Hormonal Changes In Epileptic Children with Primary Generalized Tonic-Clonic Seizures
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Abstract
We studied the hormonal changes in 24 epileptic children with primary generalized tonic-clonic seizures. Their ages ranged between 3 and 16 years with a mean of 9.08+/- 4.05 years, 13 were males and 11 were females. Electroencephalographic studies showed high voltage slow waves pattern in 17 patients while computed tomography of brain was normal in all cases. As regards the acute changes following an attack, we found significant elevation of both prolactin and ACTH levels after 20 minutes, 1, 2, and 3 hours of seizure compared with baseline level (after 24 hours). The increase in plasma ACTH level was accompanied with significant elevation in plasma cortisol level after 1, 2 and 3 hours of the seizure onset. Plasma TSH level after 1 and 2 hours were significantly higher than the baseline value. Early postictal significant elevation of growth hormone levels was observed after 20 minutes and 1 hour. Concerning chronic hormonal changes, we found that the baseline levels of prolactin, ACTH and cortisol in epileptic children with generalized tonic-clonic seizures were significantly higher than the levels recorded in healthy children while no significant differences could be detected as regards TSH and growth hormone. We suggest conducting other studies in pediatric age to assess the role of neurotransmitters in producing the variable hormonal changes following the onset of seizures.

Introduction
Epilepsy in children is not only a common problem involving seizures, but is also a disorder with many other complications. As seizure affects many brain functions, there has been long-standing interest in its relationship with endocrine system. The extensive anatomical and physiological connections between the limbic system and hypothalamus provide the basis of the effects of seizures on the neuroendocrine system (1,2). Cells, fibers and terminals containing hypothalamic peptides are found throughout the cerebral cortex and limbic system (3). Most informations concerning endocrine changes following seizures derive from studies of electrochemically induced attacks in animals (4-8) and from electroconvulsive therapy (ECT) in adult patients (9-12). The most unambiguous chronic endocrine changes with epilepsy are related to the reproductive system and prolactin (9-15) while other hormonal changes in epileptic patients especially in children have not been studied thoroughly and need to be evaluated. This study was undertaken to estimate the hormonal changes (acute and chronic) that follow generalized tonic-clonic seizures in epileptic children.

Subjects and Methods
This study included twenty four well documented cases of generalized tonic-clonic seizures who were followed up in Pediatric Outpatient Clinic for Epilepsy, King Fahd Central Hospital, K.S.A. and admitted for control of their repeated convulsive attacks. The studied cases ranged in age between 4 and 16 years and all were receiving either mono- or polytherapy with combination of anticonvulsant drugs. None of the patients were taking any other medications or under treatment for any other organic disorders. Selected cases were subjected to: (1) - Full medical history including description, duration and frequency of convulsive attacks. (2) - Thorough clinical examination with exclusion of children with any signs of neurological deficits. (3) - A description of the seizure pattern was recorded at the time of the attack by a member of the nursing staff experienced at observing patients with epilepsy and only cases with generalized tonic-clonic seizures were included in the study. (4) - Electroencephalogram during seizure - free period. (5) - Computed tomography of the brain. We tried to obtain blood samples at fixed intervals of...
Results

This study included 24 epileptic children presented with generalized tonic-clonic seizures and 10 healthy children, age and sex matched, who served as control. Electroencephalographic studies were normal in 7 cases and showed high voltage slow waves in 17 patients while all cases had normal computed tomographic (CT) images of the brain. Table (I) and figures 1, 2 and 3 portray the acute changes in the mean levels of the hormones recorded in epileptic children after 20 min., 1, 2, and 3 hours of the seizure onset compared with the mean baseline level recorded after 24 hours of seizure-free period. The group data indicated that the plasma prolactin level showed a sharp rise in the first 20 minutes after the seizure onset (generally to between 300% and 400% of baseline values in > 90% of cases), remained elevated at 1, 2 and 3 hours with significant difference from the baseline levels. The level of TSH after 20 minutes increased in 18 patients but the mean value was significantly higher than the baseline only after 1 and 2 hours then decreased and subsequently did not differ significantly from the baseline level. We found significant elevations above baseline for plasma ACTH at each time point. ACTH level increased in 21 cases after 20 minutes and after 1 hour in the remaining 3 cases. Following the elevations of plasma ACTH, plasma cortisol levels after 1, 2 and 3 hours were significantly higher than the baseline. The plasma growth hormone data for the epileptic children suggested an early postseizure (after 20 min. and 1 hour) elevations that reached statistical significance. Review of the individual data suggested that in 3 patients there was no change over time whereas in 21 others the growth hormone level did appear to be elevated after the seizure, subsequently declining with time. Table (II) shows comparison between the patients and healthy children concerning the mean baseline levels of the assayed hormones. Prolactin, ACTH and cortisol were statistically significantly higher in children with generalized tonic-clonic seizures while no significant difference could be detected as regards TSH or growth hormone.

