Evaluation of the Effects of Ischemic Cerebrovascular Event on Anterior Pituitary Functions

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Abstract

Purpose: This study aims to investigate and evaluate the effects of ischemic cerebrovascular event on anterior pituitary hormones.

Material and Method: The study included 47 patients who admitted to the Emergency Department of our hospital between 01.01.2012 and 31.10.2012 and were diagnosed with cerebrovascular disease. Patients' full blood and blood samples were collected into biochemistry tubes, centrifuged and kept at -80 °C within the initial 24 hours of admission and at month six in order to measure Thyroid Stimulating Hormone (TSH), Growth Hormone (GH), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin (PRL) and Adrenocorticotropic Hormone (ACTH) values. The results were analyzed using SSPS version 18 and p≤0,005 was considered statistically significant.

Findings: 51,1% of patient were male and 48,9% female, with a mean age of 64,68 (range 27–88). While the TSH (p=0.001), PRL (p=0.197), FSH (p=0.041) and LH (p=0.392) values of patients at month six were found higher than basal TSH and PRL, FSH and LH values, GH (p=0.158) and ACTH (p=0.002) values were lower than basal GH and ACTH values. The difference between the GH (p=0,001), FSH (p=0,001) and LH (p=0,001) levels of the control group and GH, FSH and LH values both at the basal level and at month six was statistically significant.

Conclusions: Ischemic cerebrovascular event causes significant changes in anterior pituitary functions. However, the effects of such changes on clinical outcomes should be further studied.

Keywords: Ischemic cerebrovascular event, anterior pituitary, hormone, emergency service

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Introduction

Hypopituitarism is the deficiency of one or more hormones of the pituitary gland. It is a clinical condition as a result of insufficient production and release of one or more pituitary hormones. Deficiency of one or more pituitary hormones is known as partial hypopituitarism, and the deficiency of all pituitary hormones is known as panhypopituitarism. Hypopituitarism due to pituitary gland pathologies and hypopituitarism due to hypothalamus pathologies are called primary and secondary hypopituitarism, respectively. The prevalence of hypopituitarism is 45/100.000, and its incidence is ca. 4/100.000/year cases. Three to five hormone deficiencies have been reported in about half of the cases. Mortality rate increases by 1,2 to 2,2 times compared with normal individuals (1). 80% of the gland is the anterior lobe which contains somatotropic, lactotropic, thyrotropic, corticotropic and gonadotropic cells. The main thyroid-stimulating hormone (TSH) releases adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing-hormone (LH), prolactin (PRL) and GH (2).

Pituitary hormones are involved in for responding appropriately to stress and maintaining vital body functions as well as many other functions. Basal hormone measurements and various dynamic tests are used in evaluating pituitary functions in addition to clinical findings (3,4). Main causes of the deficiency include pituitary adenomas and associated treatment complications, craniopharyngioma and hypothalamic region tumors, idiopathic and

congenital factors, lymphocytic pituitaritis, apoplexia and postpartum pituitary necrosis, infiltrative diseases, traumatic brain injury and cerebrovascular diseases (5,6). Recently, there are a large number of studies focusing on pituitary deficiency following traumatic brain injury (TBI) and MSS infection. The literature contains limited number of studies evaluating pituitary functions after cerebrovascular disease. The clinical findings of pituitary deficiency (1) depend on missing hormone, the degree of hormone deficiency and onset. Hormone deficiency in hypopituitarism due to pituitary compression or destruction occurs in the following order: GH, FSH, LH, TSH and ACTH deficiency. PRL secretion is affected latest. While the cause of admission during childhood was growth retardation, hypogonadism is the earliest symptom in adults. In this study, we aim to investigate the changes in CVE and pituitary functions.

Materials and methods

Patients

47 patients diagnosed with cerebrovascular event (CVE), who admitted to the Emergency Medicine Department of the Faculty of Medicine, Gaziantep University between 01.01.2012 and 31.10.2012, were included in this study in order to investigate anterior pituitary hormone levels in cerebrovascular events. Ethical committee approval (Ethical committee decision no: 06–2009/237, dated: 18.06.2009) was obtained from the Medical Ethics Committee of the Faculty of Medicine, Gaziantep University before the study and the tenets of the Helsinki Declaration were followed. The study was funded by the Scientific Research Projects Commission of Gaziantep University (Project no: TF.12.31). All patients included in the study were informed about the tests to be conducted. Written and signed consents, allowing the conduct of tests and necessary physical examinations, of all patients were obtained.

