**Effect of Antiepileptic Drugs on Serum Serotonin Level among Children with Idiopathic Epilepsy**

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**Abstract**

**Background:** Epilepsy represents a heterogeneous group of disorders with diverse etiologies, electrographically, behaviorally seizure patterns and pharmacological sensitivities.

**Objectives:** To evaluate the status of serotonin in newly diagnosed cases of idiopathic epilepsy and to correlate these levels to the response to therapy.

**Methodology:** An interventional clinical study was performed on 30 children with idiopathic epilepsy on their first presentation before administration of any AED and further follow-up after 3 and five months of AED therapy. Thirty apparently healthy for age and sex matched to epileptic children served as controls.Serum levels of serotonin were estimated to the included subjects. Subjects were able to give a written informed consent prior to participation in this study.

**Results:** There was significant good response to AEDs in idiopathic epileptic children since the increase in time intervals from the last seizure (P<0.001). Chalfont severity scales were significantly decreased after starting AED therapy and throughout all stages of the study baseline; 3 and 5 months follow up (P<0001).Serum serotonin median levels were increased after using AEDs, especially after 5 months from the base- line, with further significant increase in levetiracetam group (P=0.036). Median levels of serotonin were not significantly different among baseline levels, and after 3 - 5 months. However, there was a significant decrease in the median serotonin levels after 5 months in comparison to the group after 3 months; reaching almost to the baseline levels (P=0.023).

**Conclusion:** Serum serotonin levels among epileptic children are controversial and it might be multifactorial affected by using antiepileptics and therapy duration.

**Keywords:** Serum serotonin, Antiepileptic drugs, Epilepsy, Children.

**Introduction:**

Epilepsy represents a heterogeneous group of disorders with diverse etiologies, electrographically, behaviorally seizure patterns and pharmacological sensitivities. Although the causes of epilepsy are many, the fundamental disorder is secondary to abnormal synchronous discharges of a network of neurons. Epilepsy can be caused by either abnormal ionic conductance or other alteration of neuronal membranes, or an imbalance between excitatory and inhibitory influences ***(Bagdy et al., 2007).***

Serotonin 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter. Biochemically derived from tryptophan, serotonin is primarily found in the gastrointestinal (GI) tract, platelets, and in the central nervous system (CNS) of animals including humans. It is popularly thought to be a contributor to feelings of well-being and happiness ***(Young, 2007).***

In the central nervous system (CNS), serotonin modulates attention, behavior, and thermoregulation. In the peripheral nervous system, serotonin is produced primarily by intestinal enterochromaffin cells and is involved in regulating gastrointestinal motility, vasoconstriction, uterine contraction, and bronchoconstriction. Serotonin is also found in platelets where it promotes platelet aggregation ***(Mason et al., 2000).***

The functions of 5-HT on the CNS are numerous and appear to involve control of appetite, sleep, memory and learning, temperature regulation, mood, behaviour, cardiovascular function, muscle contraction, endocrine regulation, maturation of neuronal and glial cells and synaptic connections and epilepsy ***(Azmitia and Whitaker-Azmitia 1999).***

There is a decrease in 5-HT1A receptor binding on PET scanning in patients who have epilepsy and depression ***(Sargent et al., 2000),*** and this decrease is greater in those patients with both conditions compared to temporal lobe epilepsy alone ***(Hasler et al., 2007).*** In patients with comorbid epilepsy and depression there is decreased binding in the epileptic focus, as well as extension into extra-lesional limbic structures ***(Theodore et al., 2006).*** In both conditions it has been suggested that there is deficient serotonergic (and noradrenergic) neurotransmission ***(Kanner, 2009).***

**Methodology:**

**Design:**

This is an interventional clinical study, conducted on thirty children with idiopathic epilepsy who were followed up in the pediatric Neurology Outpatient Clinic, Pediatrics Hospital; Ain Shams University, from November, 2012 to April, 2013.

