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Seizure duration may increase thyroid-stimulating hormone levels in children experiencing a seizure

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Abstract

Objective: Variations in hormone levels are a direct effect of epileptic discharges in both animals and humans, and seizure can affect the hypothalamus–pituitary–thyroid axis. The purpose of this study was to determine which parameters could affect the alternation of thyroid hormones in children experiencing seizure.

Methods: We retrospectively reviewed the medical records of 181 pediatric patients with seizure and compared three thyroid hormones (serum thyroid-stimulating hormone [TSH], free thyroxine [fT4], and triiodothyronine [T3]) between initial (admission to hospital) and follow-up (2 weeks later) testing.

Results: Multivariable logistic regression models were used to determine which six parameters (gender, age, seizure accompanying with fever, seizure type, seizure duration, and anti-epileptic drug medication) could help to explain the higher initial TSH levels in pediatric seizure. Only seizure duration in patients with an increase in TSH levels was significantly longer compared with patients with normal TSH at the time of initial testing.

Conclusion: Neuronal excitability by seizure can cause thyroid hormonal changes, which likely reflects changes in hypothalamic function.

Keywords

Seizure duration, thyroid-stimulating hormone, thyroxine, triiodothyronine, pediatric seizure, hypothalamus, neuronal excitability, neuron

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Introduction

Seizure is one of the most common neurological problems in the pediatric period. The definition of seizure is a transient occurrence of signs and/or symptoms resulting from abnormal electrical activity in brain cells. Seizure may be followed by mitochondrial dysfunction and oxidative stress, and it causes dysfunction of excitatory glutamatergic and inhibitory GABAergic neurotransmission.[1] Seizure with an epileptic discharge can interact with cerebral function and affect memory and also lead to other medical complications. Variations in hormone levels are a direct effect of epileptic discharges in both animals and humans, and seizure can affect the hypothalamic-pituitary-thyroid (HPT) axis.[2–4] Postictal increases in prolactin, luteinizing hormone, follicle-stimulating hormone, and adrenocorticotrophic hormone have been revealed in patients with seizure.[5] One hypothesis accounting for these observations is that epilepsy or seizure may affect secretion of pituitary hormones. The GABAergic system modulates thyroid system function and influences all three levels of hypothalamus, pituitary, and thyroid axes.[6] Understanding endocrinological changes helps us to understand the cause of seizures, and HPT axis modulation may be important for determining the appropriate anti-seizure medication. The purpose of this study was to determine which parameters could affect the alteration of thyroid hormones in children experiencing seizure.

Methods

Patient

We retrospectively reviewed the medical records of 182 pediatric patients with seizure who attended the Daejeon St. Mary's Hospital from April 2014 to August 2017. The inclusion criteria were as follows: a blood sample that was drawn within 1 hour after initiation of the seizure, and follow-up thyroid hormone sampling that was conducted 2 weeks after the seizure. None of the patients were children with seizure resulting from metabolic abnormalities such as hypoglycemia, hyponatremia, hypocalcemia, or hypomagnesemia. Only one patient with congenital hypothyroidism who received thyroid replacement therapy was excluded from this study. This study was approved by the institutional review board (IRB) of the Catholic University of Korea, Daejeon St. Mary's Hospital (No. DC17RES10100). All participants and their parents provided written informed consent for clinical analyses.

Thyroid hormone assay

Serum thyroid-stimulating hormone (TSH), free thyroxine (fT4), and triiodothyronine (T3) were measured by electrochemiluminescence immunoassay using a COBAS e602 analyzer (Roche Diagnostics, Mannheim, Germany). The manufacturer's reference ranges were as follows: TSH, 0.27 to 4.2 μIU/mL; fT4, 0.93 to 1.7 ng/dL; and T3, 1.16 to 2.87 nmol/L. Non-parametric and robust reference intervals with the associated 90% confidence intervals for TSH and fT4, as measured using the Roche immunoassay, were provided previously.[7,8]

Statistical analyses

MedCalc Statistical Software Version 17.6 (MedCalc Software, Ostend, Belgium) was used for statistical analyses. Because serum TSH, fT4, and T3 levels between initial and follow-up (2 weeks later) measurements were not normally distributed based on the Kolmogorov–Smirnov and Shapiro–Wilk tests, continuous variables were summarized as the median with the interquartile range (IQR) or the range, and the results were compared using the Wilcoxon