Patient selection:

Patients diagnosed with CVE were selected from among patients who admitted to Emergency department of the Faculty of Medicine, Gaziantep University, diagnosed clinically and radiologically with CVE, and followed at the neurology department or intensive care unit. The study started with a total of 53 (fifty three) CVE patients; however, 6 (six) patients were excluded from the study before their follow-up at month six could be completed and the

study was completed with forty seven patients.

Inclusion criteria:

1. Being treated in an inpatient and/or outpatient setting,
2. Age greater than eighteen years old,
3. Agreeing to the study after its disclosure,
4. Being newly diagnosed (in 24 hours),
5. No previous diagnosis of ischemic or hemorrhagic CVE,
6. Undergoing no hormone replacement (thyroid hormone, growth hormone, FSH, LH, ACTH) therapy for any reasons,
7. No diagnosed meningitis, major depressive diseases and head traumas in the last 6 months,
8. Written informed consent form signed by the participant,

Exclusion criteria:

1. Written informed consent form not signed by the participant,
2. Previous history of ischemic or hemorrhagic CVE,
3. Age less than eighteen years old,
4. An endocrinologic disorder that could cause hyperprolactinemia, hyperthyroidism, or any other anterior pituitary hormone disorder,
5. Previously known history of mild, moderate or severe head traumas,
6. Previous history of any intracranial pathologies (brain tumor, brain abscess etc.) and/or surgical operations,
7. Patients with no control samples at month six for any reasons (e.g., decease, rejecting blood transfusion, being off city borders or military service).

Height, weight, body mass index and waist circumferences of all patients were measured at initial admission and at month six in order to evaluate the complications of a potential pituitary hormone deficiency. Routinely checked serum sodium (Na), potassium (K), blood urea nitrogen (BUN), calcium (Ca), phosphorus (P), fasting blood sugar (FBS), total protein, albumin, high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride, and total cholesterol levels were recorded. Polyuria symptoms were studied to identify the incidence of diabetes incipitus.

To analyze basal hormone profile, patients' venous blood samples were collected twice from their right or left arm antecubital veins during, first during hospitalization and second at month six of their follow-up period in order to measure the parameters of the Thyroid Stimulating Hormone (TSH), Growth Hormone (GH), Follicle Stimulating hormone (FSH), Luteinizing Hormone (LH), Prolactin (PRL), and Adrenocorticotropic Hormone (ACTH), which are anterior pituitary hormones. Blood samples were collected in 5 cc each biochemistry tubes for the TSH, GH, FSH, LH, PRL hormones, and in a 2,5 cc full blood tube for ACTH, centrifuged at 4000 revolutions/minute for 10 minutes and their serums were separated. Serum samples collected from the tube with a pipette were put into and recorded in separate Eppendorf tubes for TSH, GH, FSH, LH, PRL hormones, and for ACTH, and were kept in deep freezer at -80^0 C until processing of hormones.

Measurements

Measurements were carried out at the laboratories of the Department of Biochemistry, Faculty of Medicine, Gaziantep University using the same kits.

GH level was measured by Immunoradiometricassay (IRMA) method and measured in Immulite-2000 (DPC Cirrus Inc. Flanders NJ 07836 a subsidiary of Diagnostic Products Corporation, CA, USA) (Intra-assay; CV: 5,9%, theoretical sensitivity: 0.01 ng/mL). PRL, FSH, LH, and TSH were measured by RIA method (Architech C2000, Germany). ACTH levels were measured by Immunoradiometricassay (IRMA) method and measured in Immulite-2000 (DPC Cirrus Inc. Flanders NJ 07836 a subsidiary of Diagnostic Products Corporation, CA, USA).

Table 1: Reference values of measured hormones

HORMONES	Reference values of measured hormones
GROWTH HORMONE[7]	0.05–8,6 ng/mL
PROLACTINE [8]	5,18–26,53 ng/ml
ACTH[9]	10–46 pg/ml
TSH[8]	0,350–4,94 µg/dL
FSH[8]	0,7–11,1 mIU/ml[a] 26,72–133,41 mIU/ml[b] 3,03–16,69 mIU/ml[c]
LH[8]	0,8–7,6 mIU/ml[a] 10,39–64,57 mIU/ml[b] 0–74,24 mIU/ml[c]

a: male, b: postmenopausal woman, c: premenopausal woman

Statistical Data

The Kolmogorov Smirnov test was used to analyze the normal distribution of continuous variables. The Wilcoxon Test was used to compare the non-normally distributed variables between the groups, and the Paired-T Test was used to compare the normally distributed variables between the groups. Frequency, percentage and mean±standard deviation values were given as descriptive statistics. SPSS for Windows 18 was used for statistical analyses and a p value of < 0.05 indicated that the difference was statistically significant.