***Subjects will be divided into 2 groups:***

**Group (1):** includes 30 newly diagnosed cases with idiopathic epilepsy on their first presentation before administration of any AED and further follow-up after 3 and 5 months of AED therapy(According to International League against Epilepsy guidelines of epilepsy treatment; 2006).They were18 males and 12 females. Their age ranged from 3.5 to 15 years.

 **Group (2):** includes 30 children recruited from sibs of patients who were apparently healthy for age and sex matched to epileptic children served as controls. They were 9 males and 21 females. Their age ranged from 4 to 11 years.

**Inclusion Criteria:** children and adolescents aged from 5 to 15 years old, newly diagnosed cases, Regular attendee of the clinic and those who offered their acceptance of enrollment. Healthy controls will also be recruited.

**Exclusion Criteria:** patients with any condition that may cause an elevation of serotonin like serotonin syndrome or the use of drugs affecting serotonin level.

***All studied children were investigated including,*** *c*omplete blood count and liver function tests, Electroencephalogram (EEG and neuroimaging:Computed tomography (CT) or Magnetic resonance imaging (MRI) of the brain, if needed. **Serum levels of serotonin by ELISA method** at the first presentation of the child and later after three and five months follow-up. Statistical analysis was done using SPSS ver.16. All ethical considerations were taken ( A written informed consent prior to participation in thisstudy.

**Results:**

Results of this study showed that twenty four cases (80%) had generalized tonic clonic convulsions (GTC) while 6 cases (20%) had focal convulsions: 4 cases (13%) had complex partial seizures (CPS), 2 cases (7%) had focal convulsions with secondary generalization.

 Figure (1) shows that the mean serum serotonin level is not significantly decreased in epileptic children as compared to controls (P <0.05).

***Fig (1):*** Mean Serum Serotonin levels in Idiopathic Epileptic Patients and Controls

Table (1) shows that there are significant good response to AED in idiopathic epileptic patients since the increase in the time intervals from the time of last seizure (P<0.001).

**Table (1): Median values of time intervals from the time of last seizure in Idiopathic Epileptic Patients.**

|  |  |  |
| --- | --- | --- |
|  | **Last seizure** | **Wilcoxon Signed Ranks Test** |
| **Range** | **Median** | **Interquartile Range** | **Z** | **P-value** |
| **Baseline**  | 1.000 | - | 20.000 | 6.000 | 4.250 | 4.358 | <0.001\* **P1** |
| **After 3m.** | 10.000 | - | 90.000 | 65.000 | 34.250 | 4.075 | <0.001\* **P2** |
| **After 5m.** | 3.000 | - | 150.000 | 110.000 | 68.750 | 3.096 | <0.001\* **P3** |

P1: Baseline Group Vs after 3 months. / P2: Baseline Group Vs after 5 months./ P3: After 3 month Group Vs after 5 months.

Table (2) shows that the median levels of serotonin are not significantly different among baseline levels and after 3 - 5 months. However, there is a significant decrease in the median serotonin levels after 5 months in comparison to the group after 3 months; reaching almost to the baseline levels (P<0.023).

**Table (2): Median values of Serotonin in different stages of follow up at 3 and5 months after starting AED therapy in Idiopathic Epileptic Patients.**

|  |  |  |
| --- | --- | --- |
|  | **serotonin ng/ml** | **Wilcoxon Signed Ranks Test** |
| **Range** | **Median** | **Interquartile Range** | **Z** | **P-value** |
| **Baseline**  | 1.000 | - | 100.000 | 41.500 | 60.475 | -1.687 | 0.092 **P1** |
| **After 3m.** | 0.500 | - | 100.000 | 65.000 | 56.750 | -0.156 | 0.876 **P2** |
| **After 12m.** | 2.500 | - | 95.000 | 44.000 | 49.500 | -2.276 | 0.023\* **P3** |

P1: Baseline Group Vs after 3 months./ P2:Baseline Group Vs after 5 months./P3: After 3 month Group Vs after 5 months

Table (3) shows that serum serotonin median levels are generally increased after the use of AEDs especially after 5 months from the base line, with further significant increase in levetiracetam group (P=0.036).

