

# THE RELATIONSHIP BETWEEN SEROTONINE, HISTAMINE AND THE BRAIN'S ELECTRICAL ACTIVITY IN PATIENTS WITH DEPRESSION AND ENDOCRINE DISORDERS

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## ABSTRACT

**Introduction.** Depression is a persistent mental state of sadness that can affect an individual's thoughts, behavior, emotion and well-being. The electroencephalogram (EEG) is of great importance both for experimental neurophysiology and for clinical diagnosis. The purpose of our study was to establish if there is a connection between the values of serotonin, histamine and EEG in patients with depression and endocrine pathology based on the collected data.

**Materials and methods.** We included 50 individuals diagnosed with depression from Endocrinology Clinic of Craiova, over a period of 2 years (2018-2020). Serotonin and histamine were measured in blood and urine/24 hours in all the sample. Electroencephalography was performed to this patients.

**Outcomes.** In our study, 27 patients had mild depression, 17 had moderate depression and 6 had a severe disorder. Also, the serotonin values were low (normal value 80-400 µg/L) in patients with depression and endocrine pathology.

**Conclusion.** In patients with EEG abnormalities occur significant changes in the values of serotonin and histamine (increased urinary histamine and decreased serotonin levels).

**Keywords:** serotonin, histamine, EEG, depression

## INTRODUCTION

Depression is a persistent mental state of sadness that can affect an individual's thoughts, behavior, emotion and well-being [1] and it is one of the most significant causes of decreasing the quality of life in adults [2].

Also, it is well known that it affects mainly females [2]. For diagnosis and evaluation of the attention and mood disorders, depression, encephalopathies and learning disability, an electroencephalogram (EEG) may be used.

Electroencephalogram is the graphical, mediated recording of electrical brain phenomena. Following peripheral stimulation, evoked potentials in the cortex may be observed.

These evoked potentials have been interpreted as the sum of the extracellular currents in the simultaneously activated cortical neurons. However, in the absence of peripheral stimulation spontaneous fluctuations of membrane potential can be recorded in all regions of the cortex. This recording was given the name of the electroencephalogram or EEG.

There are a series of EEG changes, depending on content, topography and neurochemistry [3].

The EEG is of great importance both for experimental neurophysiology and for clinical diagnosis. Although these changes on EEG are not specific for depression, they can be helpful in the diagnosis of this pathology.

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Histamine is a biogenic amine synthesized in the posterior hypothalamus. It acts as a neuromodulator and neurotransmitter, being involved in processes such as thermoregulation, immunoregulation, food port, memory and sleep-wake cycle. Histamine is involved in some physiological processes (the gastric secretion). On the other hand, it is also involved in allergic pathologies [4].

Serotonine is a derivative of tryptophan, is synthesized in the central nervous system and in the mucosa belonging to the gastrointestinal tract. It is known for its implications in certain pathological aspects like mood disorders, vomiting, migraine and hypertension [5].

### AIM OF THE STUDY

The purpose of our study was to establish if there is a connection between the values of serotonin, histamine and EEG in patients with depression and endocrine pathology based on the collected data.

### MATERIALS AND METHODS

#### Subjects

We included 50 individuals diagnosed with depression from Endocrinology Clinic of Craiova, over a period of 2 years (2018-2020). Serotonine and histamine were measured in blood and urine/24 hours in all the sample. Electroencephalography was performed to this patients.

The approval and informed consent have been obtained, from each participant. All study methods were conducted according to the principles expressed in the Declaration of Helsinki. Experiments have been performed in compliance with the ethical principles of the assigned institutional board or national committee.