Findings

51,1% of the 47 patients were male, and 48,9% were female, with a mean age of 64,68 years (range: 27–88).

FSH: 20 of the female patients with CVE were postmenopausal. The remaining five female patients had regular menstrual cycles and this was maintained throughout the study period. Basal evaluation found the FSH values of six male patients (12,7%) to be higher than the normal values. The values were remained the same at the six-month evaluation. No new signs of FSH deficiency were found at the six-month evaluation. The FSH value was below the normal range in a postmenopausal female patient (2,12%) at basal evaluation, which improved in her six-month control. And in three postmenopausal female patients (6,38%), basal evaluation showed a normal FSH level, while six-month evaluation found the FSH value to go under the normal range (Table 2).

LH: While the LH level was normal in three postmenopausal female patients (6,38%) at basal evaluation, it was below normal values at six-month evaluation. Both basal and six-month values were below the normal range in a postmenopausal female patient (2,12%). Basal LH values were over normal range in two male patients (4,25%), with the six-month controls in normal range (Table 2).

TSH: TSH basal values were below normal values in seven patients (14,9%). Six-month evaluation showed that TSH values were maintained below normal values in three of these patients (6,38%), and TSH values returned to normal values in four of them. While TSH values were normal in all patients at basal evaluation, six-month evaluation found no new signs of FSH deficiency (Table 2).

PRL: PRL basal values were below normal values in seven patients (14,9%). Six-month evaluation showed that the PRL level returned to normal in three (6,38%) of these patients. And the six-month values of 5 patients (10,6%) with normal basal PRL value levels were over normal range. PRL levels were found to be over normal range in both basal and six-month evaluation in two patients (4,25%).

ACTH: ACTH value was below normal values in one patient (2,12%) both at basal and six-month evaluations. While the basal values were normal in eight patients (17,02%), ACTH values at month six were under the normal range (Table 2).

GH: GH value was found to be below the normal range in three patients (6,38%) in basal evaluations. In one patient, the condition continued at six-month evaluation too. While the basal values were within normal range in 11 patients (23,4%), six-month GH values were found to be under the normal range (Table 2).

CVE, was found to be higher than the six-month TSH (p=0.001), PRL (p=0.197), FSH (p=0.041) and LH (p=0.392 values basal TSH, PRL, FSH, and LH values of patients. And six-month GH (p=0.158) and ACTH (p=0.002) values were found to be lower than basal GH and ACTH values (Table 3).