Discussion

In this research we tried to study the acute and chronic hormonal changes in epileptic children with primary generalized tonic-clonic seizures. There was an immediate and significant rise in serum prolactin (PRL) following generalized tonic-clonic seizure in more than 90% of our patients and this elevation ranged between 3 and 4 times baseline value. This finding is in harmony with those reported by other researchers that PRL rises rapidly following spontaneous and induced generalized seizures in human beings reaching a peak between 15 - 25 minutes after the seizure and that these prolactin changes can serve as a reliable confirmation of the
Table (I) : Mean and standard deviation of hormonal values in 24 epileptic children 20 min., 1, 2, 3 and 24 hours after generalized tonic-clonic seizure.

<table>
<thead>
<tr>
<th></th>
<th>20 minutes</th>
<th>1 hour</th>
<th>2 hours</th>
<th>4 hours</th>
<th>24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>65.9 **</td>
<td>49 *</td>
<td>35 *</td>
<td>26 *</td>
<td>19</td>
</tr>
<tr>
<td>ng / ml</td>
<td>(7.56)</td>
<td>(6.48)</td>
<td>(4.52)</td>
<td>(6.0)</td>
<td>(3.9)</td>
</tr>
<tr>
<td>TSH mU/L</td>
<td>3.72</td>
<td>4.87 *</td>
<td>5.22 *</td>
<td>4.00</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>(0.97)</td>
<td>(0.92)</td>
<td>(0.82)</td>
<td>(1.03)</td>
<td>(0.78)</td>
</tr>
<tr>
<td>ACTH pg/ml</td>
<td>85 *</td>
<td>73 *</td>
<td>67 *</td>
<td>52 *</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>(11.94)</td>
<td>(10.65)</td>
<td>(10.13)</td>
<td>(9.79)</td>
<td>(9.38)</td>
</tr>
<tr>
<td>Cortisol nmol/L</td>
<td>317 (24.4)</td>
<td>365 *</td>
<td>405 *</td>
<td>345 *</td>
<td>310</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(28.6)</td>
<td>(28.2)</td>
<td>(30.3)</td>
<td>(30.2)</td>
</tr>
<tr>
<td>Growth H. mU/L</td>
<td>7.76 *</td>
<td>6.82 *</td>
<td>6.5</td>
<td>6.36</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>(1.9)</td>
<td>(1.2)</td>
<td>(1.5)</td>
<td>(1.14)</td>
<td>(1.04)</td>
</tr>
</tbody>
</table>

* significant compared to baseline value (24 hours value)  P < 0.05  ** significant  P < 0.0001 .

Figure (1) : Plasma prolactin response to a single generalized tonic-clonic seizure. Arithmetic mean for the group of patients studied is shown . Asterisks * indicate significant difference from baseline values at 24 hours .
Figure (2) : Plasma TSH and growth hormone responses to a single generalized tonic-clonic seizure. Arithmetic mean of studied patients is shown. Asterisks * indicate significant difference from baseline values at 24 hours.

