Fragile X Syndrome and Epilepsy: case report

Síndrome do X Frágil e Epilepsia: relato de caso

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ABSTRACT

Introduction: Learning disabilities is defined by intelligence quotient of less than or equal to 70 associated with limited learning functions such as cognition, language, motor function and social skills activities. Epilepsy is more common in individuals with learning disabilities and its frequency increases progressively considering severe intellectual impairment. Fragile X syndrome is the most common genetic cause of learning disability and 10-20% of these children have epilepsy. Methods: We describe a patient with fragile X syndrome, who had febrile seizures leading to temporal lobe epilepsy. Results: Male patient, 36 years old. He had several episodes of febrile seizures from one to seven years old and at the age of 27 he started with spontaneous dyscognitive seizures with possible temporal lobe origin. His brother, who also has the diagnosis of fragile X syndrome, presented a single afebrile seizure as a child. Patient's MRI showed left hippocampal atrophy. Conclusion: The relationship between febrile seizure and temporal lobe epilepsy in the context of fragile X syndrome is discussed in this article. Fragile X syndrome turns patients more vulnerable to have any kind of seizures. Therefore, we have to prevent febrile seizures in these patients.

Keywords: fragile x syndrome, epilepsy, febrile seizure, temporal lobe epilepsy

RESUMO

Introdução: O déficit de aprendizagem é definido por quociente de inteligência inferior ou igual a 70 associado às funções limitadas de aprendizagem, tais como a cognição, a linguagem, a função motora e as habilidades sociais. Epilepsia é mais comum em indivíduos com dificuldades de aprendizagem e sua incidência aumenta progressivamente em pacientes com deficiência intelectual grave. Síndrome do X Frágil é a causa genética mais comum de deficiência de aprendizado e 10-20% destas crianças têm epilepsia. Métodos: Nós descrevemos um paciente com síndrome do X frágil, que teve convulsões febris e evoluiu com epilepsia do lobo temporal. Resultados: O paciente apresentou dois episódios de convulsão febril durante a infância e, com 27 anos, iniciou crises discognitivas típicas de lobo temporal. Seu irmão, que também tem síndrome do X frágil, apresentou crise afebril única na infância. A RM do paciente mostrou atrofia hipocampal à esquerda. Conclusão: A relação entre a convulsão febril e epilepsia do lobo temporal no contexto da síndrome do X frágil é discutida neste artigo. Pacientes com síndrome do X frágil são mais suscetíveis a ter qualquer tipo de crise epiléptica. Portanto, temos que tentar evitar crise febril prolongada nestes pacientes.

Palavras-chave: síndrome do x frágil, epilepsia, crise febril, epilepsia de lobo temporal

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INTRODUCTION

Learning disabilities, also known as mental retardation, is defined by intelligence quotient of less than or equal to 70 associated with limited learning functions such as cognition, language, motor function and social skills activities. It is considered a developmental disorder in which the individual was never able to acquire educational and functional skills expected for his/her age or, in early life, the individual suffered an insult that hindered his development leading to the absence of functional gains. Epilepsy is more common in individuals with learning disabilities and its frequency increases progressively considering severe intellectual impairment. The prevalence of epilepsy in those with mild to moderate deficit (IQ 50-70) is 15%, while in those with severe impairment (IQ <50) it is 30%. This well established relationship between epilepsy and learning disabilities was interpreted as a possible central injury leading to the two conditions. However, with the advancement of studies in this area, it is known that there are learning disabilities syndromes in which epilepsy is not as prevalent.

Fragile x syndrome (FXS) is the most common genetic cause of learning disability and 10-20% of these children have epilepsy, commonly with seizures easily controlled with anti-epileptic drugs (AEDs) and age-related EEG pattern showing centrotemporal spikes. They also may have sensory hypersensitivity and autism spectrum disorder. The syndrome is the result of functional loss of "fragile X mental retardation 1" (Fmr1) gene present on the X chromosome, leading to discontinuation of "fragile X mental retardation protein" (FMRP). FMRP plays a role in RNA transport and local protein synthesis and, therefore, is related to synaptic plasticity, a mechanism related to learning and memory. The basis of the relationship between the syndrome and epilepsy is focused on the theory of glutamatergic metabotropic receptors and gama-aminobutyric acid (GABA) receptors. However, FMRP is also expressed in glial cells and, there is a recent interest in studies of neuronal development of astrocytes and their relationship to the pathophysiology of the disease.

Jacobs and Doering reported that mice with FXS exhibit development changes of hippocampal synapses at early stages in their development, these abnormalities suppression at early stages of life can result in abnormal patterns of hippocampal dendritic branching. Astrocytes of FXS mice were deficient in the ability to regulate synapse development, and culture of affected neurons showed decreased number of pre and post synaptic proteins. FMRP also regulates phosphorylation "glycogen synthase kinase-3"(GSK3), which was reduced in affected mice. Yuskaitis et al. used the same animal model to examine the role of GSK3 as a potential combination of FXS and inflammation, reporting evidence of increased reationalastrogliosis. Together, these studies indicate that FXS results in dysfunction of astrocytes, which may be associated with deficits in learning and increasing the risk of epilepsy.

