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Evaluation of latent-transforming growth factor beta-binding protein-1(LTBP-1), dopamine and serotonin in patients with chronic epilepsy according to disease type and body mass index

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ABSTRACT: The study aimed to evaluate some biochemical, immunological, physiological and neurotransmitter variables in chronic epilepsy patients. The study comprised 60 patients with epilepsy and a control group of 30 healthy persons, aged between 15 and 60 years. Samples were collected in the Neurosciences Hospital in Baghdad (Saad Al Watri Hospital), the investigation involved quantifying the amounts of dopamine, serotonin, latent-transforming growth factor beta-binding protein 1 (LTBP1), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). The findings of the present investigation indicated the following: A notable reduction ($p \leq 0.01$) in the levels of latent transforming growth factor binding proteins (LTBP1) relative to the control group. A notable elevation ($p \leq 0.01$) in the levels of dopamine, alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) was observed in comparison to the control values. A substantial elevation ($p \leq 0.05$) in serotonin levels was observed relative to the control data. This study concuded a reduction in the levels of LTBP1. The concentration of dopamine, serotonin, AST, ALT, and ALP is elevated in patients with persistent epilepsy compared to healthy individuals. Epilepsy has a clear effect on the studied variables, as it caused a decrease in the concentration of latent-transforming growth factor beta-binding protein 1.

Keywords: Epilepsy, BMI, LTBP1, dopamine, serotonin, AST, ALT, and ALP

1. INTRODUCTION

Epilepsy is defined as a group of neurological disorders that result from disturbances in electrical signals in brain cells and are characterized by recurrent seizures(1). Epileptic seizures can vary from short, almost undetectable periods to long periods of severe convulsions. These seizures can also lead to physical injuries, including bone fractures in some cases (2). The cause of epilepsy participants was as a result of brain injury, stroke, brain tumors, brain infections, or birth defects (3). Epilepsy is most common among older adults. In the developed world, new cases appear most often in children and the elderly, while in the developing world, they appear in older children and young adults, due to the different frequency of underlying causes (4) Epileptic seizures are a group of clinical manifestations

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that occur as a result of abnormal electrical discharges in the brain. These clinical manifestations occur suddenly and include disturbances in consciousness, sensation, and movement (5). Dopamine is a chemical that sends messages within the midbrain in the substantia nigra. It is a hormone-like chemical that regulates the group of catecholamines (6). Dopamine transmits chemical signals between nerve cells that control movement and regulate emotions and mood (7). Serotonin is secreted by nuclei arising from the medial raphe within the brain stem, and is connected to many sites of the brain and spinal cord, especially the dorsal horns of the spinal cord and to the hypothalamus (8). It acts as an inhibitor of pain pathways in the spinal cord and has an inhibitory effect on higher areas of the nervous system, and is thought to help control a person's mood, and may induce sleep. Serotonin is the chemical mediator that the brain relies on to regulate human behavior. If its level is increased or decreased, it affects a person's life and personal behavior. If there is a deficiency in the concentration of serotonin in the blood, this deficiency leads to the individual suffering from a disturbance in psychological balance. There are individual differences in the brain's activity in producing serotonin. The reason for these genetic differences is that its percentage in the nervous system is 2% of its percentage in the human body (9, 10). Latent-transforming growth factor beta-binding protein 1 is a transforming growth factor-β (TGFβ) cytokines are a multifunctional family that exerts a variety of effects on both normal and transformed mammalian cells. TGFβ exists as three mammalian isoforms (TGFβ1, TGFβ2, TGFβ3) (11). The current study aimed to evaluate the levels of some biochemical, immunological, physiological and neurotransmitter variables in patients with chronic epilepsy and to study the effect of weight and type of epilepsy on the values of the studied variables, in addition to studying the correlation between the variables and the extent of changes resulting from the presence of the disease, in addition to the possibility of using research variables as diagnostic functions for the disease.

2.MATERIALS AND METHODS

2.1 Subjects

Blood samples were collected from patients with epilepsy who were attending the Neurosciences Hospital in Baghdad (Saad Al Watri Hospital). Patients aged between (15-60) years were selected after their condition was diagnosed by the specialized medical staff. The total number of participants was (90) samples(60 patients and 30 control). Patients were divided according to gender, age, BMI, type of epilepsy and type of treatment. Patients were subjected to a Questionnaire that included a number of information related to the research topic.

