

## Current Literature

In Clinical Science



## Stress and Seizure Control in Children: Where to Now?

**Stress Sensitivity of Childhood Epilepsy Is Related to Experienced Negative Life Events.**van Campen JS, Jansen FE, Steinbusch LC, Joëls M, Braun KPJ. *Epilepsia* 2012;53:1554–1562.

**PURPOSE:** To evaluate the effect of stress on seizure frequency in childhood epilepsy, and to assess possible differences between children in whom seizures are precipitated by stress and those in whom they are not. **METHODS:** Parents or caregivers of children with active epilepsy (aged 2–16 years) were sent questionnaires on developmental and epilepsy characteristics, life-time stress exposure, and the effect of stressful periods and moments of acute stress on seizure frequency in their child. Further information was extracted from patient files. **KEY FINDINGS:** Parents or caregivers of 153 children with a median age of 8.8 years responded to the questionnaires. Thirty-nine percent reported an increase in seizure frequency during periods of stress, with a median increase of 2.5 times the frequency compared to nonstressful periods. Thirty-seven percent reported that seizures were precipitated by acute stress, with stress being a precipitating factor in 33% (median value) of the seizures. Overall, 51% of the patients reported stress sensitivity of seizures. A higher number of negative life events experienced in total life was related to an increase in seizure frequency in stressful periods (odds ratio [OR] 1.3,  $p = 0.01$ ) as well as to the precipitation of seizures by acute stress (OR 1.3,  $p = 0.02$ ). **SIGNIFICANCE:** Stress sensitivity is reported in half of the children with epilepsy. Results of this study suggest a relation between experienced negative life events and stress sensitivity of childhood epilepsy. One possible explanation could be that experiencing negative life events may cause a larger response to daily stressors, thereby increasing the likelihood to induce epileptic activity.

**Commentary**

This is the first study to examine the relationship of both recurrent and acute stressors (noncatastrophic) with seizure frequency in a large sample of 153 children and adolescents with epilepsy and their association with life events. The findings demonstrate that seizure frequency increased in about half the children in this sample and is associated with both types of stressors, that about 25% of children responded to both recurrent and acute stressors, and that both recurrent negative and positive stressors were related to increased seizure frequency. Similar to adults (1–5), children with epilepsy appear to respond to recurrent and acute noncatastrophic stressors with increased seizure frequency.

The study's many strengths include its large sample size, the well-defined inclusionary and exclusionary criteria; inclusion of demographic, developmental, and IQ variables in the analyses; the separation between positive and negative stress factors; examination of the role of sleep, medication noncompliance, and seizures as stressors; and comparison of the 153 participants and 192 nonparticipants in the study in terms of their age, sex, and epilepsy-related variables.

Although the authors provided a good discussion of the study's limitations, they did not consider several additional potential confounding factors. The study included children

aged 2 to 16; yet, the article includes no information on how many children were in the different age groups, nor how the distribution of the subjects in this wide range of age groups was related to the study's findings. In addition, they did not indicate if and how the 17.1% of subjects treated with ketogenic diet, vagal nerve stimulator, and adrenocorticotrophic hormone (ACTH) might have contributed to the direction of the study's stressor findings. The authors found a significant association between arousal, anger, fear, and nervousness with acute stress, as well as between arguments with stress sensitivity and negative stressors. However, they provide no information on how they defined and differentiated between these behaviors. Furthermore, since these phenomena could be preictal manifestations in children, parents might misinterpret them as stressors that increase seizure frequency. The smaller number of antiepileptic drugs and stressful events in the medical charts of the nonparticipants could imply a selection bias in the participant parents who had children with more difficult to control seizures and stressful life events.

Nevertheless, the clinical and research implications of the study's findings are important and underscore the need for well-designed treatment programs and studies. Children without epilepsy who have psychiatric diagnoses and behavior problems have difficulty coping with stress (6). Evidence for psychiatric diagnoses, including high rates of anxiety disorders and internalizing behavior problems, in children with new onset epilepsy (see Hamiwka et al. for review [7]), together with the findings of van Campen et al., suggest that psychiatric treatment at onset of the disorder might improve seizure con-



trol. Well-designed, double-blind, randomized control studies of cognitive behavior therapy focused on coping with stress in children with new onset epilepsy are needed to determine short-term and long-term effects of early treatment on both seizure control and psychiatric comorbidity.

Since the present study by van Campen et al. was conducted on patients treated in a tertiary center, most of whom were on several antiepileptic drugs, the need for early intervention is particularly relevant for these children. These children also experience the added stress of having cognitive, linguistic, and learning difficulties and associated poor self-esteem, depression, and anxiety (see Hamiwka et al. for review [7]).

As reported in adult studies on stressors and precipitants of seizures (1–5), poor quality and reduced quantity of sleep during periods of stress were related to an increase in seizure frequency. But sleep deprivation and tiredness can negatively affect children's ability to cope with stress and precipitate seizures by activating mechanisms involving the hypothalamic-pituitary-adrenal (HPA) axis. Seizures can also increase baseline steroid levels, which in turn reduce the seizure threshold and lead to a vicious cycle involving stress, sleep deprivation, and seizures (see Maguire and Salpekar for review [8]). Studies are clearly warranted to delineate the mechanisms underlying the complex relationship among stress, sleep deprivation, and seizures to identify how best to intervene to stop this vicious cycle in children with epilepsy.

From the methodological perspective, studies on acute and chronic stressors and their association with seizure frequency are difficult to design for several reasons. First, they need to be prospective and conducted for a reasonable period to ensure an adequate number of seizures. Second, use of patient diaries is a significant burden, whether filled out by parents or by their children, and can lead to subject attrition, selection of a particular personality type of parent with time available to commit to the study's demands, unreliable data, or all of these. Third, parents' perception of stressors might not accurately reflect how children perceive their life events. Fourth, the perception of stressors, whether by parents or by children, might reflect their underlying psychiatric diagnoses as well as family dysfunction and problem parenting. Fifth, low socioeconomic class and minority status, variables related to increased stressors, have not been examined in prior adult and child studies on stress and seizures. Sixth, a large sample size would be needed to take all these potentially confounding factors into account.

However, an alternative approach would be to identify children who might be at risk for stress-related increased seizure frequency using biomarkers. This can be done by studies of the HPA axis similar to those conducted in children without epilepsy who have depression (see meta-analysis by Lopez-Duran [9]) and anxiety (10, 11). More specifically, children with depression have higher baseline cortisol values, atypical responses to the dexamethasone suppression test, and an overactive response to psychologic stressors than nondepressed control subjects (9). In terms of anxiety, stress induces increased baseline saliva sample cortisol levels and a reduction in hippocampal volume over a 12- to 18-month period in chronically stressed children with post-traumatic stress disorder, when controlling for pubertal maturation and sex

(10). Trait anxiety is related to increased evening cortisol levels in adolescents and to flat diurnal cortisol profiles (11).

The importance of seizure control for the cognitive, linguistic, and academic performance of children with epilepsy (see Hamiwka et al. for review [7]), the relationship of these comorbidities and the psychiatric comorbidities with the long-term outcome of pediatric epilepsy (12–14), and the previously described methodological problems involved in designing studies on stress and seizures emphasize the need to use biomarkers, such as saliva samples of cortisol levels, to identify children at risk for stress sensitivity.

by Rochelle Caplan, MD

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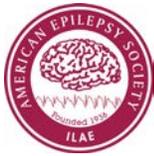
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