difficulties, perseverative speech), and epilepsy. In most cases, seizures are rare and electroencephalography (EEG) findings resemble those found in benign epilepsy with centrotemporal spikes (BECTS). Status epilepticus (SE) seems exceptional in FXS, particularly as an initial epileptic manifestation. We report the clinical features and EEG and magnetic resonance imaging (MRI) findings of five FXS children (see Tables 1 and 2), who presented with SE as their initial seizure. Hypotheses for a prolonged seizure propensity in FXS are discussed in the light of a recent literature review.

Patient 1

This patient presented with an initial focal clonic seizure at 5 years. The seizure lasted for 1 h, and stopped with 10 mg rectal diazepam. The initial workup at our center, where the child was rapidly transferred because of respiratory difficulties, revealed a positive nose swab for influenza A virus (seasonal flu). The EEG, performed 2 days later, showed diffuse slowing and bioccipital (right predominant) and left frontocentral biphasic spikes activated by stage 1 and 2 sleep. The cerebral MRI, performed 1 month later, revealed a mild hyperintense signal in the left hippocampal region only visible on fluid-attenuated inversion-recovery (FLAIR) sequences, consistent with a transient seizure-related abnormality.

Six months later this boy presented a second focal status epilepticus episode manifesting as partial loss of consciousness, head and eye deviation to the right, and right arm and leg hypertonia. Pallor and vomiting were also noted. The event lasted for 2 h, and stopped after the administration of 5 mg rectal diazepam. A repeat EEG performed on the same day showed the persistence of the previously described bioccipital spikes, but predominant on the left side. Rare diffuse slow spikes and polyspikes were also present. A third similar episode was noted 1 month later. Antiepileptic treatment was started and has been efficient so far.

Patient 2

This boy presented after breakfast with vomiting and speech difficulties, followed by loss of consciousness. He was admitted to our hospital, with erratic eye movements and nystagmus, hypotonia, and intermittent abnormal tonic posturing of the feet and hands; the seizure lasted for 2 h. The cranial computed tomography (CT) scan showed a normal brain parenchyma. The emergent EEG showed diffuse slowing, but no epileptiform discharges. The EEG

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Table 1. Patient characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Clinical phenotype	Mental retardation		Mental retardation	Mental retardation	Mental retardation
Comorbidities	Urinary collecting system dilation, supernumerary toes	Divergent strabismus	None	Interventricular communication operated at 16 months	Convergent strabismus (left amblyopia)
Age at 1st SE	5 years	9 years	5 years	8 years	14 years
SE duration	1 h	2 h	30 min at least	35 min at least	40 min
Previous seizures	No	No	No	No	1 Febrile convulsion at 11 months
SE clinical manifestations	Right arm tonic posture, nystagmus, head and eye deviation to the right, vomiting, respiratory difficulties after 0.5 mg/kg rectal diazepam	Vomiting, speech difficulties, nystagmus and eye deviation, right arm tonic posture	Clonic movements of the four limbs, alternate with generalized hypertonia	Dysarthria with sialorrhea, tonic and clonic movements of the right arm, head deviation to the left	Confused, then generalized convulsions
Associated symptoms	Fever (38.8°C)	Fever (38.4°C)	None	None	None
Associated diagnosis	Influenza A	None	None	None	None
Recurrent SE (number, etiology)	Yes (3, unknown), similar motor symptoms, but left-sided. Associated autonomic symptoms (pallor, vomiting, sweating), no fever, during 2 h	No	Yes (1, unknown), 3 months after initial episode, right arm myoclonias, shifting to the left side	No	Yes (4, unknown)
Additional seizures	Yes (1 tonic–clonic)	No	No	Two episodes of complex partial seizures	Two episodes of complex partial seizures
Treatment	VPA	No	CBZ	CBZ	LEV and TPM

FXS, fragile X syndrome; SE, status epilepticus; VPA, valproate; CBZ, carbamazepine; LEV, levetiracetam; TPM, topiramate.

Table 2. EEG and MRI findings

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Distant EEG	Diffuse slowing, bilateral occipital and left FC spikes	Some slowing theta anteriorly during wakefulness, slow during sleep. Left posterior parietal slow waves	Diffuse slowing, mostly left posterior. Multifocal spikes, anterior bilateral and right posterior	Slow theta–delta right posterior dysrhythmia. Right frontal and frontocentral biphasic spikes, increasing during sleep, sometimes bilateral	Left posterior slow waves
Brain imaging	1 month after SE: mild hyperintense signal on FLAIR sequences in the left hippocampal region	CT scan day 0: sinusitis	MRI: diffuse white matter abnormalities	MRI: arachnoid cyst anterior to the cisterna magna	MRI: normal

FXS, fragile X syndrome; EEG, electroencephalography; SE, status epilepticus, FC, frontocentral; CT , computed tomography; MRI, magnetic resonance imaging.

performed 3 days after the event showed anterior bursts of slow activity in the theta range during wakefulness and diffuse slowing during sleep. The patient did not receive any medication, and has remained seizure-free at 6 months follow-up.

Patient 3

This 5-year-old boy was known for FXS since the age of 21 months. His initial seizure was prolonged. He was found on awakening with fixed gaze, loss of contact, and sialorrhea; clonic movements of the four limbs alternated with generalized hypertonia. The seizure lasted for at least 30 min, and stopped rapidly after a single dose of 10 mg rectal diazepam. The EEG performed 12 days later showed diffuse slowing, mostly in the left posterior region, and multifocal spikes, predominant in the anterior bilateral and right posterior regions.