#### Assessment of depression

Depressive symptoms were assessed with Hamilton scale. The Hamilton Depression Rating Scale is a questionnaire used to diagnose the severity of depression and it is also helpfull to evaluate the recovery process. This Scale use 17 to 21 items, depending of the type and the severity of depression, scored on 3 to 5 point scale. The items are: the depressed mood, feelings of guilty, insomnia (early in the night, middle of the night, early hours of the morning), work and activities, retardation, agitation, anxiety psychic, anxiety somatic, somatic symptoms gastro-intestinal, general somatic symptoms, genital symptoms, hypochondriasis, loss of

weight, insight and diurnal variation, depersonalization/ derealization, paranoid symptoms, obsessional/ compulsive symptoms. Interpretation for the 17 items scale is (a higher total score indicate a more pronounced degree of depression) : the total score between 0 and 7 – normal, 8-17 mild depression, 17-25 moderate depression, > 25 severe depression [1].

#### Biochemical and hormone assays

Serum samples were assayed for hormones using an automated electrochemiluminescence assay system (ECLIA).

For measuring serotonin, it was used high-pressure liquid chromatography . patients were previously warned to avoid foods/medicines that may influence the quality of the analysis (monoamine-oxidase inhibitors, medicines containing lithium, methylidopa, morphine, reserpine.

For urinary histamine – liquid chromatography coupled with mass spectrometry. Patients are advised to avoid eating foods rich in histamine (fermented foods, cheeses, soy, nuts, smoked sausages, alcoholic beverages, sweets, vinegar etc.). Sedatives and antidepressants were forbidden.

#### Electrical brain activity

Electroencephalography was realized with a machine adjusted with aplicators at the time constant of 0.3 seconds, the filter at 70 Hz, the international standard amplitude 1 cm = 100 PV, and the speed of the paper was 30 mm/sec.

For the realization of the electroencephalogram, the subject must be simultaneously at rest physically and mentally, with normal glycemic values, rested, without fever or painful sensations. Exploration is carried out with the patient being in comfort both thermally and acoustically and bright. It is also contraindicated to consume food/drinks/medicines that can have exciting/depressing effects, such as: chocolate, coffee, alcohol, sedatives, vitamins, etc.

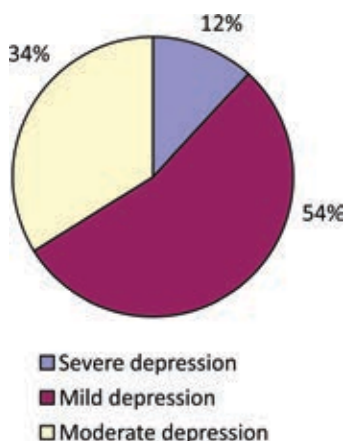
#### Statistical analysis

The acquired results in this study were processed and analyzed using the statistics program SPSS. Standard deviation (SD) is used for data which are “normally distributed” to provide information on how much the data vary around their mean. SD indicates how much a set of values is spread around the average. A range of one SD above and below the mean (abbreviated to  $\pm 1$  SD) includes 68.2% of the values. Distributions of categorical variables are expressed as percentages.

Then we performed the statistical processing of their data. In all analyses, a  $p < 0.05$  was considered as statistically significant.

### RESULTS

We enrolled 50 cases with depression in the study, 45 females (90%) and 5 males (10%). Their age was between 18-70 years, the mean was 42 years  $\pm$  14.2 DS.

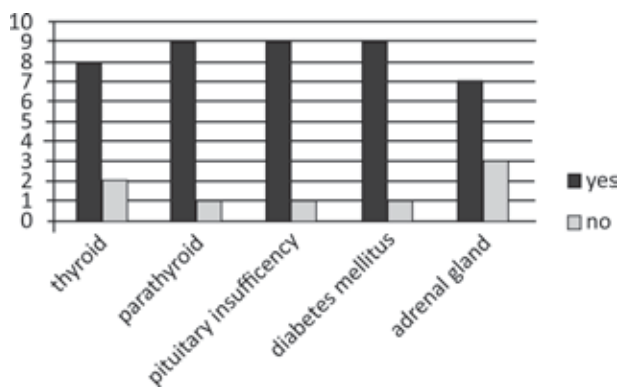


**FIGURE 1.** Depression grades (Hamilton Scale) in our patients

In our study, 27 patients had mild depression, 17 had moderate depression and 6 had a severe disorder (Figure 1).

