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Increased hair cortisol and antecedent somatic complaints in children with a first epileptic seizure

Ioannis Stavropoulos [a,b,*], Panagiota Pervanidou [c], Charalampos Gnardellis [d], Nomiki Loli [b], Virginia Theodorou [b], Aimilia Mantzou [e], Faye Soukou [e], Olga Sinani [b], George P. Chrousos [a,c,e]

[a] The Science of Stress and Health Promotion, School of Medicine, National and Kapodistrian University of Athens and Biomedical Research Foundation, Academy of Athens, Soranou Ephessiou Str. 4, 11527 Athens, Greece
[b] Department of Pediatric Neurology, "Aghia Sophia" Children's Hospital, 11527 Athens, Greece
[c] Unit of Developmental and Behavioral Pediatrics, First Department of Pediatrics, School of Medicine, National and Kapodistrian University of Athens, "Aghia Sophia" Children's Hospital, 11527, Athens, Greece
[d] Technological Educational Institute of Western Greece, 30200 Messolonghi, Greece
[e] Unit on Clinical and Translational Research in Endocrinology, First Department of Pediatrics, School of Medicine, University of Athens, "Aghia Sophia" Children's Hospital, 11527 Athens, Greece

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ABSTRACT

Objective: Stress is the most frequent seizure-precipitating factor reported by patients with epilepsy, while stressful life events may increase seizure susceptibility in humans. In this study, we investigated the relations between both biological and behavioral measures of stress in children with a first epileptic seizure (hereafter called seizure). We hypothesized that hair cortisol, a biomarker of chronic stress reflecting approximately 3 months of preceding exposure, might be increased in children with a first seizure. We also employed standardized questionnaires to examine presence of stress-related behavioral markers.
Methods: This was a cross-sectional clinical study investigating stress-related parameters in children with a first seizure (First Epileptic Seizure Group (FESG), n = 22) in comparison to healthy children without seizures (Control Group, n = 29). Within 24 h after a first seizure, hair samples were collected from children for the determination of cortisol. In parallel, perceived stress and anxiety and depressive symptoms were examined with appropriate self- and parent-completed questionnaires, and history of stressful life events during the past year was recorded. Emotional and behavioral problems were also assessed by parent-reported validated and widely-used questionnaires.
Results: Higher hair cortisol measurements were observed in the FESG than control children (7.5 versus 5.0 pg/mg respectively, p = 0.001). The former were more likely to complain of somatic problems than the latter (59.8 vs. 55.4 according to DSM-oriented Scale, p = 0.021); however, there were no differences in perceived stress and anxiety or depressive symptoms between the two groups. Using ROC analysis of hair cortisol measurements for predicting disease status, the maximum sensitivity and specificity were observed for a cut-off point of 5.25 pg/mg.
Significance: Increased hair cortisol indicates chronic hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis prior to the first seizure. This might have contributed to the epileptogenesis process and may help explain the higher incidence of antecedent somatic complaints in the first seizure group.

1. Introduction

Epilepsy and disorders associated with seizures are the most common neurological diseases of childhood, with the lifetime prevalence of seizure disorders in children estimated at about 1% [1]. These children may have developmental, mental, and physical comorbidities and are at high risk for emergency use of health care services [1]. The developing human brain is more vulnerable to seizures than the adult brain, as its excitatory functions mature earlier than the inhibitory ones [2].

Patients suffering from epilepsy and parents of children with epilepsy often report stress as a precipitating factor for their seizures. Emotional

Abbreviations: ACTH, Adrenocorticotropic Hormone; BMI, Body Mass Index; CBCL, Child Behavior Checklist; CDI, Children's Depression Inventory; CRH, Corticotropin-releasing Hormone; FESG, First Epileptic Seizure Group; HPA axis, Hypothalamic-Pituitary-Adrenal axis; LC-NE, Locus Coeruleus–Norepinephrine; PSS, Perceived Stress Scale; SNS, Sympathetic Nervous System; SRRS, Social Readjustment Rating Scale; STAI-C, State Trait Anxiety Inventory for Children.

* Corresponding author at: Niovis 3 Str., 16344 Athens, Greece.
E-mail addresses: ioannstavropoulos@gmail.com, istaurop@med.uoa.gr (I. Stavropoulos).

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stress as well as physical stress could both lead to seizure aggregation [3–8]. The majority of studies refer to adults and are based on self-reported questionnaires with a retrospective character or on prospective diary studies [9]; available data for children are limited. A prospective study has shown an increase in the frequency of seizures in children with epilepsy who live in war zones compared to those who live in areas without conflicts [10]. In a study by Van Campen et al. [7], parents of 153 children with active epilepsy completed questionnaires about demographic, developmental, and epilepsy characteristics of their children, including exposure to acute and/or chronic stress. These results revealed that half of the participants had increased susceptibility to seizures when they experienced stress, especially negative life events. A rise in seizure frequency in stressful periods was reported for 39% of children, while 37% of the parents reported that an acute stressor could have led to seizures [7]. It should be noted, however, that an older study in 100 adult Israeli citizens with known epilepsy showed a poor relation between psychological distress and seizure frequency during the First Gulf War [11].

In addition to clinical reports, animal studies have shown that exposure to stress for a brief period could either increase or decrease susceptibility to seizures, depending on the type of stressor. Thus, acute stress does not have a clear pro-epileptic or anti-epileptic effect [12]. However, the effects of chronic stress seem to be more stable. In a study in gerbils, chronic stress exposure was related to a clear increase in the frequency of seizures, but also to a progressive deterioration of its characteristics, such as an increase in frequency of generalized tonic-clonic seizures [13]. Similar findings have been reported in studies of other rodents exposed to chronic stress [12].