2.2 Sample collection

Five ml of venous blood was withdrawn using a disposable syringe, then the blood was placed in clean, sterile plastic tubes and left at room temperature until the blood clotted, then the serum was separated using a centrifuge (3000g) for (15 minutes) to ensure obtaining a sufficient amount of serum free of traces of red blood cells, then the blood serum (filtrate) was withdrawn using a micropipette and the serum samples were divided into (3) parts for each patient, and were kept frozen at a temperature of (20°C-) until biochemical, immunological, physiological and neurotransmitter tests were performed.

2.3 Estimation Of Latent-transforming growth factor beta-binding protein 1 (LTBP1), Dopamine(DA), and Human 5-hydroxytryptamine in Blood Serum by ELISA

It used firm Fine test-China's competitive enzyme-linked immunosorbent assay (ELISA) technology. The target material was pre-coated on the microtiter plate. The target substance in the sample or standard solution competes with a set amount on the solid phase supporter for biotinylated detection antibody sites during the reaction. After washing off excess conjugated and unbound chemicals from the sample or standard solution, Streptavidin Conjugate (SABCHRP-) was added to each microtiter plate well and incubated. A basic TMB solution was applied to each well. The enzyme base ash reaction was stopped by adding sulfuric acid solution, and the color shift was observed at 450 nm. The samples' OD value was compared to the standard curve to determine the target substance concentration.

2.4 Statistical analysis

The results were statistically analyzed using the statistical program (Minitab ver.17) according to the analysis of variance (ANOVA) test, and the arithmetic means were compared according to Duncan's Multiple Range test at a probability level of $p \leq 0.05$.

3. RESULTS AND DISCUSSION

Table (1) shows there is a highly significant decrease ($p \leq 0.01$) in the activity of Latent-transforming growth factor beta-binding protein 1 in epilepsy patients, where it was (545±45.2) pg/ml compared to healthy individuals, which was (1040±54.2) pg/ml. As for dopamine, Serotonin, AST, ALT, note a highly significant increase ($p \leq 0.01$) in epilepsy patients (18.92±2.95 ng/mL, 1.220 ± 0.551 ng/mL, 33.8±4.8 U/L, 30.60±3.0 U/L, 214.9±34.8 U/L) compared to healthy subjects (5.90±1.85 ng/mL, 0.757 ± 0.249 ng/mL, 22.3±3.1 U/L, 20.83±2.23 U/L, 214.9±34.8 U/L). At p-value <0.05

Table (1): Shows the mean ± standard deviation, t-test value and P value for patients and healthy controls.

Groups / Prameters	Mean ± SD		P-value
	Patients	Control	

**0.0003	1040 ± 54.2	545 ± 45.2	**Latent-transforming growth factor beta-binding protein1 (pg/ml)**
**0.0003	5.90 ± 1.85	18.92 ± 2.95	**Dopamine (ng/mL)**
*0.049	0.757 ± 0.249	1.220 ± 0.551	**Serotonin (ng/mL)**
**0.0002	22.3 ± 3.1	33.8 ± 4.8	**AST (U/L)**
**0.0002	20.83 ± 2.23	30.60 ± 3.0	**ALT (U/L)**
**0.008	177.3 ± 38.8	214.9 ± 34.8	**Alkaline Phosphatase (U/L)**

***p-value< 0.05**
****p-value< 0.001**
ns: No significnt differences

Table (2) indicates a significant increase ($P \leq 0.01$) in Latent-transforming growth factor beta-binding protein 1 concentration in epilepsy patients of the first category (637±56.0 pg/ml) compared to the second and third categories (572.0±64.0 and 565.6±82.2), respectively. There was no significant difference between the second and third categories. Dopamine levels significantly increased ($p \leq 0.05$) in epilepsy patients in the second and third groups, reaching 21.47±3.87 and 19.09±3.37 ng/mL, respectively, compared to the first category (15.67±2.37). Results also indicate no significant difference in Serotonin or HT-5 concentrations among epilepsy patients, with values of (0.740±0.271) (1.520±0.191) (1.337±0.457) ng/mL, respectively. In addition, the study shows no significant difference in ALT and ALP in regarding to BMI.