Compared with epilepsy in the general population, epilepsy in people with learning disabilities is more often refractory to AEDs and is associated with higher mortality. The prevalence of seizures in FXS is relatively low (11.8% to 13.1%) and it is more common in boys (14-14.5%) than girls (6 to 8.3%). The age of seizure onset is between 4 to 10 years with a mean age of 5 years. The seizures are usually infrequent, with 69% of boys and 89% of girls seizure free in 6 months after AED start. Febrile seizures can also be seen. Regarding treatment, patients suffering from epilepsy in FXS have mild or moderate severity, with 85% of boys and 100% of girls in use of one or two anti epileptic drugs.

This article aims to review the literature of epilepsy in the context of FXS and to report a case of temporal lobe epilepsy preceded by febrile seizure in a patient with FXS.

CASE REPORT

We presented a case of a 36 years old patient, male, who was sent to our service when he was 27 years old because of high seizure frequency. He had the diagnosis of FXS with delayed psychomotor development, learning disability, impairment of concentration and integration at school.

He had a generalized tonic-clonic seizure when he was 1 year old, during an episode of fever. Phenobarbital was started at the time. At the age of three years, he presented a similar episode. At the age of seven years, he presented three more generalized seizures, always with fever. Phenobarbital withdrawal was tried several times, but it triggered afebrile generalized tonic-clonic seizures. At the age of 27, he started with seizures described as head version to the right side, associated with gaze deviation, loss of consciousness and secondary generalization. He reported no auras. At this time, the dose of phenobarbital was increased to 200mg per day and diazepam 5 mg per day was introduced. He was then referred to our epilepsy clinic. He has a younger brother, also diagnosed with FXS, who had an episode of generalized tonic-clonic seizure at age of 1 year, afebrile and without recurrence. Neurological examination revealed moderate cognitive impairment.

Brain magnetic resonance imaging (MRI) showed left hippocampal atrophy and hyperintense FLAIR signal. Electroencephalogram (EEG) only showed irregular generalized slow waves. Currently, he is in use of clobazam 15mg per day and carbamazepine 1200mg per day and he has a seizure frequency of one to two dyscognitive seizures per month.

DISCUSSION

We reported a patient that shows the FXS vulnerability to have seizures in childhood. This patient presented two episodes of febrile (probably prolonged) seizures that has well-established relationship with temporal lobe epilepsy. This relationship becomes even clearer when the patient is compared to his brother, who had a seizure in childhood with no fever, and no recurrence.

A study with thirty FXS patients grouped patients according to the pattern of seizures: i) seizures and normal EEG; ii) seizures and abnormal EEG iii) well-controlled seizures and abnormal EEG and, iv) abnormal EEG with frequent seizures refractory to AED treatment. It showed that the spectrum of seizures in patients with FXS is quite large, but this is usually also observed in patients with epilepsy due to other etiological factors. Based on that, we cannot relate specific types of seizure directly with the FXS, as the febrile seizures or the temporal lobe seizures presented by our patient.

In studies with animal models of FXS, astrocytes were proved to be deficient in the ability to regulate synaptic development, and culture of affected neurons showed decreased numbers of pre and post-synaptic proteins. Further characterizations of these changes established that these findings return to normal during the animals development, which explains the good control seen in most patients with FXS and epilepsy.
The literature also shows that, because of the complexity of neural development, any insult in early life to the dendritic branching and synaptogenesis can lead to the development of cognitive impairment or epilepsy, as the febrile seizures that affected our patient. Electrophysiological studies showed a reduction in long-term potential in the cortex and increased long-term depression in hippocampus affected by the genetic mutation related to FXS, which can also lead to epileptic seizures.

Regarding febrile seizures as a risk factor for the development of hippocampal sclerosis and temporal lobe epilepsy, high temperatures should be prevented in children with increased susceptibility to seizures, as in patients with FXS. It is not clear in the literature the direct relationship between FXS and temporal lobe epilepsy, which makes us think about the role of hippocampal alterations secondary to the syndrome and its relation with the additional insult represented by febrile seizures. The severity of the epilepsy and clinical patterns were not correlated with the increased number of the CGG trinucleotide repeat in the FMR 1 gene.

A therapeutic target for treatment of seizures in patients with FXS could be the "Striatal-Enriched protein tyrosine Phosphatase" (STEP), involved in the inappropriate AMPA and NMDA receptors internalization, and ERK1/2 pathway dysregulation observed in FXS animal models. Moreover, animal studies show changes in the GABAergic system and the functional inhibitory neurotransmission in brain regions that are relevant to the phenotype of FXS, including the amygdala, cortex, hippocampus and striatum. This should be considered in the study of new treatment options for neurological manifestations of this syndrome, including seizures.

CONCLUSION

Although the relationship between FXS and epilepsy is well documented, studies on the pathophysiological mechanisms linking the two conditions are necessary, especially if we consider the cases of refractory epilepsy that evolve beyond the period of childhood. Furthermore, attention should be paid to the prevention of febrile seizures in these patients, given the susceptibility to seizures and the relationship between febrile seizures and temporal lobe epilepsy.

REFERENCES


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