**Table (3): Median values of Serotonin with different types of AEDs at 3 and 5 months after starting AED therapy in Idiopathic Epileptics**.

|  |  |  |
| --- | --- | --- |
| **Drugs**  | **Serotonin ng/ml** | **Kruskal-Wallis Test** |
| **Range** | **Median** | **Interquartile Range**  | **X2** | **P-value** |
| **Baseline**  | VPA | 1.0 | - | 100.0 | 38.00 | 82.35 | 1.347 | 0.510 |
| CBZ | 32.0 | - | 72.0 | 55.00 | 32.50 |
| LTM | 38.0 | - | 100.0 | 69.00 | 80.45 |
| **After 3m.** | VPA | 0.50 | - | 100.0 | 65.00 | 60.25 | 0.187 | 0.911 |
| CBZ | 38.0 | - | 90.0 | 65.00 | 41.50 |
| LTM | 40.0 | - | 100.0 | 70.00 | 65.45 |
| **After 5m.** | VPA | 5.00 | - | 90.0 | 50.00 | 49.75 | 6.654 | 0.036\* |
| CBZ | 2.50 | - | 35.0 | 22.00 | 24.38 |
| LTM | 80.0 | - | 95.0 | 87.50 | 50.54 |

VPA: Valproate/ CBZ: Carbamazepine/ LTM:Levetiracetam.

Chalfont severity scales are significantly decreased after starting the AED therapy and throughout all stages of the study; 3 and5 months (P<0.001). Correlation matrix among Serotonin levels, Chalfont severity scale, dose of AED levels and Disease duration are not significant. However, Serum Serotonin showed mild negative correlation with Chalfont Severity Scale (r;-0.404, P<0.062).

**Discussion:**

Studied children were 60% males and 40% females with a male to female ratio of 1.5:1.These findings coincide with the results of **El-Khayat et al. (1994)** reported a male to female ratio in primary school children suffering of epilepsy about 1.4:1.**Luders et al. (2003)** found that males were more affected than females.

Studied children had an age ranged from 3.5 to 15 years (Mean= 6.87 + 2.88 years). This is consistent with the overall incidence of idiopathic childhood epilepsy from birth to 16 years is approximately 4 /10,000 children per year ***(Camfield et al., 1996),*** and 5 to 7 cases /10,000 children per year ***(Cowan, 2002).*** The incidence in the first year of life is 120 /100.000, between one and ten years of age, the incidence is 40-50/ 100.000 and then drops in the older ages***(Hauser and Hesdorfer, 1990).*** The cumulative lifetime incidence of epilepsy is 3% and more than half of cases begin in childhood ***(Johnston, 2008).*** It is estimated that 0.5-1% of all children have epilepsy, with the majority presenting during infancy or early childhood ***(Ottman, 2001).***

The current study showed that there was a positive family History in 6.6% of studied children, this is consistent with **Panayiotopoulos (2005)**who mentioned that idiopathic epilepsy is epilepsy of predominantly genetic origin and in which there are no gross neuroanatomical and/or neuropathological abnormalities***.*** It has been known for a long time that genetic factors play a major role in the etiology of idiopathic epilepsy***.***

Results of the present study showed that most of children (80%) had generalized tonic clonic (GTCS) while 20% had focal convulsions; 6.67 % out of them had focal convulsions with secondary generalization. This is in concordance with**Kotsopoulos et al. (2002**) who reported that GTCS or various types of partial seizures dominate about 75% of childhood epilepsy syndromes. Absence epilepsy accounts for approximately 15%, and other generalized epilepsies account for only 10***%***.