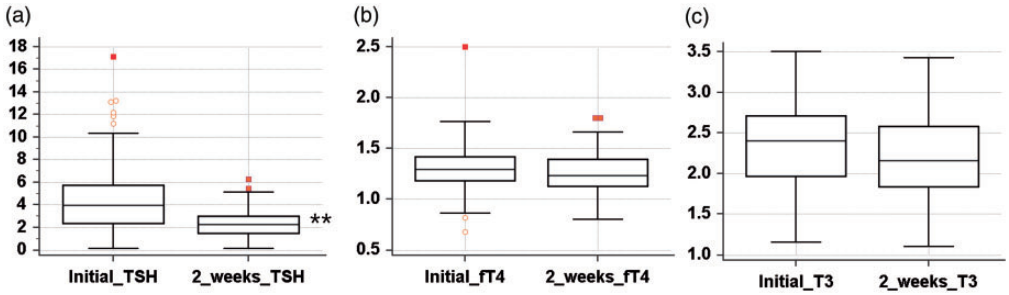

Figure 1. Median with interquartile range of (a) TSH (μIU/mL), (b) fT4 (ng/dL), and (c) T3 (nmol/L) between initial and follow-up (2 weeks later) testing; $^{**}P < 0.05$.

signed-rank test. To investigate which parameters influenced the change in thyroid hormone levels, a multivariate logistic regression analysis was performed. Nonsignificant predictors were removed using backward elimination (probability threshold for removal was 0.1). Spearman's correlation was tested to estimate the direction and strength of an association that existed between two continuous variables. Statistical significance was accepted at $P < 0.05$.

Results

Among the 181 patients, 117 were boys and 64 were girls. The median seizure duration was 2.8 minutes (range, 0.5–20.4 minutes). The seizures consisted of febrile seizure (66 patients, 36%), complex febrile seizure (14 patients, 8%), first nonprovoked seizure (30 patients, 17%), epilepsy (68 patients, 37%), and status epilepticus (3 patients, 1%). Among the three thyroid hormones, TSH levels was relatively higher at the time of initial testing compared with follow-up (2 weeks later) test results (median, 3.97 μIU/mL; IQR, 2.37–5.70 μIU/mL), and the TSH levels had decreased to within the normal range at the 2-week follow-up (median, 2.24 μIU/mL; IQR, 1.51–2.96 μIU/mL; $P < 0.0001$). Of the 181 children, 55 (30%) who experienced seizure showed an abnormally high TSH level (>4.2 μIU/mL for the reference range). However, the changes in fT4 and T3 levels were not statistically significant (Figure 1a–c).

Multivariable logistic regression models were used to determine which six parameters described in Table 1 could help to explain the higher initial TSH levels in pediatric seizure. In a backwards stepwise logistic regression model, only the seizure duration of patients with increased TSH levels was longer compared with patients with normal TSH at the time of initial testing, and this change was statistically significant ($P = 0.023$). However, in patients with febrile seizure, the change in the TSH levels was statistically significant at 2 weeks after the seizure compared with the initial level ($P = 0.001$), and no significant changes were found in fT4 and T3 levels. Similarly, in patients with nonfebrile seizures, changes in the TSH level were statistically significant at 2 weeks compared with the initial level ($P = 0.001$), and no significant changes were found in fT4 and T3 levels.

Discussion

The acute effects of seizure in the neuroendocrine system have been studied after focal and generalized seizure,[9,10] but the mechanisms underlying the hormonal changes remain unknown. Multiple factors such as seizure type, brain structural abnormalities, seizure duration, anti-seizure drugs, and

Table 1. Initial patient characteristics.

Children experiencing seizures	N = 181
Boys	117 (65%)
Age, years	4.5 (0.25–18)
Groups	
Febrile seizure*, N	80 (44%)
First attack, non-provoked seizure, N	30 (17%)
Known epilepsy, N	71 (39%)
Type of seizures	
Focal, N	63 (35%)
(TLE, FLE, OLE, and others)	(23, 14, 12, and 14)
Generalized, N	118 (65%)
Duration of seizures, minutes	2.8 (0.5–20.4)
Anti-epileptic drug medication, N	66 (36%)

*Children 6 months to 5 years of age.
TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy.