We studied 10 cases of each of the following gland pathologies: thyroid diseases, parathyroid dysfunction, pituitary insufficiency, diabetes and adrenal gland pathology (Figure 2).

For each electroencephalogram record, primary parameters represented by the rhythm index; the amplitude and wave frequency (for some situations extending the calculation and for pathological rhythms).



**FIGURE 2.** EEG abnormalities in depression

We also observed: wave morphology; modulation of alpha waves in spindles and their duration; the reaction of blocking the alpha rhythm when

opening the eyes; the presence of pathological graphoelements, their index and location.

EEG abnormalities in patients with depression was represented by the presence of diffuse fast frequencies with hypovoltate route, decreased alpha incidence and increased beta index. The most significant change in EEG for patients with depression was alpha inher-hemispheric asymmetry. In our study, from 50 patients with depression, 42 had EEG abnormalities.

Patient T.E – F, 41 years, registration number 931/2019. Alpha index below 50%, alpha amplitude, to the lower limit of normal

In our study, as it is observed (Figure 4), the urinary histamine values were high (normal value  $< 3.8$  mg/24 h) in patients with depression and endocrine pathology. The mean value of urinary histamine was 6.04 mg/24 h ( $\pm 1.91$  DS) in patients with thyroid diseases, 4.94 mg/24h ( $\pm 1.26$ DS) for those with parathyroid pathologies, 4.65 mg/24 h ( $\pm 0.8$ DS) for those with pituitary insufficiency, 5.09 mg/24 h ( $\pm 1.26$ DS) had patients with diabetes mellitus and 4.3 mg/24 h ( $\pm 1.94$ DS) for those with adrenal gland dysfunction.

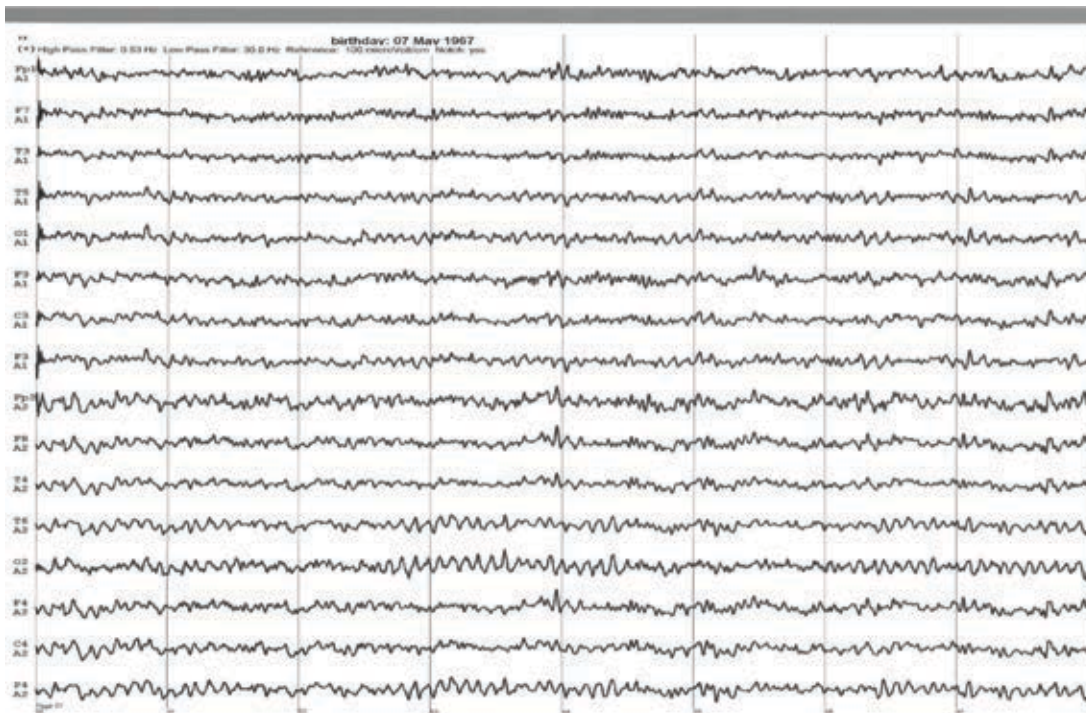
In our study, as it is observed (Figure 5), the serotonin values were low (normal value 80-400  $\mu$ g/l) in patients with depression and endocrine pathology. The mean value of serotonin was 64.7  $\mu$ g/l ( $\pm 23.9$  DS) in patients with thyroid diseases, 58.5  $\mu$ g/l ( $\pm 22.56$ DS) for those with parathyroid pathologies, 61.5  $\mu$ g/l ( $\pm 23.65$  DS) for those with pituitary insufficiency,  $\mu$ g/l ( $\pm 24.67$  DS) had patients with diabetes mellitus and 50.7  $\mu$ g/l ( $\pm 22.03$ DS) for those with adrenal gland dysfunction.