The present study showed that most of children were clinically responsive on monotherapy for the whole period of the study, this is evidenced by the significant good response to AED in idiopathic epileptic patients since the increase in the time intervals from the time of last seizure (P>0.001) throughout the whole study.This is in agreement with **Benbadis (2006),** who demonstrated that monotherapy was effective in 80 to 90 percent of idiopathic generalized epilepsy (IGE) and that the response often occurs at relatively low doses of these medications.

In addition, results of the present study showed that Chalfont severity score dramatically decreased with further follow throughout all stages of the study (0, 3and 5 months) indicating that seizure severity is decreasing by time and that our patients were better controlled and responsive to AEDs.

In the mean time; this is reflected on the "last seizure" in days as a marker of controllability which is subsequently increased from a median of 6 - 65 to 110 days (P <0.05), and this agrees with ***Berg and his colleagues*** in 2010 who mentioned that idiopathic epilepsy is pharmacoresponsive.

Results of the present study showed that most of the patients (73.3%) were on valproate as a monotherapy. This is in agreement with **Benbadis et al. (2006),** who reported that valproate is considered the "first line" choice for treatment in idiopathic generalized epilepsy (IGE)

Those patients who are on valproate had a serotonin level at o month of 38ng/ml, with an initial increase up to 65ng/ml in the 3 month follow up; to explain these results, two hypotheses are proposed: an inhibiting effect of anticonvulsant drugs on 5-HT catabolizing enzymes, or an increased tryptophan in CNS/tryptophan in the blood ratio, induced by therapy). But later on, after the 5th month it declined (50ng/ml) but not reaching the original level.

These findings are inconsistent with the study of **Chiodi et al.(1981);** who studied serotonin level in a 32 epileptic patients, receiving anticonvulsant therapy compared to normal controls. They found that 5-HT blood levels in epileptics were significantly decreased in the second measurement probably in consequence to the use of anticonvulsant drugs. Moreover 5-HT blood levels decreased more outstandingly in those patients who were treated with more than one anticonvulsant drug.

Regarding the patients who were on carbamazepine had a serotonin level at o month of 55ng/ml, with an initial increase up to 65ng/ml in the 3 month follow up but later on the 5th month it declined (22ng/ml) even lower than the original level. These findings are partially supported by **Dailey et al. (1997)** claiming that carbamazepine releases serotonin as part of the pharmacodynamic action by which it suppresses convulsions in GEPRs and it releases serotonin in non-epileptic Sprague-Dawley rats. Trying to explain why did the serotonin level decrease that much to the extent being below the original level of drug prescription, is that serotonin stores are depleted and consumed at some point of time during the treatment.

While those who received levetiracetam had a serotonin level at o month of 69ng/ml, with an increase up to 70ng/ml in the 3 month follow up and later on the 5th month it elevated again to 87ng/ml, this continuous increase in the level of serotonin can be justified by the mechanism of action of levetiracetam which is a serotoninergic one.

The results of the current study showed that at recruitment the mean serum levels of Serotonin were lower (47.14+35.10 ng/ml) than that of the control group (52.5+23.9ng/ml). Yet, this finding is not statistically significant. This finding suggests that serotonin levels may be falling during the process of epileptogenesis, confirming that serotonin plays a role in pathophysiology of epilepsy. These findings were supported by the earlier finding of **Pranzatelli et al. (1995)** who reported low concentrations of the serotonin metabolite, 5-hydroxyindoleactic acid in CSF of patients with progressive myoclonus epilepsy, suggesting a hypofunctional serotonergic neurotransmission.

Correlation matrix in this study showed no significant correlations among serum serotonin levels and any of the other studied parameters including Chalfont severity scale, dose of AED and disease duration. Also, the median values of serotonin in different types of seizures, showed non significant difference (P >0.05) at 3 and5 months after the starting AED therapy in Idiopathic Epileptics.