epileptiform discharge on EEG have been implicated in the hormonal alternations, but a definite cause has not been confirmed. The most characteristic feature of epilepsy is a steady increase in neuronal excitability that causes an unduly sustained and synchronous discharge by a group of neurons. Neuronal hyperactivity in a seizure stimulates the hypothalamus through specific neurotransmitter changes or through the release of other substances.[11] Additionally, seizure can impact to the hypothalamic–pituitary–gonadal/thyroid/adrenal axis and thereby alter the hormonal function and affect neurological health.[12–14] A postictal elevation in prolactin, luteinizing hormone, and follicle-stimulating hormone was shown in patients with both generalized tonic–clonic and focal seizures.[5] Plasma levels of adrenocorticotropic hormone, beta-endorphin, beta-lipotropin, prolactin, and vasopressin were increased shortly after the seizure.[15] Epileptic patients have an increased basal level of stress hormones including corticosterone, which is further increased after seizure.[5] Cortisol and prolactin levels were elevated in patients during the postictal period compared with control groups.[15,16] One study suggested that transient elevation of prolactin levels can differentiate an epileptic seizure from a nonepileptic movement that resembles seizure.[17] Seizure causes a significant and sustained elevation of thyrotropin releasing hormone (TRH) in specific extrahypothalamic rat brain regions related to epileptic foci such as the amygdala, hippocampus, pyriform cortex, and anterior cortex.[18] Electroconvulsive treatment induced an elevation in serum prolactin, adrenocorticotropic hormone, and thyrotropin in humans.[19] Animal studies have shown that electrical seizures modify monoamine mechanisms, including those that affect pituitary hormone release.[20] Rao et al.[21] reported that, concomitant with the increase in prolactin, an increase in serum thyrotropin was shown in patients with epileptic seizure. Because prolactin, thyrotropin, growth hormone, and cortisol levels increased during or after epileptic seizure, but not after a psychogenic nonepileptic seizure, then decreased to normal ranges, it is likely that epileptic seizures cause the impact on the hypothalamic-pituitary axis.

In this study, there was a significant increase in serum TSH levels following seizure. This suggests that neurogenic

stimulation is partly responsible for the postictal TSH release. In children with febrile seizure, GABA levels in cerebrospinal fluid were significantly lower compared with the control group within 2 hours after seizure,[22] and based on the above hypothesis, this could explain the elevated postictal TSH levels that were observed in our study. For the HPT axis, electroconvulsive treatment can cause an acute increase in thyrotrophic secretion that is related to the seizure duration.[23]

The reason for the hormonal changes is multifactorial. A complex, bidirectional interdependence exists between hormones and seizure, which is that hormones influence seizures, while seizures affect hormones and thereby disrupt endocrine function. The neuronal excitability during a seizure activates the hypothalamus either directly through specific neurotransmitter alternations or indirectly through the release of other substances. Hormones were affected by psychosocial factors, comorbidity, the use of anti-seizure medications, and the seizure. Some anti-seizure medications are associated with changes in thyroid function.[11] However, it is difficult to distinguish the direct effect of epileptic discharge, independent of the many factors that are involved. The mechanism underlying the transient, postictal increase of TSH in seizure is not fully understood. The postictal changes in serum TSH probably reflect alternations in the hypothalamic function. TRH is secreted by neurons that are located in the hypothalamus and it is transported to the anterior pituitary, where it drives TSH secretion.[1] TSH, in turn, stimulates thyroid hormone secretion. Because the hypothalamus and limbic systems have a functional connection, seizure involving the limbic system may contribute to making the HPT axis susceptible to changes by affecting TRH secretion. The postictal changes in serum TSH presumably reflect modulation of hypothalamic function by seizure.

In our study, seizure duration in patients with abnormally elevated TSH was longer compared with patients with normal TSH levels ($P = 0.023$). Prolonged neuronal excitability is thought to affect in hormonal changes. In an uncontrolled seizure, it is important to determine the hormonal alternations early to prevent endocrinological problems. Serum TSH does not completely differentiate seizure from syncope or seizure-like activities. TSH elevation after seizure may help to distinguish seizures from non-epileptic seizures. The exact anatomical, functional, and pharmacological relationships between seizure and TSH should be further studied in seizure patients. Pediatric neurologists should keep in mind and consider the endocrine effects that are induced by the seizure. However, data were insufficient to establish the TSH release pattern after seizure. Further research is required to demonstrate transient TSH elevation after seizure. The exact anatomical, functional, and pharmacological associations between seizures and TSH secretion should be further investigated.

Our study had several limitations. This study was retrospective and did not control for the effects of anti-seizure medication on the HPT axis. We also did not know the pre-seizure thyroid function test results. Most patients had febrile seizure (44%), and therefore, many patients had a fever. We did not check other pituitary hormones and the number of patients included in the study was relatively small.

