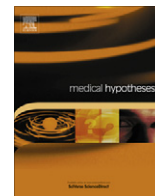


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## Medical Hypotheses

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### Sudden unexpected death in children with epilepsy: The many faces of fungal pathogenicity

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#### ABSTRACT

Epilepsy is one of the most prevalent neurological diseases worldwide. The mortality rates are considerably higher in people with epilepsy than would be expected in a healthy population and sudden unexpected death in epilepsy (SUDEP) is the most frequent epilepsy-related category of death. Most children had seizures before the occurrence of the fatal event and autonomic dysfunction has been proposed as mechanisms of sudden death in this population. In this sense, we raise the question whether there is a possible relationship between SUDEP in children and fungal pathogenicity. Indeed, the role of fungal pathogenicity in the establishment of epilepsy and even in cases of SUDEP has an interesting role in this scenario. Moreover, maternal infections during pregnancy have been associated with an increased risk for several brain disorders, however, this fact is still considered uncertain with respect to epilepsy.

Based on this information and considering that maternal-fetal yeast infection is directly associated with an increased risk for epilepsy in childhood and that some patients have medically intractable epilepsy, the chances of these children suffering a fatal event cannot be overlooked by healthcare professionals. Thus, as exact knowledge regarding this association is lacking, some possibilities could be evaluated, and more emphasis on translational research would contribute to further progress to the knowledge of SUDEP.

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Epilepsy is one of the most prevalent neurological diseases worldwide. A major proportion of patients with epilepsy falls in the pediatric group (18 years old or less), and approximately 25% of those patients have medically intractable epilepsy [1]. Unfortunately, mortality rates are considerably higher in people with epilepsy than would be expected in a healthy population and sudden unexpected death in epilepsy (SUDEP) is the most frequent epilepsy-related category of death [2]. Currently, SUDEP has an incidence among adults between 1:500 and 1:1000 patient-years [3]. SUDEP is mainly, but not exclusively, an issue in patients with refractory epilepsy [3]. In parallel, although different mechanisms may play separate roles in different cases, mechanisms to play a role in SUDEP are autonomic, i.e., respiratory (central apnea) and cardiovascular (cardiac arrhythmias) [3]. On the other hand, it is important to emphasize that SUDEP has been less studied in childhood, probably because the incidence of sudden death is higher in adults than in children [4]. Actually, SUDEP occurs more commonly

in children with refractoriness of the epileptic condition and the literature reports rates of SUDEP in childhood between 1.1 and 4.3/10,000 patient years [4,5]. Furthermore, most children had seizures before the occurrence of the fatal event and autonomic dysfunction has been proposed as mechanisms of sudden death in this population [4,5]. Following this line of reasoning, we reviewed the incidence of SUDEP in a cohort of children in our epilepsy unit over an 8-year period [6]. Briefly, from 835 patients evaluated, 12 had suffered SUDEP and nearly all of the SUDEP cases in our children are related to chronic uncontrolled epilepsy (daily-50.0%, two to four/week-41.7%, monthly-8.3%) [6]. Thus, our study is totally in agreement with previous results evaluated in children and adults with epilepsy, where increased mortality was recorded in those individuals who had not responded to treatment [2–5]. Taken all these data together, is there a possible relationship between SUDEP in children and fungal pathogenicity? Yes, there is.

Firstly, we have to remember that the most common risk factors for epilepsy are cerebrovascular disease, brain tumors, alcohol, traumatic head injuries, malformations of cortical development, genetic inheritance, and infections of the central nervous system [2]. In resource-poor countries, endemic infections seem to be ma-

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major risk factors [2]. Furthermore, approximately 40 million people who have epilepsy live in countries with poor resources and the major cause of this higher rate is related with endemic parasitic diseases [2]. In these lines, the role of fungal pathogenicity in the establishment of epilepsy and even in cases of SUDEP has an interesting role in this scenario. As we know, multiple factors influence the outcome of fungal infection of the central nervous system (CNS) [7]. Although 70,000–1500,000 fungal species exist and nearly 300 species have been associated with human infection, there are about a dozen yeasts and about 30 molds that are commonly identified as human pathogens encountered in the CNS [7,8].

Second, maternal infections during pregnancy have been associated with an increased risk for several brain disorders, however, this fact is still considered uncertain with respect to epilepsy [8]. What is known is that the seasonal pattern of births of children with epilepsy indicates that infections or other environmental exposures with seasonal variation may play a causal role in the cause of epilepsy [8,9]. In 2006, Whitehead et al. [10] examined the effect of pregnancy and neonatal factors on the subsequent development of childhood epilepsy in a population-based cohort study. There were 648 new cases of epilepsy diagnosed among 124,207 live births, for an overall rate of 63 per 100,000 person-years. In adjusted analyzes, maternal infections during pregnancy were associated with an increased incidence for epilepsy in childhood [10]. Two years later, Sun et al. estimated directly the association between prenatal exposure to maternal infections and the subsequent risk for epilepsy in childhood [8]. Briefly, the authors clearly demonstrated that prenatal exposure to some maternal infections, including vaginal yeast infection, was associated with an increased risk for epilepsy in childhood [8].

