

The Effect of STH Hypersecretion on Neuro-psychic Function

BOGDAN VIRGIL COTOI¹, NIKOLAOS MAVRITSAKIS^{2*}, ANCA GANESCU³, ELENA IONESCU^{4*}

¹ University of Medicine and Pharmacy, 2 Petru Rares Str., 200349, Craiova, Romania

² 1 decembrie 1918 University, Faculty of Law and Social Sciences, Department of Sport, 5 Gabriel Bethlen, 510009, Alba Iulia, Romania

³ University of Craiova, Faculty of Sciences, 107i Bucuresti Str., Craiova, Romania

⁴ University of Medicine and Pharmacy, 2 Petru Rares Str., 200349, Craiova, Romania

C: I: Parhon and his colleagues have drawn attention to the existence of psychic disorders, especially manic-depressive and delusional, in a range of endocrine disorders such as acromegaly, gigantism, adipose-genital dystrophy, highlighting the aggressiveness of patients with acromegaly. A number of clinical trials have shown that pituitary dysfunction can be associated with schizophrenia and even epilepsy. In this study, 19 patients were diagnosed with acromegaly following STH dosing, resulting in values higher than the upper limit (ie above 5 ng / mL in men or over 10 ng / mL in females). These patients had complete neurological examination, electroencephalogram, psychological examination, and the Hamilton depression scale.

Keywords: STH hypersecretion, epilepsy, depressive syndrome.

Many pituitary adenomas are capable of synthesizing adenohipophyseal hormones, clinically outlining characteristic hypersecretory syndromes by: excess of prolactin (PRL), growth hormone (GH), corticotrophic hormone (ACTH), and rarely thyroid stimulating hormone (TSH) with their appropriate clinical phenotypes.

Other pituitary adenomas are incapable of producing biologically active hormones, thus being non-functional, clinically manifested by pituitary hypopuncture.

Monotropic or pluritropic hypopituitarism may appear insidious within the adenomas that compress, distort and subsequently affect the secretory capacity of normal pituitary (non-tumoral) or interfere with the transport and synthesis of hypothalamic hormone releasing.

Tumor syndrome occurs by compressing the adenoma exerted on various pituitary anatomical pituitary formations.

In 1913, becoming professor of neurology and psychiatry in Iasi, C.I.Parhon undertook a series of researches on endocrine diseases in patients with neurological and psychiatric disorders, observations that place him among the pioneers of endocrine-psychiatry. He developed the endocrine theory of affective psychoses considering that there are pineal hyper- and hypopuncture syndromes.

He suspected that there were local hormones, which he called *topohormons*, which later turned out to be central nervous system mediators of endorphins and encephalins.

C: I: Parhon and his colleagues have drawn attention to the existence of psychic disorders, especially manic-depressive and delusional, in a range of endocrine disorders such as acromegaly, gigantism, adipose-genital dystrophy, highlighting the aggressiveness of patients with acromegaly.

A number of clinical trials have shown that pituitary dysfunction can be associated with schizophrenia and even epilepsy.

Experimental part

The central nervous system connections by cortical-limbic pathway with the hypothalamus are, according to Von Eiff, the biological stress basis [1,2]. Depending on the stressor, neurovegetative responses are differentiated. In

the case of active behavior of defense emotions (characterized by anger, rage, horror, followed by attack or escape), an additional activation of the sympathetic vegetative nervous system and the adrenaline and noradrenaline secretion by adrenal medulla is produced. At a greater intensity of these emotions, the hypothalamic-pituitary-cortical adrenal axis is also activated, producing excess ACTH and cortisol, but also; [3,4] so other adenohipophyseal hormones, especially somatotrophs and prolactin. In the passive behavior of resignation, abandonment, emotion of defeat, only the hypothalamic-pituitary axis is activated, followed by a slight increase of cortisol, the process manifesting in the psychic sphere by a depressive state [5].

In this study, 19 patients were diagnosed with acromegaly following STH dosing, resulting in values higher than the upper limit (ie above 5 ng / mL in men or over 10 ng / mL in females) [6].

Hormonal investigations involved growth hormone (STH) determination

For this we used the Elecsys 1010 dosing system produced by the Roche Diagnostics company, equipped with the Clinical Laboratory of the County Emergency Clinical Hospital of Craiova, together with the appropriate reagent sets for STH determination. It uses electrochemiluminescence method as a working method [7].