Three months later he presented a second SE episode. He was found in his bed on awakening with loss of contact

and right-sided clonic jerks; the seizure continued, despite the administration of 5 mg rectal diazepam, with myoclonias shifting to the left side. The seizure ceased with a second dose of 5 mg rectal diazepam. Ninety minutes later, however, he presented a generalized tonic seizure. Under carbamazepine, no recurrence of seizures has been noted at 18 months of follow-up.

Patient 4

This boy had been diagnosed with FXS on the basis of developmental delay and severe speech difficulties. At 8 years, he was hospitalized for a first episode of SE. One morning his teacher noted acute expressive speech difficulties with sialorrhea. Tonic posturing and clonic movements of the right arm and left deviation of the head were noted subsequently. More than 35 min later, the episode ceased after the administration of rectal diazepam. The EEG performed 24 h later showed right posterior low voltage theta–delta activity and right frontal and frontocentral biphasic spikes, increasing during sleep. This child had a few more focal seizures later on, eventually controlled with carbamazepine.

Patient 5

This 18-year-old patient presented at 11 months with a prolonged febrile convulsion, which lasted for 20 min. The diagnosis of FXS was made at 7 years, based on developmental and motor delay. The first SE episode was observed at 14 years: The patient was confused and poorly reactive. He rapidly lost consciousness, and was described as pale and cyanotic. He was admitted 40 min later in the hospital, where benzodiazepines stopped the seizure. The EEG performed 2 weeks later showed left occipital slowing. Valproic acid was started, but a second SE episode was noted 5 months later. The seizure was reported as partial with secondary generalization. Topiramate did not prevent a few breakthrough seizures, but levetiracetam allowed good seizure control.

Discussion

Our patients presented with SE as their first seizure, and some of them had recurrent episodes of prolonged seizures on follow-up. This is remarkable because, overall, SE appears to be rare in FXS. Moreover, prolonged seizures have been described only in FXS children previously known for epilepsy (Incorpora et al., 2002; Di Bonaventura et al., 2006). Despite this initial severity, our patients did not evolve to refractory epilepsy, and presented only rare additional seizures. Given that, although the risk of recurrent prolonged seizures may exist, long-term antiepileptic drugs might not be necessary in such cases.

Epilepsy is a frequent manifestation in FXS patients, particularly in boys; its prevalence ranges from 1350% (Sabaratnam et al., 2001). Various mechanisms have been proposed to explain the seizure susceptibility of FXS patients. Louhivuori et al. (2009) showed that those patients with a *Val66Met* mutation on the gene coding for the brain-derived neurotrophic factor were more prone to develop epilepsy. This mutated gene had been previously shown to be associated with cerebral malformations, neuropsychiatric disorders, and epilepsy in the general population (Louhivuori et al., 2009). El Idrissi et al. studied γ-aminobutyric acid $(GABA)_A$ receptor expression in FXS mice, and found decreased hippocampal, diencephalic, and brainstem expression, and increased glutamic acid decarboxylase expression, as compared to normal subjects. This imbalance in the inhibition–excitation system provoked an increased susceptibility to seizures (El Idrissi et al., 2005). Various seizure types may be noted, which include simple or complex partial seizures, and primary or secondary generalized tonic–clonic seizures. These events may start as early as 6 months, but are usually not observed before 2 years (Incorpora et al., 2002). The interictal EEG frequently reveals midtemporal biphasic or triphasic spikes activated by sleep, a pattern reminiscent of the functional spikes found in BECTS. Less often, focal rhythmic slowing or generalized polyspike-waves are observed. The natural course of epilepsy in FXS patients is often favorable: Seizures remain rare and the EEG abnormalities disappear after a few years in the majority (Berry-Kravis, 2002). Interestingly, two of our patients and one of the previously reported children had clinical seizures and EEG findings more suggestive of Panayiotopoulos syndrome (PS) than of BECTS. Seizures in PS are typically prolonged, and often manifest as vegetative symptoms, such as emesis, pallor, temperature dysregulation, and cardiac and respiratory frequency modifications. Eye deviation and/or behavioral changes are also common. In rare patients, severe ictal bradycardia or respiratory arrest has been described. The etiology of PS is unknown, but some authors suspect it to be genetic: A family history of febrile seizures is frequently reported in PS patients, and mutations on a gene coding for a sodium-channel (*SCN1A*) have been described in a few of them (Livingston et al., 2009). *SCN1A* gene mutations are common in Dravet syndrome and in additional epilepsy phenotypes in which SE is particularly frequent (Harkin et al., 2007), suggesting a potential implication of its product in seizure duration. Whether this gene plays a role in FXS patients, who present with prolonged seizures, remains to be demonstrated. Finally, as observed previously in PS (Panayiotopoulos, personal communication), one of our patients exhibited severe respiratory complications after receiving rectal diazepam. Although a direct link between the treatment and the respiratory difficulties is difficult to demonstrate formally, our observation suggests that a reduction in the dosage of emergency benzodiazepines may be

necessary in FXS patients who present with predominantly vegetative ictal symptoms.

Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

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