Conclusions

In this study, we reviewed thyroid function tests from children who had seizures. We found that TSH levels were increased after a seizure, and in the group with abnormally elevated TSH, the seizure duration was significantly related to the TSH increase. We suggest that the seizure can affect the HPT axis and transiently alter TSH levels.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Tamijani SM, Karimi B, Amini E, et al. Thyroid hormones: Possible roles in epilepsy pathology. *Seizure* 2015; 31: 155–164. DOI: 10.1016/j.seizure.2015.07.021.
2. Feeney DM, Gullotta FP and Gilmore W. Hyposexuality produced by temporal lobe epilepsy in the cat. *Epilepsia* 1998; 39: 140–149.
3. Herzog AG. A relationship between particular reproductive endocrine disorders and the laterality of epileptiform discharges in women with epilepsy. *Neurology* 1993; 43: 1907–1907.
4. Banczerowski P, Csaba Z, Csernus V, et al. Lesion of the amygdala on the right and left side suppresses testosterone secretion but only left-sided intervention decreases serum luteinizing hormone level. *J Endocrinol Invest* 2003; 26: 429–434.
5. Luef G. Hormonal alterations following seizures. *Epilepsy Behav* 2010; 19: 131–133. DOI: 10.1016/j.yebeh.2010.06.026.
6. Wallis K, Sjögren M, Van Hogerlinden M, et al. Locomotor deficiencies and aberrant development of subtype-specific GABAergic interneurons caused by an unliganded thyroid hormone receptor α1. *J Neurosci* 2008; 28: 1904–1915.
7. Henderson MP and Grey V. Establishing and evaluating pediatric thyroid reference intervals on the Roche Modular Analytics E 170 using computational statistics and data-mining techniques. *Clin Biochem* 2011; 44: 767–770. DOI: 10.1016/j.clinbiochem.2011.05.006.
8. Kulasingam V, Jung BP, Blasutig IM, et al. Pediatric reference intervals for 28 chemistries and immunoassays on the Roche cobas 6000 analyzer–a CALIPER pilot study. *Clin Biochem* 2010; 43: 1045–1050. DOI: 10.1016/j.clinbiochem.2010.05.008.
9. Pritchard PB 3rd, Wannamaker BB, Sagel J, et al. Endocrine function following complex partial seizures. *Ann Neurol* 1983; 14: 27–32.
10. Wroe S, Henley R, John R, et al. The clinical value of serum prolactin measurement in the differential diagnosis of complex partial seizures. *Epilepsy Res* 1989; 3: 248–252.
11. Svalheim S, Sveberg L, Mochol M, et al. Interactions between antiepileptic drugs and hormones. *Seizure* 2015; 28: 12–17. DOI: 10.1016/j.seizure.2015.02.022.
12. Pritchard PB 3rd. The effect of seizures on hormones. *Epilepsia* 1991; 32: S46–S50.
13. Herzog AG. Altered reproductive endocrine regulation in men with epilepsy: Implications for reproductive function and seizures. *Ann Neurol* 2002; 51: 539–542. DOI: 10.1002/ana.10230.
14. O'Toole KK, Hooper A, Wakefield S, et al. Seizure-induced disinhibition of the HPA axis increases seizure susceptibility. *Epilepsy Res* 2014; 108: 29–43. DOI: 10.1016/j.eplepsyres.2013.10.013.
15. Aminoff MJ, Simon RP and Wiedemann E. The hormonal responses to generalized tonic-clonic seizures. *Brain* 1984; 107: 569–578.
16. Sifianou P, Mengreli C, Makaronis G, et al. Prolactin levels in febrile and afebrile seizures. *Eur J Pediatr* 1995; 154: 925–927.
17. Trimble MR. Serum prolactin in epilepsy and hysteria. *Br Med J* 1978; 2: 1682.
18. Shapiro S, Kubek M, Sanders S, et al. Regional changes in central nervous system thyrotropin-releasing hormone after pentylenetetrazol-induced seizures in dogs. *Neurosurgery* 1992; 31: 935–939; discussion 939.
19. Parra A, Velasco M, Cervantes C, et al. Plasma prolactin increase following electric stimulation of the amygdala in humans. *Neuroendocrinology* 1980; 31: 60–65.

20. Grahame Smith DG, Green AR and Costain DW. Mechanism of the antidepressant action of electroconvulsive therapy. *Lancet* 1978; 1: 254–257.
21. Rao ML, Stefan H and Bauer J. Epileptic but not psychogenic seizures are accompanied by simultaneous elevation of serum pituitary hormones and cortisol levels. *Neuroendocrinology* 1989; 49: 33–39. DOI: 10.1159/000125088.
22. Löscher W, Rating D and Siemes H. GABA in cerebrospinal fluid of children with febrile convulsions. *Epilepsia* 1981; 22: 697–702.
23. Dykes S, Scott AI, Gow SM, et al. Effects of seizure duration on serum TSH concentration after ECT. *Psychoneuroendocrinology* 1987; 12: 477–482.