Table (2): Levels of some biochemical, immunological, physiological and neurotransmitter variables in the blood serum of chronic epilepsy patients and healthy individuals according to BMI

G3 (30-Above)	G2 (25-29.9)	G1 (18.5-24.9)	Groups / Parameters
Patients N = 18	Patients N = 23	Patients N = 19	

572.0 ± 64.0 B	565.6 ± 82.2 B	637.0 ± 56.0 A	**Latent-transforming growth factor beta-binding protein1 (pg/ml)**
19.09 ± 3.37 A	21.47 ± 3.87 A	15.67 ± 2.37 B	**Dopamine (ng/mL)**
1.337 ± 0.457 A	1.520 ± 0.191 A	0.740 ± 0.271 A	**Serotonin (ng/mL)**
30.94 ± 5.77 B	36.04 ± 5.86 A	33.68 ± 6.66 Ab	**AST (U/L)**
32.94 ± 3.33 A	29.57 ± 4.76 A	29.79 ± 5.48 A	**ALT (U/L)**
210.4 ± 39.0 A	215.2 ± 33.3 A	212.4 ± 34.2 A	**Alkaline Phosphatase (U/L)**

Different letters mean there is a significant differences

Table (3) shows a significant decrease ($p \leq 0.01$) in Latent-transforming growth factor beta-binding protein 1 effectiveness in patients with partial and complete epilepsy, reaching (673.4±43.80) (508.5±43.36) pg/ml compared to healthy individuals (1039.8±52.40) pg/ml. Dopamine concentration significantly increased ($p \leq 0.01$) in epilepsy patients compared to healthy individuals, with partial and full epilepsy patients reaching (15.36±2.60) (22.72±3.00) ng/mL and healthy individuals averaging (5.90±1.84) ng/mL. Also the result found that its concentration was higher in full epilepsy patients than in partial epilepsy patients. No significant differences in Serotonin concentrations between epilepsy patients and the control group. Patients with partial and complete epilepsy had concentrations of (1.164±0.469) (1.276±0.581) ng/mL, while healthy individuals had a concentration of (0.757±0.249) ng/mL.

Table (3): Level of some biochemical, immunological, physiological and neurotransmitter variables in the blood serum of chronic epilepsy patients and healthy individuals, according to the type of epilepsy.

P-value	**Healthy**	Type of epilepsy		**Groups** / **Parameters**
		complete **G2=29**	partial **G1=31**	

**0.0007	1039.8 ± 52.40 A	508.5 ± 43.36 b	673.4 ± 43.80 B	**Latent-transforming growth factor beta-binding protein1 (pg/ml)**
**0.0008	5.90 ± 1.84 C	22.72 ± 3.00 A	15.36 ± 2.60 B	**Dopamine (ng/mL)**
ns0.134	0.757 ± 0.249 A	1.276 ± 0.581 A	1.164 ± 0.469 A	**Serotonin (ng/mL)**
**0.0005	22.30 ± 4.05 B	36.17 ± 5.35 A	31.52 ± 5.42 A	**AST (U/L)**
**0.0004	20.83 ± 2.23 B	28.48 ± 2.93 A	32.68 ± 3.86 A	**ALT (U/L)**
*0.013	177.3 ± 38.8 B	210.9 ± 39.0 A	218.6 ± 31.6 A	**Alkaline Phosphatase (U/L)**

***p-value< 0.05**
****p-value< 0.001**
ns:non significnt differences

Figure (1) shows the statistical analysis of the ROC curve, where the AUC value was 0.77 and the cut-off value was (0.833). This demonstrates the possibility of using the variable Jed as a diagnostic function for the disease.