Electrochemiluminescence (ECL) is a form of chemiluminescence (CL) where the light-generating reaction is preceded by an electrochemical reaction. The advantages of CL are maintained, but the electrochemical reaction allows control of the moment and position of the light emitting reaction [8]. By controlling time, light emission can be delayed until the immune or enzyme-catalyzed reaction occurs. Although similar control can be exerted by other detection methods such as fluorescence, the equipment is much more sophisticated and more expensive. Position control can be used to limit light emission to a region that is precisely located relative to the detector, thus increasing sensitivity by increasing the signal / noise ratio. A good example is the combination of ECL with magnetic field technology, which allows the tracer to

be coupled by the traveler unbuilt without requiring an intermediate separation step.

Statistical and mathematical processing

Data processing used EPI2000 software packages, distributed by WHO, SPSS, specialized in statistical statistical calculations, produced by SPSS, StatSoft's STATISTICA program, and MICROSOFT EXCEL's Data Analysis module together with the XLSTAT suite for MS Excel.

EXCEL patient data recording produced the baseline database from which the significant aspects of this study were extracted [9].

The actual processing was done with the help of:

- CrossTab, BasicTables, General Tables, Correlate, Regression and Factor Analyzis, SPSS,
- ANALYSIS module of the EPI2000 program specializing in the execution of graphs, tables and statistical tests,
- the nonparametric test module in the STATISTICA program for calculating the Spearman correlation coefficient
- Pivot Tables, Functions-Statistical and Chart commands from MS Excel, and commands from the XLSTAT module for making ROC curves

In all calculations, the following statistical indicators [10] were used:

The arithmetic mean of a series of values. It is a simple and at the same time very synthetic indicator, being a very good indication of the value around which data is grouped together. Write down the letter m or, if the set of values is denoted by a capital letter as X or Y, the average is marked with $\bar{x}$ or $\bar{y}$. The formula is the one known:

Average is the indicator that shows the central trend of the value series, and usually shows where the data tend to cluster. Often, the values in the series are mostly near the average, and a smaller part of them are located to the left or right of the media.

In acromegaly patients, GH was 20.96ng / mL, with a minimum of 6.8ng / mL and a maximum of 72.7ng / mL at a standard deviation of 14.25 (table 1).

Tumors	GH
Number	19
Minimum	6.8
Maximum	72.7
Average	20.96
St.Dev.	14.25
C.V.	67.99

Table 1

Of the 19 patients with acromegaly, the neurological clinical examination supplemented with electroencephalogram (EEG) and psychological examination was performed.

The EEG is one of the most current and complex exploration techniques for cortical activity.

Electroencephalographic investigation is required for:

- Precise diagnosis - in neurology, neurosurgery, psychiatry, intensive care for the assessment of the coma degree;
- Evaluation of treatment efficiency especially in epileptic pathology;
- Forensic expertise or work capacity;
- Neuro-physiological research.

For the psychological exam we used the Hamilton Depression Rating Scale (Minulescu M -2000).

Hamilton depression scale

The exploration of depression and anxiety was done by using Hamilton's depression scale, which is commonly used to measure the severity of depression. There have been many variants of 17 or 21 items over time, as well as other variants with a variable number of items. The Hamilton scale proves to have a reliable coefficient and acceptable acceptability and a moderate sensitivity to changes over time and after treatment.

The most useful is the scale of 17 items.

Hamilton depression scale items are quoted on a scale of either 5 steps from 0 to 4, or 3 steps from 0 to 2, for the Hamilton scale with 17 items - the total score ranges from 0 to 50. The 5-step gradation is equivalent to landmarks representing

- absent
- weak
- moderate
- severe
- Extremely severe

while the 3-step gradation reflects the separation in:

- absent
- weak
- obviously, distinct, severe

Scores of 7 and less are considered normal; 8-13 mild depression; 14-18 moderate depression; 19-22 severe depression and 23 and over severe depression.

Grading the scale is based on the interview with the patient and the observations.

Items of the Hamilton Depression Rating Scale

Item 1: depression (depressed mood, sadness, hopelessness, uselessness). Depression is not always easy to assess. There may be feelings of sadness, apathy, despair, pessimism about the future, worry, irritability, despair. The patient's tendency to cry tends to a score of 3 points, and severe symptoms with 4 points.