We tried to find a link between EEG abnormalities and the variations of serotonin and histamine. In our study, this hypothesis was correct. We found a  $p$  value  $< 0.082$  for serotonin and  $< 0.036$  for urinary histamine.

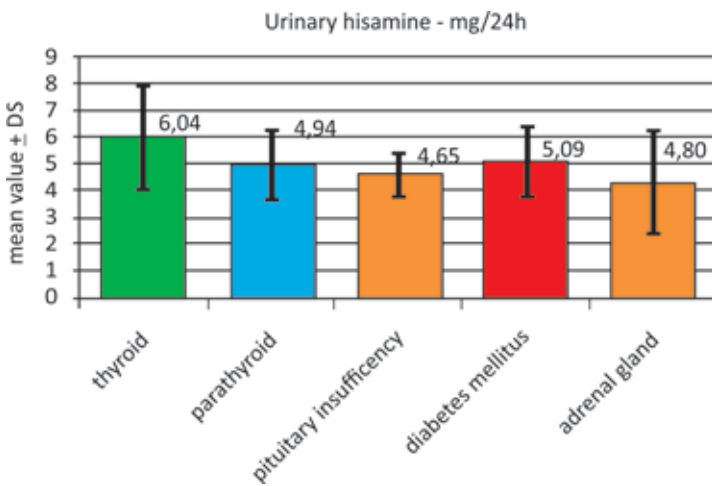
### DISCUSSION

Statistically, there are very strong correlations between serum serotonin and the degree of depression. According to the literature, a study conducted by Cowen and Browning clarified that low serum serotonin levels cause clinical symptoms of depression, and that sometimes despite drug treatment, patients may experience [6]. Also in our low serotonin study has direct link to depression.

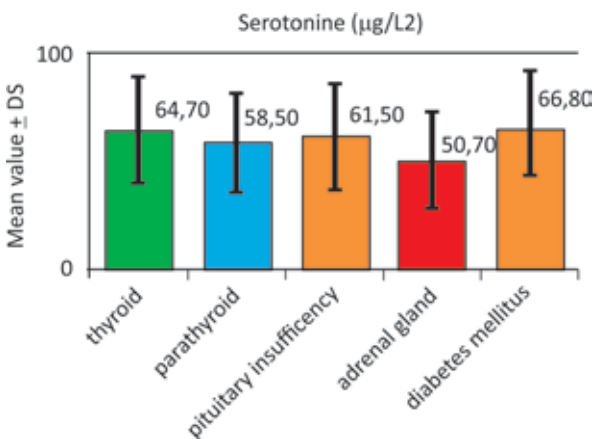
Analyzing urinary histamine levels in patients studied, we obtained that they were even higher with the level of depression. Perez Garcia et al.



**FIGURE 3.** EEG of a patient with depression



**FIGURE 4.** Mean value ±DS of urinary histamine



**FIGURE 5.** Mean value ± DS of serotonin

study suggests that histamine receptor blockage has no anxiolytic effect, but may have an antidepressant effect [7]. Kano et al. concluded that the

decrease of brain H<sub>1</sub>R binding is connected with the severity of symptoms in patients with depression. Also, it is found that the histaminergic neuron system is the central piece in the pathological mechanism which leads to depression and it is an important thing when it comes to cure [8].