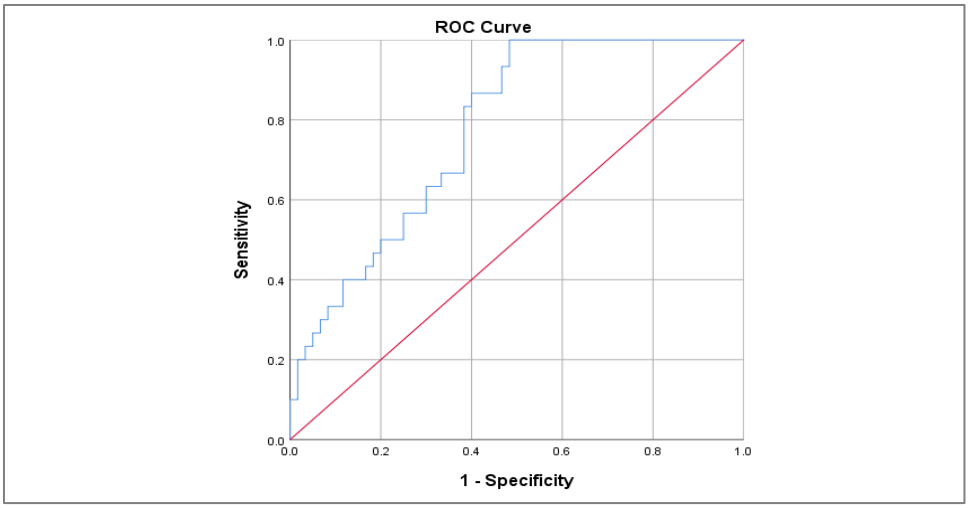

Figure (1) ROC curve for transforming growth factor beta-binding protein 1 in epilepsy patients and healthy controls.

Figure (2) shows the statistical analysis of the ROC curve, where the AUC value was 0.88 and the cut-off value was (9.633). This demonstrates the possibility of using the variable very well as a diagnostic function for the disease.

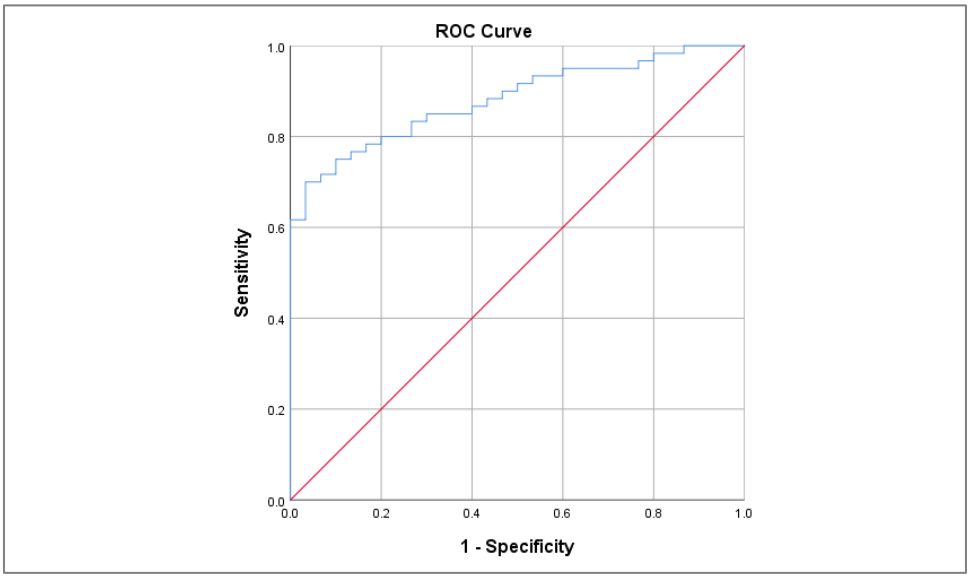

Figure (2) ROC curve of dopamine in epilepsy patients and healthy controls

Figure (3) shows the statistical analysis of the ROC curve, where the AUC value was 0.66 and the cut-off value was (0.597). This demonstrates the possibility of using the average variable as a diagnostic function for the disease.