Item 2: Feeling guilty (culpability) rated 0-4.

It aims to capture the perception of guilt as a continuity, from self-reproaching to auditory and visual hallucinations. Thoughts of guilt are marked by 2, the presence of delusional ideas of guilt must be quoted 3; current psychotic symptoms should be quoted with 4.

Item 3: suicide, rated 0-4.

The absence of the idea of suicide is scored by 0, suicide attempts by 4. Thoughts that life is not worth living 1 point, passive suicide ideas 2 points suicide plans 3 points.

Item 4, 5, 6: initial, mean, tardive 0-2 insomnia.

Item 7: Work and activities, quoted 0-4. It refers to loss of efficiency and extra effort to perform certain tasks. Fatigue score 1, when it is no longer working due to the present condition, is quoted 1 point.

Item 8: Lumbar, rated 0-4.

It is one of the most difficult points to assess. There is a slowing of speech, fixation of expression, decrease of the rate of spontaneous movements - quote 1; the monotone voice and the delay of the answer are quoted by 2.

Item 9: agitation, rated 0-4. Extreme agitation is rare. Unfortunate -2 points, the tendency to walk through the room 3-4 points.

Item 10: Mental anxiety, rated 0-4. The presence of a subjective sensation of tension, internal nervousness, or difficulty in relaxing involves a score of at least 1. The concern for unimportant problems is quoted as 2. Concern and diffuse fear -score 3.

Item 11: somatic anxiety, rated 0-4. The physiological systems at the level of which various symptoms occur

are: respiratory system (hyperventilation, hiccups), cardiovascular (palpitations), gastrointestinal (dry mouth, bloating, indigestion) and urinary (frequent micturition), dizziness, blurred vision, ringing the ears.

Item 12: 0-2 gastrointestinal somatic symptom symptom. Evaluate loss of appetite or development of a constipation symptom.

Item 13: General Somatic Symptomatology, rated 0-2. Two major categories of symptoms are considered: the first is fatigue or energy loss, the second symptom is muscle aches, hard to define or localized anatomically. Score 1 is attributable to mild symptoms, and score 2 is attributable to severe symptoms, both in the frequency of the accusations and severity.

Item 14: Genital symptomatology rated 0-2. It refers to changing the level of sexual interest or ease of sexual arousal independent of the current level of sexual activity.

Item 15: Hypochondria, rated 0-4. Rarely the occurrence of delusional ideas of body corruption. When a 4-point score is justified, giving more attention to body functions and physical symptoms ranges from 1 to 3, depending on their magnitude.

Item 16: weight loss, rated 0-2. Determine the weight before the disease and its current weight. If there is a net weight loss (2.5 kg or more), the relationship with the disease must be established. The score is 0 if it dropped before the disease, but it stopped falling.

Item 17: discernment, rated 0-2. It will be attempted to determine whether the patient is aware of the disease as being related to a psychiatric depression syndrome or whether he provides a rational interpretation of the symptoms (1) or if he or she denies the disease (quote 2).

In this syndrome, headache was the initial onset symptom, and eventually reached the status of the majority of patients. It should be noted that headache in acromegaly was more intense than in other syndromes, as well as other authors (Becker KL, 2001).

Results and discussions

Headache was found to be one of the most debilitating manifestations of acromegaly and was not due to the mass effect of the adenoma, as it was found that its severity is independent of tumor size, as is also apparent from the literature [11,12].

Visual disturbances due to overgrowth of the tumor are due to compression at various levels of the optic chiasm with changes in the visual field.

Presentation due to severe headache or visual field changes due to large tumors is unusual in women as they address the physician early as a result of menstrual disorders or galactorrhoea, long before the tumors reach large size [13].

In contrast, men with pituitary tumors are often late in their care because of symptoms due to tumor size, rather than due to impotence, loss of libido or infertility.

Thus, the average duration of the disease leading to physician presentation and clinical diagnosis was 5.01 +/- 4.07 years and was significantly lower in women than in men (4.43 +/- 3.59 years, compared to 5.86 +/- 4.57 years, lower p 0.05).

Paralysis of the cranial nerves through lateral tumor development in the cavernous sinuses, involving pairs III, IV, V and VI, has been encountered in one case.