Early life stress seems to be an issue of special interest. There is a small amount of evidence in humans examining the linkage of prenatal or early life stress with epilepsy. The results of these studies are controversial and cannot prove a strong relation [14,15]. On the other hand, experimental studies have shown that prenatal or early life stress is consistently pro-convulsant in various animal models. In these studies, however, the type of stressor differed and the effect was stable as to the direction of increased susceptibility to seizures. Yet, injection of specific stress hormones did not reproduce the same direction-stable pro-convulsant effect [16].

Epilepsy has also been linked with depression and anxiety disorders, indicating possible common genetic, pathophysiologic, and environmental etiologic factors [1]. Especially for the associations between epilepsy and depression, a vast amount of evidence supports a steady and strong relation between the two diseases, both in children and adults [1,17–20]. Data show that epilepsy is a risk factor for the onset of depression, and that, conversely, individuals with a history of depression have a 4- 7-times higher risk of developing epilepsy [21]. This strong association could not be explained only by epilepsy imposing severe restrictions on daily life, for 2 reasons: first, it is a bidirectional phenomenon and, second, the severity of depression is related to the type and control of seizures. Therefore, common pathogenetic mechanisms might underlie both depressive and epileptic disorders [22].

Stress, the state of threatened homeostasis, is associated with acute activation of the hypothalamic-pituitary-adrenal (HPA) axis and the locus coeruleus-norepinephrine (LC-NE)/sympathetic-nervous-system (SNS). The majority of studies examining the underlying mechanism linking stress and epilepsy have focused on the activity of the HPA axis and the LC-NE/SNS on the circulating concentrations of their end-effectors cortisol and the catecholamines norepinephrine and epinephrine.

A seizure is a stressful life event per se, thus, adrenocorticotropic hormone (ACTH) and cortisol concentrations are increased after a partial or generalized seizure [23,24]. Patients with epilepsy show disinhibition of the HPA axis, a prolonged increase in cortisol concentrations and a sluggish return to the basal levels following the exposure to a stressor [24,25]. In addition, studies of HPA axis dysfunction in patients with epilepsy have shown high levels of ACTH and cortisol and low levels of allotetrahydrodeoxycorticosterone, a stress related steroid metabolite [12,26–28]. A recent experimental study revealed that epileptic mice had increased basal levels of corticotropin-releasing hormone (CRH) and corticosterone, which increased further after a seizure, and that this rise could increase seizure susceptibility [29].

There is accumulating evidence that hair cortisol is a valid biomarker of HPA axis function in chronic stress [30,31]. In contrast to serum and salivary cortisol measurements, cortisol concentrations in hair are not influenced by acute stress, and instead assess the integrated levels of cortisol over extended periods of time before sampling [30–32]. Thus, a 3-cm hair sample from the scalp end reflects the average exposure to cortisol for the preceding 3-month period (given that the human hair grows with a rate of about 1 cm per month). Further advantages are the easy storage of the sample at room temperature, the small quantity of sample required for the measures, and the non-invasive procedure that makes it suitable for the study of children [31].

In summary, there is an overwhelming amount of human and animal data connecting epilepsy with stress. Most of these data are derived from adult studies both based on self-reported questionnaires and/or measurements of serum stress hormone concentrations and are associated with the frequency and severity of epileptic seizures, hereafter called "seizures". Little evidence exists, however, on stress and new-onset epilepsy in children. We conducted a clinical study to assess the chronic function of the HPA axis via hair cortisol measurements reflecting the 3-month period before the first seizure. In parallel, we assessed perceived stress and anxiety and depression symptoms in participating children and their parents, as well as recorded the existence of major stressful life events during the preceding year.

The primary aim of this study was to identify determinants of disease status in association with the first seizure of children, including stress, i.e. perceived stress, anxiety and depressive symptoms, stressful life events, and hair cortisol concentrations reflecting the 3-month period prior to the first seizure.

2. Methods

2.1. Procedure and participants

This was a clinical cross-sectional study using a convenience sample of children with a first seizure and a healthy control group. The study group consisted of children evaluated at the Department of Pediatric Neurology of Aghia Sophia Children's Hospital, Athens, Greece for a first epileptic seizure (First Epileptic Seizure Group (FESG), $n = 22$). All patients recruited had characteristics of benign childhood epilepsy syndromes (i.e. Rolandic epilepsy, Panayiotopoulos syndrome) after clinical and electrophysiological evaluation made by experienced pediatric neurologists. A comparison group of healthy age-matched children without seizures (Control Group, $n = 29$) was recruited during the study period. The protocol was approved by the Ethics Committee of the “Aghia Sophia” Children's Hospital as consistent with the Declaration of Helsinki. Written informed consent was obtained from the parents of the participating children after being provided with detailed information about the study aims and procedures. Inclusion criteria were: children with a first-onset seizure, aged between 6 and 12 years old. Excluded were children with a symptomatic cause of seizures, such as fever, head injury, infection or structural brain lesion; those with underlying serious chronic illnesses, such as cardiac, hepatic and renal diseases; those receiving medications, such as corticosteroids, antidepressants, benzodiazepines and neuroleptics; and girls post-menarche. Children with developmental delays, autism spectrum disorders, and/or genetic or chromosomal abnormalities were also excluded from the study. Children in the FESG were assessed within 24 h after the seizure. Identical evaluations were performed in the control children.