Also in our study, depressed patients are associated with a low frontal alpha asymmetry on the EEG and that may even be related to their suicidal behaviour [9,10]. As presented in the study of Jiang et al., oscillating brain activity in patients with depression occurs, posterior alpha power was negatively related to depression severity [11]. To distinguish between changes which appear in EEG at patients with depression and other psychiatric disorders, more research needs to be done [12].

Interhemispheric alpha asymmetry and the measurement of the severity of depression may be the

basis of further research to strengthen the depression-EEG connection [13].

## CONCLUSIONS

Depression is a frequent disease sometimes associated with endocrine pathology. It is reflected by changes in electrical brain's activity with abnormal rhythms and waves.

In patients with EEG abnormalities occur significant changes in the values of serotonin and histamine (increased urinary histamine and decreased serotonin levels).

There are some limitations due to the small group, so further long-term studies on large cohorts of patients are needed to better clarify the link between the levels of serotonin, urinary histamine and EEG. Follow-up studies are required to evaluate if long-term association is still available.

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## REFERENCES

- Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci*. 2003 Mar;58(3):249-65.
- Parker G, Brotchie H. Gender differences in depression. *Int Rev Psychiatry*. 2010;22(5):429-36.
- Fingelkurts AA, Fingelkurts AA. Altered structure of dynamic electroencephalogram oscillatory pattern in major depression. *Biol Psychiatry*. 2015 Jun 15;77(12):1050-60.
- Parsons ME, Ganellin CR. Histamine and its receptors. *Br J Pharmacol*. 2006 Jan;147 Suppl 1(Suppl 1):S127-35.
- Mohammad-Zadeh LF, Moses L, Gwaltney-Brant SM. Serotonin: a review. *J Vet Pharmacol Ther*. 2008 Jun;31(3):187-99.
- Cowen PJ. Serotonin and depression: pathophysiological mechanism or marketing myth? *Trends Pharmacol Sci*. 2008 Sep;29(9):433-6.
- Pérez-García C, Morales L, Cano MV, Sancho I, Alguacil LF. Effects of histamine H3 receptor ligands in experimental models of anxiety and depression. *Psychopharmacology (Berl)*. 1999 Feb;142(2):215-20.
- Kano M, Fukudo S, Tashiro A, Utsumi A, Tamura D, Itoh M, Iwata R, et al. Decreased histamine H1 receptor binding in the brain of depressed patients. *Eur J Neurosci*. 2004 Aug;20(3):803-10.
- Park Y, Jung W, Kim S, Jeon H, Lee SH. Frontal Alpha Asymmetry Correlates with Suicidal Behavior in Major Depressive Disorder. *Clin Psychopharmacol Neurosci*. 2019 Aug 31;17(3):377-387.
- Segrave RA, Cooper NR, Thomson RH, Croft RJ, Sheppard DM, Fitzgerald PB. Individualized alpha activity and frontal asymmetry in major depression. *Clin EEG Neurosci*. 2011 Jan;42(1):45-52.
- Jiang H, Popov T, Jylänki P, Bi K, Yao Z, Lu Q, Jensen O, van Gerven MA. Predictability of depression severity based on posterior alpha oscillations. *Clin Neurophysiol*. 2016 Apr;127(4):2108-14.
- Koo PC, Thome J, Berger C, Foley P, Hoepfner J. Current source density analysis of resting state EEG in depression: a review. *J Neural Transm (Vienna)*. 2017 Feb;124(Suppl 1):109-118.
- Jesulola E, Sharpley CF, Bitsika V, Agnew LL, Wilson P. Frontal alpha asymmetry as a pathway to behavioural withdrawal in depression: Research findings and issues. *Behav Brain Res*. 2015 Oct 1;292:56-67.