

When your child with epilepsy die suddenly: febrile seizures are part of the process?

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ABSTRACT

Febrile seizures (FS) affect almost 2-5% of children and factors related to an increase susceptibility of children to FS may involve an imbalance of inflammatory cytokines and genetic factors. FS had low morbidity, but may be associated with the occurrence of late chronic epilepsy. Here we describe factors related to FS and its possible correlation with SUDEP.

Key words: epilepsy, sudden death, febrile seizures.

Quando seu filho com epilepsia morre subitamente: crises febris fazem parte do processo?

RESUMO

Crises febris (CF) afetam aproximadamente 2-5% das crianças e os fatores envolvidos com essa maior susceptibilidade das crianças às CF podem estar relacionados com uma ação inadequada de citocinas inflamatórias, além de fatores genéticos. As CF têm baixa morbidade, mas podem estar associadas à ocorrência de epilepsia crônica. Nós discutiremos os fatores relacionados com CF, considerando-se sua possível associação com SUDEP.

Palavras-chave: epilepsia, morte súbita, crises febris.

Febrile seizures (FS) affect almost 2-5% of children¹ and are defined as a seizure, occurring in a child after 1 month of age associated with a febrile illness not induced by an infection of the central nervous system (CNS), without previous neonatal seizures, a previous unprovoked seizure or an acute symptomatic seizure². Factors related to an increase susceptibility of children to FS are not totally enlightened and are probable multifactorial. Some authors had reported an imbalance of inflammatory cytokines, specially an increased production of interleukin 1 β that have a proconvulsant effect in patients with FS³. Also, the high prevalence of family history of FS and occurrence of FS in homozygous twins suggest that genetic factors may play an important role in

FS events³. Usually, FS had low morbidity and deaths directly related do these seizures had not been reported, except when considering febrile *status epilepticus*⁴.

The main morbidity related to FS is the development of long term epilepsy reported with a variable incidence risk that may be as low as 0.1% and as high as 44% of the patients, with a mean risk of 5.8% of the cases⁴. Evidences from epidemiological studies suggest that approximately 25% of the patients with epilepsy evolve with medically intractable seizures, with a major proportion of patients in the pediatric group⁵. Unfortunately, individuals with epilepsy are at a higher risk of death than those from the general population and each year, about 1:500 to 1:1000 patients with chronic epilepsy will die sud-

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denly, suffering of sudden unexpected death in epilepsy (SUDEP)⁶. SUDEP is defined as a death that occurred suddenly, unexpectedly and of non-traumatic and non-drawing, witnessed or unwitnessed, with or without the evidence of a seizure, excluding *status epilepticus*, and without a toxicological or anatomical cause of death in *post-mortem* examination^{7,8} and will be responsible for about 7.5 to 17% of all deaths in epilepsy⁹. Individuals with epilepsy are at a higher risk to suffer of SUDEP. Although there was no suggestion in the literature that FS were related to SUDEP^{1,4} there is a significant association of refractory epilepsy and a history of FS¹⁰⁻¹². Risk factors possible associated with SUDEP are refractoriness of the epilepsy, occurrence of generalized tonic-clonic seizures, antiepileptic drugs polytherapy, early age of epilepsy onset, long term seizure disorder (more than 15 years), winter temperatures¹³, cardiovascular and pulmonary abnormalities¹⁴ and genetic factors¹⁵.

Cardiac mechanisms may have a main role in SUDEP occurrence and repetitive cardiac damage and arrhythmias during seizures may induce autonomic imbalances with sympathetic stimulation and the development of fatal arrhythmias^{16,17}. In accordance to this, *post-mortem* examinations in people that died of SUDEP have shown pulmonary edema and cardiac abnormalities, such as supraventricular and ventricular arrhythmias during epileptic seizures¹⁸. Schuele et al. reported an incidence of ictal asystole in 0.27% of patients submitted to video-electroencephalographic monitoring¹⁸ confirming a possible association between ictal events and cardiac dysfunction.

Others common cardiac abnormalities observed in patients with epilepsy and SUDEP are the lengthening of corrected QT cardiac repolarization time (QTc), alteration of T wave, bradycardia and increased QT dispersion¹⁷. Surges et al., studying 25 patients observed prolongation of QTc in 12% of them¹⁹. This finding may suggest that QTc interval may have a role in SUDEP^{20,21}. QTc is higher in epileptic patients as compared to normal subjects, and it appears to be related to disease duration, particularly over the early history of disease. It is unrelated to patient age or recent reported seizure frequency²² but may be triggered by interictal epileptiform discharges, suggesting that transient dysfunction of cortical networks can interfere with cardiac repolarization²³.

Mutation in potassium channel genes (KCNQ1, KCNH2, KCNE1 and KCNE2) and sodium channel genes (SCN5A) has been related to neonatal seizures and long QT syndrome²⁴ and over one third of referred cases of SUDEP were found to harbor a genetic arrhythmia-susceptibility mutation^{20,25}. Physiologic changes of mutated channels causing seizures or cardiac arrhythmias are similar²⁵. Also, FS is currently observed in patients with epileptic syndromes associated with genetic mutations in

genes of sodium channels subunits as SCN1B, SCN1A and SCN2A²⁶. Sodium channel mutations of the genes SCN1A, SCN1B and SCN2A had been reported in patients with generalized epilepsy and FS (GEFS+), an autosomal dominant epilepsy^{27,28}, with some of these patients developing latter on temporal lobe epilepsy^{11,12}. Hindocha et al. reported two cases of SUDEP in a family with typical GEFS+ and a novel mutation of SCN1A and raised the hypothesis of a unique mutation to be responsible for both epilepsy and sudden death¹⁰. Corroborating this theory is the finding that SCN1A gene products are present in various regions of the heart in animal studies²⁹⁻³¹.

Up to now, studies suggest that acute FS do not trigger a SUDEP event, but it is not clear if a susceptibility to FS could be associated with a major risk of SUDEP in patients that developed chronic epilepsy. Corroborating this hypothesis, Kinney et al.³² demonstrated a high incidence of FS history in children that suffered of sudden death, not related to epilepsy. SUDEP is the most important direct epilepsy-related cause of death and while the exactly mechanisms or set of factors involved on SUDEP occurrence are still not clear the principal effort in preventing SUDEP should be prompt and optimal seizure control, especially generalized convulsive seizures and identification of cardiovascular associated diseases³³.

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