	EEG					
LOT	irritatingroute	Lesionroute	Irritating,lesion	Normal	Not taken	Total
GH	1	1	0	9	8	19

Hypothalamic syndromes are performed by compression of the adenoma by the extension of the adenoma, resulting in disorders of thermoregulation, sleep, food intake (obesity or weakness), vegetative disorders (sweating, tachycardia) and behavioral disorders. They have been seen as postoperative complications rather than onset symptoms.

Signs and symptoms of intracranial hypertension with headache accentuation, inoperable vomiting unprecedented by nausea, bradycardia, have been encountered in a case of a patient with macroadenoma STH secretory overload.

Psychiatric disorders: Depressive syndrome with variable intensity from emotional mood disorders, psychic lability, hypomnesia, hypoprosexia, marked psychiatric asthenia prevailed. There were no major psychiatric disorders.

Obesity occurred in 21 patients (20%).

A redundant complication of hypogonadism-isoporosis has been seen in a high percentage of cases, clinically

Table 2

ASSESSMENT OF DEPRESSION

	PSYCHOLOGICAL TESTING				
LOT	DU	DM	DS	Without depression	Total
GH	4	5	8	2	19

manifested by lumbar sprains, diffuse bone pain, and rarely spontaneous fractures - rhinitis and vertebral compression.

Following the psychological testing of patients with STH secretory pituitary tumors, we have encountered the following types of depressive disorders: depressive disorders and other disorders associated with acromegaly: 8 of the STH secreting pituitary patients had severe depression (closely related to the dismorphism present in these patients), 5 had mean depression, 4 mild depression patients, and only 2 of acromegaly had no depressive symptoms. The risk of depression in acromegaly patients

Results of psychological testing

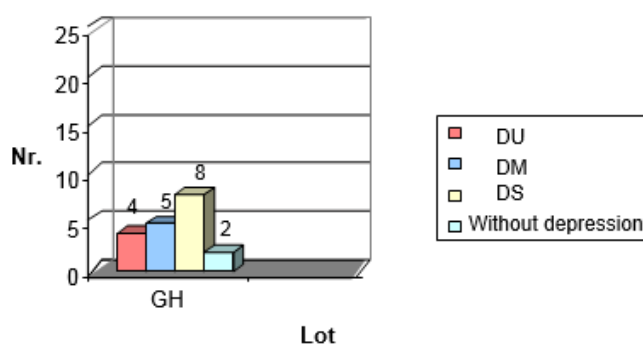


Fig. 1. Graphical depiction of depression grades

is greater than the risk of this mental manifestation in other pituitary disorders (table 2, fig. 1).

Other symptoms noted in patients with acromegaly were: psychoemotional lability, physical and mental asthenia, decreased initiative, inhibition, SOCIAL INSERTION TREND, mood and prosex difficulties, terrifying

Table 3

DISTRIBUTION OF PATIENTS ACCORDING TO THE EEG ROUTE

insomnia / dreams, irritability, easy crying, depressive ideation, panic attack, fatigue, anxiety, hallucinations.

From the group of 19 STH secretory pituitary adenomas, one patient had an irritant EEG tract, and one patient with a pituitary tumor (60 mm in the largest diameter),

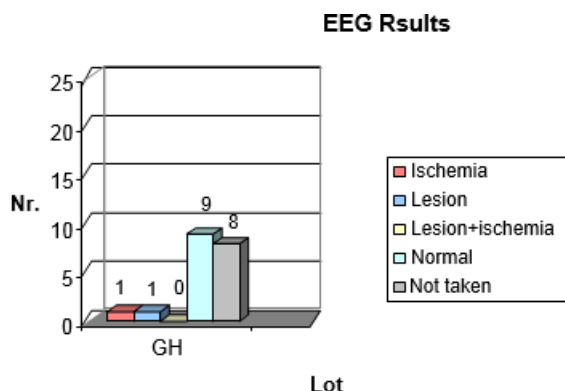


Fig. 2. Graphical representation of the type of EEG overweight and intracranial hypertension (HIC) had a EEG tract of both irritant and lesion type (table 3, fig. 2).

Conclusions

Was reported the existence of psychic disorders, especially manic-depressive and delusional, in a series of endocrine disorders such as acromegaly, gigantism, adipose-genital dystrophy, highlighting aggressiveness of patients with acromegaly. A number of clinical trials have shown that pituitary dysfunction can be associated with schizophrenia and even epilepsy.