**Conclusion and Recommendations:**

 It could be concluded that serotonin levels among epileptic patients are controversial and it might be multifactorial affected by the antiepileptic drug used and duration of therapy. Therefore, authors recommend a further study on the serum serotonin level among intractable epilepsy patients as well as epileptics receiving antiepileptic drugs, as a monotherapy as well as polytherapy for a longer duration of follow up. Further pharmacological evaluation of selective activation or inactivation of the 5-HT2C receptor subtype with selective agonist/positive modulators and antagonists will provide important information about the therapeutic contribution of this receptor to the epileptic circuitry in the brain. Future development of serotonergic antiepileptic drugs will be a significant addition to the therapeutic armamentarium against epilepsy.

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**تأثير الأدوية المضادة للصرع على مستوى السيروتونين في الدم بين الأطفال الذين يعانون من الصرع الاولي**

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**خلفية الدراسة:**

الصرع من أهم الأمراض العصبية التى تصيب الأطفال، ومعرفة محددات المرض وديناميكياته تساعد على الاكتشاف المبكر وتحسن طرق العلاج.

**الهدف من الدراسة:**

تهدف الدراسة الى تقييم مستوى السيروتونين في مصل دم الحالات التى يتم تشخيصها حديثا من الصرع الاولي وعلاقته بالاستجابة للعلاج للأدوية مضادة الصرع.

**المنهجية:**

**نوع الدراسة:**  هذه الدراسة اكلينيكيه تتبعية مقارنه بين الحالات المرضيه (حالات الصرع الاولى) وتشمل 30 حالة تم تشخيصها حديثا قبل تعاطي أى دواء وتم متابعتها لمدة ثلاثة و خمسة أشهر (قياس مستوى السيروتونين فى مصل الدم باختبار إليزا)و العلاج و الحالات الطبيعيه الضابطه وتشمل على 30 طفلا من الذين يتمتعون بصحة جيدة ومتطابقة بالنسبة للعمر والجنس للأطفال بالمجموعة الاولى.

**معايير الادراج للحالات:** الحالات التي تم تشخيصها حديثا - 5-15 سنة من العمر- الحضور المنتظم في الدراسة -قبول الالتحاق بالدراسة

**معايير الاستبعادللحالات:**  استخدام الأدوية التي تؤثر على مستوى السيروتونين مثل: أميتريبتيلين، سماتربتان، فلوكستين- الحالات ذات الاسباب الثانوية للصرع

**النتائج:**

أظهرت نتائج الدراسة أن متوسط ​​مستويات السيروتونين في الدم لم تظهر أي فرق ذو دلالة بين المرضى الجدد للصرع (في بداية الدراسة) والمجموعة الضابطة، في الوقت نفسه لم يكن هناك اختلاف كبير لوحظ بعد 3 أشهر من الدراسة. ولكن الدراسة أظهرت أن مستوى السيروتونين انخفض بمستوى كبير في مجموعة المرضى بالصرع مقارنة بالمجموعة الضابطة بعد 5 أشهر من المتابعة. وعلاوة على ذلك، فإن الدراسة لم تظهر أي ارتباط ملموس بين مستوى السيروتونين ومدة المرض، ونوع من الأدوية المضادة للصرع المقررة، وكذلك مقياس شدة تشالفونت.

**الخلاصة:**

يمكننا أن نستنتج من خلال هذه الدراسة أنه على الرغم من أن السيروتونين هو ناقل عصبي معروف حتى الآن، ليس لديه تأثير كبير على حدوث نوبات الصرع بالمقارنة مع الناقلات العصبية في الدماغ الأخرى. ومع ذلك، أظهرت الدراسة أن مدة العلاج بالعقاقير قد يكون لها تأثير على مستوى السيروتونين. ولذلك، فإننا نوصي بدراسة أخرى على مستوى السيروتونين في الدم لدى مرضى الصرع المستعصي وكذلك المصابون بالصرع والذين يخضعون للعلاج بالأدوية المضادة للصرع لمدة أطول من المتابعة.