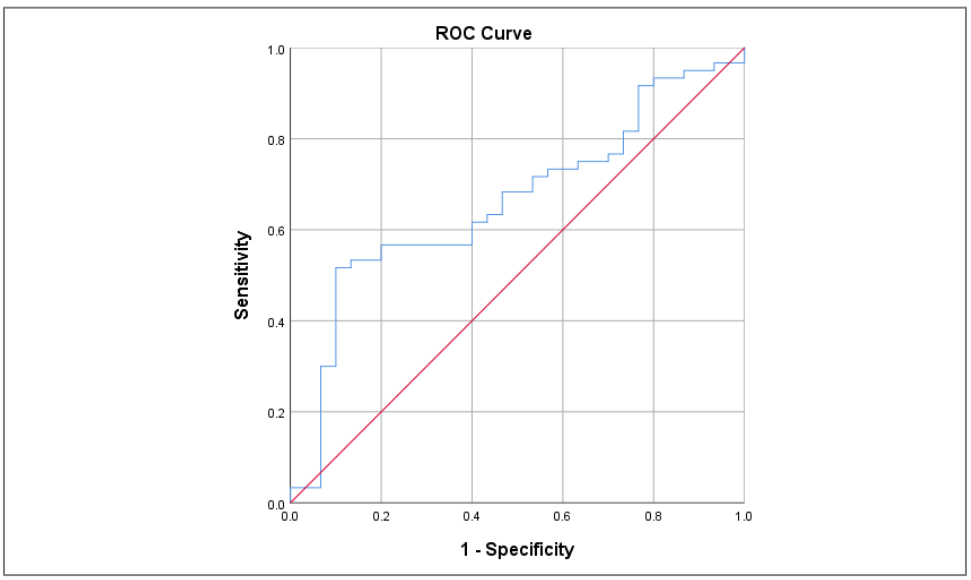

Figure (3) ROC curve of serotonin in epilepsy patients and healthy group

The results show a highly significant decrease ($p \leq 0.01$) in the activity of Latent-transforming growth factor beta-binding protein 1 in epilepsy patients. The results are similar to those found in a recent

2023 study by Liu and his group, where the researchers observed a decrease in the activity of LTBP1 in epilepsy patients. LTBP1 expression levels were found to be decreased in samples taken from people with epilepsy compared to their levels in normal tissues and cells. They found that LTBP1 is an important factor in the biological system, as it can affect inflammation-related pathways and inflammatory responses by activating the TGFβ/SMAD signaling pathway. This activation can lead to the promotion of epilepsy development and increase its frequency. In addition, there is a possibility that inhibiting LTBP1 expression can play a role in controlling the occurrence of epilepsy and providing protection to the nervous system. This means that reducing LTBP1 activity may have a positive effect on preventing and onset of epileptic seizures (12).

As for dopamine, highly significant increase ($p \leq 0.01$) in epilepsy patients compared to healthy people. According to a recent study, a significant increase in the expression of dopamine receptors D1, D2, D4, and D5 was observed in patients with transient lobar epilepsy (TLE) compared to a group of healthy people. This finding indicates changes in the levels of expression of dopamine receptors, which are the structures through which dopamine connects to the nervous system. It was found that the expression of dopamine receptors D1, D2, D4, and D5 is one of the things that can affect the nervous system's response to dopamine and the nervous balance. If there is an increase in the expression of these receptors in cases of transient lobar epilepsy, this increase may affect the activity of the nervous system and its ability to stimulate, which may affect epileptic seizures and their development (13). The results showed a significant increase ($p \leq 0.05$) in the concentration of serotonin in epilepsy patients compared to healthy individuals. A study conducted in 2018 on a group of patients with epilepsy, which included 41 patients, reached similar results. This study investigated the effect of serotonin levels in the body on individuals with epilepsy. Murugesan and colleagues observed an increase in serotonin levels in a group of patients with generalized tonic–clonic seizures (GTCS) in hereditary generalized epilepsy, compared to the control group. It is believed that this increase in serotonin levels may be related to the nature and type of seizures experienced by these patients, which are characterized by severe muscle contractions (14).

As for the concentration of AST, ALT, and Alkaline Phosphatase, we note a significant increase in patients with epilepsy. In a recent study conducted in 2020, AST, ALT were measured in patients and healthy people. ALT concentrations showed a significant increase in epilepsy patients compared to the healthy group (15). However, in one study, AST, ALT were measured in epilepsy patients and a group of healthy people, and all of these chemical parameters showed insignificant differences in their levels between the patient group and the healthy group (16). The reason for the high rate of liver enzymes is due to antiepileptic drugs (AEDs), as they are known to stimulate the production of liver

enzymes, including AST and ALT, as the liver tries to process and remove these drugs from the body. This process can lead to increased enzyme levels (17). The results of this study are consistent with previous studies, as there is evidence of increased levels of ALP in epilepsy patients, and one study suggests that increased levels of ALP in epilepsy patients may be a feature of seizures and not a result of drug administration (18).