Other symptoms noted in patients with acromegaly were: psychoemotional lability, physical and mental attenuation, decreased initiative, inhibition, social inserion trend, mood and prosexic difficulties, terrifying insomnia / dreams, irritability, easy crying, depressive ideation, panic, fatigue, anxiety, hallucinations.

Following the psychological testing of patients with STH secretory pituitary tumors, we encountered the following types of depressive disorders: depressive disorders and other disorders associated with acromegaly: 8 of the patients with STH-secreting pituitary tumor had severe depression (in close connection with the present dismorphism in these patients), 5 had mean depression, 4 patients with mild depression and only 2 of acromegals had no depressive symptoms. The risk of depression in acromegaly patients is greater than the risk of this mental manifestation in other pituitary disorders.

From a group of 19 STH secretory pituitary adenomas, one patient had an irritant EEG tract and one patient with a pituitary tumor (60 mm in the largest diameter) with

overweight and intracranial hypertension (HIC) had an EEG tract of both irritative and lesional type.

References

1. POMBO, M., POMBO,CM., GARCIA, A., et al. Hormonal control of growth hormone secretion. *Horm Res* 2001;55:11-16.
2. PATEL, YC., EZZAT, S., CHIK, CL., RORSTAD, OP., SERRI, O., Ur, E., WILKINS, GE.,- Guidelines for the diagnosis and treatment of acromegaly: a Canadian perspective. *Clinical & Investigative Medicine-Medicine Clinique et Experimentale*. 23(3):172-87, 2000 Jan.
3. SHEPPARD, MC., Primary medical therapy for acromegaly. *Clin Endocrinol (Oxf)* 2003;58:387-399.
4. TANNENBAUM, GS., EPELBAUM, J., BOWERS, CY., Interrelationship between the novel peptide ghrelin and somatostatin /growth hormone-releasing hormone in regulation of pulsatile growth hormone secretion. *Endocrinology* 2003;144:967-974.
5. WEBB, SM., PRICTO, L., BADIA, X., ALBAREDA, M., CATALA, M., GAZTAMBIDE, S., LUCAS, T., PARAMO, C., PICO, A., LUCAS, A., HALPERIN, I., OBIOLS, G., ASTORGA, R.,: Acromegaly Quality of Life Questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties. *Clin Endocrinol*. 2002;57:251-258.
- 6.*** LABORATOR SYNEVO., Referintele specifice tehnologiei de lucru utilizate 2010. Ref Type: Catalog.
- 7.IONESCU, E., CHIRITA ,A., COTOI, B.V., GANESCU, A., Hyper-production Hydrogenic of STH Patology Generation of Clinical - paraclinical Disorde, *Rev. Chim.(Bucharest)*, **70**, no. 4 , 2019,p. 1319-1321
8. MAVRITSAKIS, N., URSU, V.E., GANESCU, A., IONESCU, E., Clinical and Biological Study on the Relevance of Hiperfibrinogenemye in Cardiovascular Pathology of the Obez, *Rev.Chim. (Bucharest)*, **70**, no 3, 2019, p. 950-955.
9. POPESCU, IG.,SECHEL, G.,LEASU, FG., TANTU, MM., COTOI, BV., ROGOZEA, LM., Correlations on the protection of personal data and intellectual property rights in medical research, *Rom.J. Morphol. Embryol*,59, no. 3,2018,p. 1001-1005.
10. MAVRITSAKIS, N., URSU, VE., IONESCU, E., GANESCU, A., Actual Study Regarding Quantitative Determination of Tetracyclines by Electrical Analysis Techniques and Methods Potentiometric sensors for tetracycline, *Rev Chim. (Bucharest)*, **70**, no 2, 2019, p. 671-675.
11. YOUNG,WF., et al: Gonadotroph –secreting adenoma of the pituitary gland. *Mayo Clin Proc*. 2001;71-649.
12. GIUSTINA, A., BARKAN, A., CASANUEVA, FF., et al. Criteria for cure acromegaly: a consensus statement. *J Clin Endocrinol Med* 200;85:526-529.
13. KINEMAN, RD., TEIXEIRA, LT., AMARGO, GV., et al. The effect of GHRH on somatotrope hyperplasia and tumor formation in the presence and absence of GH signaling. *Endocrinology* 2001;142:3764-3773.

Manuscript received: 15.01.2019