Figure (3) : Plasma ACTH and cortisol responses to a single generalized tonic-clonic seizure. Arithmetic mean for the group of patients studied is shown. Asterisks * indicate significant difference from baseline values at 24 hours.
occurrence of a seizure but its absence does not exclude completely the occurrence of a seizure as PRL rises only with the limbic seizures and that bilateral limbic seizure activity was usually required before PRL increases were seen (19, 21-25). In our study PRL level after 3 hours was still significantly higher than the baseline value which is different from what reported by others (13, 16) in epileptic adults that PRL level is reverting to normal in about 2 hours after seizure. Furthermore, we found that the mean baseline PRL level in epileptic children is significantly higher than that in healthy control which is the same result recorded by Molaie M and his colleagues (26). This finding supports the notion that interictal discharges in epileptics with primary generalized tonic-clonic seizures spread to suprahypothalamic structures, such as the limbic system, thus a moderate increase in PRL baseline level may be the result of interference by these discharges with either PRL inhibitory mechanisms mediated by dopaminergic pathway (27) or PRL stimulating factors such as neuropeptides (28). The level of TSH increased after 20 minutes of seizure in 18 cases but reached significant difference only at 2 time-points; after 1 and 2 hours while the difference between the baseline values in both patients and control was not statistically significant. The same finding was reported by other investigator (29) who found a significant increase in TSH only 30 minutes after electroconvulsive therapy (ECT) and explained it by the antidopaminergic effect of ECT at either the pituitary or the hypothalamic level. We found significant elevations above the baseline for plasma ACTH at each time point followed by a significant increase in plasma cortisol after 1 hour of the seizure onset and this difference was still significant after 3 hours. These findings are consistent with the results reported by other investigators (30-33) who found elevation of plasma ACTH and cortisol levels following ECT and generalized tonic-clonic seizures. Furthermore, like our finding concerning prolactin, the mean baseline plasma ACTH and cortisol levels in epileptic children with primary generalized tonic-clonic seizure were significantly higher than the baseline levels in healthy children. This result is similar to that described in one of the most interesting studies concerning the chronic changes in endocrine functions in adults with epilepsy which concluded that patients with intractable epilepsy had higher mean plasma ACTH and cortisol concentrations than normal adults. This consistent chronic elevation of PRL and ACTH can be explained by the presence of common pathway or mechanism involved in pituitary release of PRL and ACTH (34). Acute and chronic changes in growth hormone level had a special interest in our study due to its direct impact on growth and because the previously mentioned data concerning changes in this hormone following ECT are conflicting. Unlike others (13, 18, 35 - 37) who did not find elevation in growth hormone level postictally in adults, our results showed significant elevation in G.H after 20 minutes and 1 hour in 21 children with epilepsy. Our result is supported by other researchers (25, 38, 39) who

<table>
<thead>
<tr>
<th></th>
<th>Epileptic cases (n = 24)</th>
<th>Control (n = 10)</th>
<th>t Value</th>
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</thead>
<tbody>
<tr>
<td>Prolactin ng/ml</td>
<td>19(3.9)</td>
<td>12.6(3.27)</td>
<td>4.93*</td>
</tr>
<tr>
<td>TSH mU/L</td>
<td>3.7(0.78)</td>
<td>3.58(1.19)</td>
<td>0.29</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>43(9.38)</td>
<td>35(10.17)</td>
<td>2.13*</td>
</tr>
<tr>
<td>Cortisol nmol/L</td>
<td>310 (30.3)</td>
<td>243(85.8)</td>
<td>2.40*</td>
</tr>
<tr>
<td>Growth H. mU/L</td>
<td>6.0 (1.04)</td>
<td>5.72 (3.24)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

* Significant (P < 0.05)
described a significant increase in growth hormone level within 30 minutes of ECT in adults. This variability in hormonal changes makes it difficult to be attributed completely to non-specific stress reactions which cannot be excluded at the same time as different classes of stress may produce different patterns of hormonal responses. Hypothalamic peptides now are known to act in other parts in the brain as neurotransmitters or neuromodulators and their role in hormonal responses to generalized seizures should be considered. The results of this study clearly imply that the neuroendocrine system is susceptible to pathologic plasticity as a result of generalized tonic-clonic seizures. This task is particularly important for children where the consequences of seizure-related neuroendocrine disruption have greater significance for the developing nervous system. It is suggested that attempts to alter hormonal release following seizures using various drugs that block neurotransmitters may lead to a further understanding of the neurochemistry of epilepsy that might minimize the impact of seizures on the quality of life.

References

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ACKNOWLEDGEMENT

The authors would like to express their deep appreciation and thanks to their patients and colleagues in K.F.C.H . Thanks to our nursing staff : Mr Ashraf Taqie Al-Din , our computer programmer and Mr FA . Lukammbi ( M.Phil , FIMLS , London ) for his efforts in the hormonal assay