Based on this information and considering that maternal-fetal yeast infection is directly associated with an increased risk for epilepsy in childhood and that 1/4 of those patients have medically intractable epilepsy, the chances of these children suffering a fatal event cannot be overlooked by healthcare professionals. Thus, as exact knowledge regarding this association is lacking, some possibilities could be evaluated (see Fig. 1).

In this context, an interesting proposal would follow the current principles of translational research. As well established, the exciting discoveries in biomedical research and their promise for the future of medicine continue to expand. One of the reasons of such advancement is due to the onset of translational research. In general lines, the term translational research specifically aims at taking the integration of the advancements in basic science with clinical trials, taking research from the “bench-to-bedside” [11]. This perspective will improve health and, in doing so, gain knowledge for people with some chronic diseases [11], but can still be considered rare among epileptologists and infectologists. Obviously, although this possibility still only present a speculative basis, this perspective is quite plausible. For that, we suggest that after the diagnosis of vaginal yeast infection in the pregnant woman have been performed, should be part of clinical routine of the infectologist contact the epileptologist to let you on notice. As a considerable percentage of mothers with vaginal yeast infection can lead to children with epilepsy and 25% of these children may be refractory to pharmacological treatment and unfortunately, may also have chances of dying suddenly, both infectologists and epileptologists should work in convergence and always treated the patients in a “translational manner”.

In sum, more emphasis will be put on translational research. Obviously, future work in this area will examine that potential, and the degree to which it is being achieved, however, we must

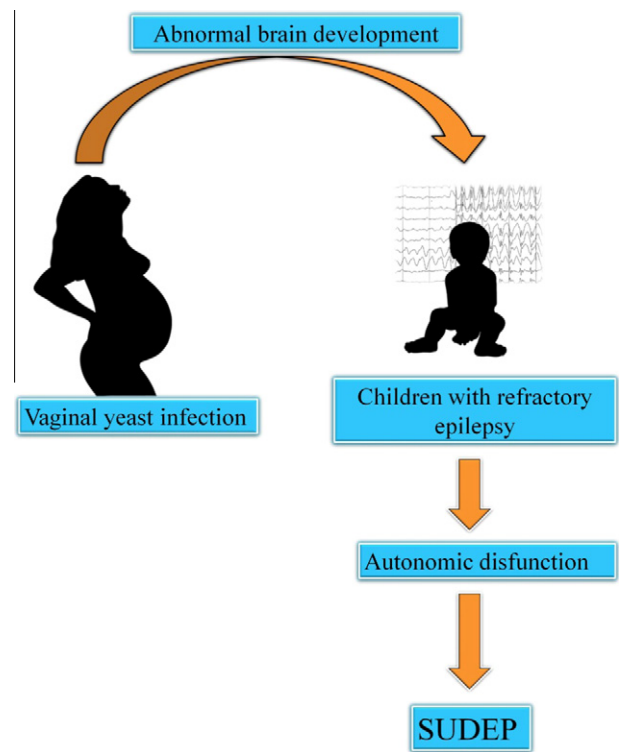


Fig. 1. Representation of the possible link between yeast infection and SUDEP.

remember that we are in an era that further progress will depend upon continued collaborative efforts by the translational scientific community.

#### Conflict of interest

None declared.

#### References

- [1] Carter OS. Surgical treatment of medically refractory epilepsy in childhood. *Brain Dev* 2001;23:199–207.
- [2] Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet* 2006;367:1087–100.
- [3] Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. *Nat Rev Neurol* 2009;5:492–504.
- [4] Milroy C. Sudden unexpected death in epilepsy in childhood. *Forensic Sci Med Pathol* 2011;7:336–40.
- [5] Meyer S, Shamdeen MG, Gottschling S, Strittmatter M, Gortner L. Sudden unexpected death in epilepsy in children. *J Paediatr Child Health* 2011;47:326–31.
- [6] Terra VT, Scorza FA, Sakamoto AC, Pinto KGFD, Fernandes RMF, Arida RM, et al. Does sudden unexpected death in children with epilepsy occur more frequently in those with high seizure frequency? *Arq Neuropsiquiatr* 2009;67:1001–2.
- [7] Redmond A, Dancer C, Woods ML. Fungal infections of the central nervous system: a review of fungal pathogens and treatment. *Neurol India* 2007;55:251–9.
- [8] Sun Y, Vestergaard M, Christensen J, Nahmias AJ, Olsen J. Prenatal exposure to maternal infections and epilepsy in childhood: a population-based cohort study. *Pediatrics* 2008;121:e1100–7.
- [9] Procopio M, Marriott PK. Seasonality of birth in epilepsy: a danish study. *Acta Neurol Scand* 1998;98:297–301.
- [10] Whitehead E, Dodds L, Joseph KS, Gordon KE, Wood E, Allen AC, et al. Relation of pregnancy and neonatal factors to subsequent development of childhood epilepsy: a population-based cohort study. *Pediatrics* 2006;117:1298–306.
- [11] Goldblatt EM, Lee WH. From bench to bedside: the growing use of translational research in cancer medicine. *Am J Transl Res* 2010;2:1–18.