The results showed a significant increase at the probability level ($P \leq 0.01$) in the concentration of Latent-transforming growth factor beta-binding protein 1 in epilepsy patients of the first category, while we did not observe any significant difference between the second and third categories of epilepsy patients. In another recent study, the presence of genes carrying rare variants affecting the protein was discovered, including the LTBP1 gene in relation to height and the GPR75 gene in relation to body mass index (19). As for Dopamine, we note a significant increase ($p \leq 0.05$) in epilepsy patients of the second and third categories compared to the first category. Trindade-Filho et al., 2022(19), a study on a group of mice with epilepsy indicated that dopamine concentration increases in epilepsy patients. The results also showed an inverse relationship between dopamine concentration and body mass index, as dopamine concentration decreases with increasing body mass index, which is considered an indicator of obesity (20). Despite this inverse relationship between dopamine concentration and body mass index, Volkow's study did not clearly indicate a significant association between body mass index and dopamine concentration in epilepsy patients. This could be due to the variability in antiepileptic drugs taken by patients (21), as Vafaee-Shahi's study conducted in 2022 shows the effect of antiepileptic drugs on body mass index, and this effect can be positive or negative and depends on the type of drug (22). The results showed no significant difference in the concentration of serotonin or (HT-5) in the epilepsy patient groups. A study conducted in 2021 by Singh indicates that the concentration of serotonin is elevated in epilepsy patients. This increase in serotonin concentration can be partly attributed to the medications taken by epilepsy patients (22). Regarding the relationship between serotonin and body mass index, it was found that the relationship is inverse, as serotonin decreases with increasing BMI (23). The results of the study conducted by Büyükgöl and Güneş in 2020(24) show that the concentration of the liver enzyme "AST" increases in epilepsy patients, and this increase is usually attributed to the use of antiepileptic drugs taken by patients. This increase in the concentration of these enzymes is considered a side effect of antiepileptic drugs (25). A study conducted in Bangladesh showed that BMI affects the levels of three liver enzymes. This means that an increase in BMI can cause an increase in the levels of these enzymes (26). Regarding the concentration of the ALT enzyme, it is

noticeable that the concentration of this enzyme in the blood is higher in patients with epilepsy, but the research did not indicate a relationship between the increase and BMI (27).

A highly significant decrease ($p \leq 0.01$) in the activity of LTBP1in patients with partial and complete epilepsy compared to healthy controls as compared to healthy controls, while do not notice a significant difference between patients with partial epilepsy compared to patients with complete epilepsy. The results of a 2023 study conducted by Liu and colleagues showed that LTBP1 protein expression levels were lower in epilepsy patients' samples compared to healthy controls. This decrease demonstrates the importance of LTBP1 in the development of brain functions and may play a role in the development of epilepsy. These results indicate that changes in LTBP1 protein concentration may be associated with the occurrence of epilepsy. It is worth noting that this relationship was independent of the type of epilepsy and was not associated with the difference in epilepsy type, indicating that changes in LTBP1 levels may be common between different types of epilepsy (12). As for dopamine, we note a highly significant increase ($p \leq 0.01$) in epilepsy patients compared to healthy individuals, as its concentration reached 10.0 in patients with partial and complete epilepsy compared to healthy individuals. Also the study noted that there is a clear significant difference between patients with complete epilepsy compared to patients with partial epilepsy, as its concentration was found to be higher in patients with complete epilepsy than in patients with partial epilepsy. The results of one study showed that dopamine levels were higher in people with epilepsy compared to healthy people (28), and these results were confirmed by a study conducted in 2023, indicating changes in dopamine levels associated with epilepsy (15). The results showed no significant differences between epilepsy patients and the control group in the concentration of serotonin or (HT-5). The study by Vashadze and colleagues found that serotonin levels in the body are associated with epilepsy, and this association depends on several factors, such as the nature of the seizures, the medications used to treat it, and the duration of epilepsy. Serotonin levels can rise or fall in some cases, so there may be no significant differences in its levels (10).

4. CONCLUSION

This study concluded a decrease in the concentration of latent-transforming growth factor beta-binding protein 1. While an increase in the concentration of dopamine, serotonin, AST, ALT, and Alkaline phosphatase in patients with chronic epilepsy compared to healthy people. BMI was found to have a clear effect on some of the studied variables, as some of them increased and others decreased.

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