Table 2: Basal and month 6 values of measured hormones

NO	SEX	AGE	M.0 TSH	M.6 TSH.	M.0 GH	M.0 GH	M.0 FSH	M.6 FSH	M.0 LH	M.6 LH	M.0 PRL	M.6 PRL	M.0 ACTH	M.6 ACTH
1	F	83	0,53	0,38	0,550	1,58	62,91	66,69	20,14	18,16	14,27	10,8	117	144
2	F	68	2,15	2,18	0,210	0,19	29,65	29,13	7,48	7,05	20,07	19,02	42	14
3	F	46	3,6	1,52	1,140	3,15	63,28	61,46	22,81	25,35	34,92	7,35	31,8	5
4	M	57	1,04	2,23	1,070	0,734	2,28	2,47	3,98	4,64	7,98	13,35	11,6	6,43
5	F	75	0,59	0,69	0,050	0,449	50,42	50,48	16,55	23,54	6,54	6,19	12,1	14,4
6	M	58	0,61	1,31	0,166	0,568	2,4	2,9	3,71	2,8	5,66	10,05	21,5	5
7	M	75	0,25	0,28	0,225	0,198	13,51	13,1	14,24	13,43	8,06	7,7	13,8	17,5
8	M	72	1,15	0,71	1,090	1,08	7,84	4,78	9,67	7,13	25,8	24,28	5,29	1,32
9	F	60	1,56	1,78	0,211	0,322	89,92	72,31	28,92	15,44	24,26	20,83	56,5	48,2
10	F	59	1,07	1,81	3,880	1,47	72,4	110,85	23,47	39,87	24	24,51	20,1	28,7
11	M	46	0,72	1,36	0,107	0,562	3,68	5,64	4,54	8,2	15,89	6,69	16,5	5
12	M	64	1,67	1,3	2,140	0,111	18,8	16,42	9,24	8,67	25,8	28,48	18,7	11,9
13	F	45	1,05	1,03	0,432	0,325	3,04	4,32	1,93	0,98	26,86	24,1	16,7	6,23
14	F	48	1,61	12,65	0,488	0,36	98,15	102,8	37,16	45,6	10,16	12,6	13,8	5,21
15	M	38	2,03	1,12	0,050	0,271	4,5	4,82	4,07	2,97	12,37	13,53	18	14
16	F	73	1,42	2,89	0,575	0,168	16,13	55,52	1,25	17,19	13,03	10,67	21,6	14,3
17	F	80	1,22	1,8	0,301	0,298	35,23	41,89	10,81	11,84	11,3	8,66	17,7	9,34
18	M	69	2,27	3,65	0,842	0,021	6,09	7,41	4,74	3,98	26,44	29,32	15,6	12,9
19	M	65	0,25	0,41	0,534	0,059	4,32	3,51	2,98	3,6	7,67	9,18	19,6	15,9
20	M	63	0,28	0,28	0,280	0,147	7,98	9	9,37	7,02	17,17	19,3	59	64
21	M	57	0,11	0,83	0,101	0,05	1,33	2,02	1,39	2,97	14,83	12,14	39,4	31,2
22	M	66	0,44	1,18	0,101	0,01	29,83	23.87	13,16	11,7	10,28	13,7	12,8	5,1
23	F	37	0,82	0,37	0,229	0,117	7,74	10,79	7,49	59,8	11,06	27,69	11,7	14,6
24	F	63	0,48	1,72	0,076	0,012	33,77	46,58	16,06	18,73	12,48	16,8	21,8	18,7
25	F	64	1,16	2,07	0,372	0,021	3,91	5,31	1,15	2,17	12,42	14,6	24,9	23,8
26	M	76	0,93	2,25	0,851	0,032	30,03	32,6	11,29	14,2	4,32	6,24	11,7	13,8
27	M	77	1,34	2,19	0,356	0,013	11,48	10,8	6,63	5,21	9,52	11,5	14,1	17,8
28	F	82	1,76	12,55	0,454	1,67	63,26	18,05	23,01	3,13	26,83	26,9	21,7	17,9
29	F	71	1,57	2,45	0,731	0,032	49,07	64,8	26,49	34,87	9,21	13,74	23,9	26,8
30	M	74	0,88	1,33	0,269	0,05	2,1	2,8	2,02	2,36	14,69	7,99	23,5	19
31	F	65	0,77	1,45	0,100	0,02	30,34	36,8	9,12	11,4	15,95	16,73	32,8	29,7
32	M	81	0,01	0,04	0,192	1,27	7,76	5,61	13,48	7,33	12,74	31,45	12,6	13,6
33	M	41	0,31	0,52	0,050	0,05	3,74	3,22	4,09	2,08	7,31	10,77	13,2	13,9
34	M	72	0,98	1,3	0,194	0,28	36,29	41,9	16	11,16	7,44	8,55	21,5	24
35	M	73	3,47	4,64	0,068	0,096	5	7,96	6	8,24	10,74	13,03	56,3	51,4
36	M	74	1,54	1,13	0,466	0,179	5,57	7,38	7,71	9,09	41,95	18,32	13,8	15,9
37	F	49	1,05	1,32	0,250	0,977	46,3	2,4	19,55	2,71	9,03	11,33	17,8	5
38	F	88	0,95	1,48	1,490	0,01	60,12	75,4	16,73	19,87	84,57	100,7	16,7	14,6
39	F	70	1,88	1,58	0,145	0,142	125,71	147,83	83,36	105,67	18,43	13,02	20,5	22,6
40	F	69	0,68	1,59	0,261	0,104	36,29	19,34	14,92	6,73	6,38	30,37	23,7	17,1
41	M	27	0,68	0,38	0,081	0,06	1,85	2,24	6,62	7,61	4,21	14,58	34,8	31,8
42	F	82	0,74	2,38	0,472	4,26	45,67	78,86	13,66	48,76	67,59	25,62	42	23
43	M	53	0,63	3,24	0,870	0,265	29,65	2,18	4,04	6,24	32,51	23,48	29	34
44	F	71	1,24	2,76	6,36	4,15	33,11	56,8	9,1	36,8	10,7	7,35	42	24
45	F	72	0,29	1,56	0,577	1,254	39,23	48,56	2,45	4,64	10,7	14,75	33	56,2
46	M	72	0, 9	2,46	0,480	0,328	49,51	50,48	17,9	23,14	5,93	6,19	33	12,8
47	F	70	1,95	1,31	0,547	0,568	69,23	86,6	29,07	36,8	10,3	23,4	29	36

M: Month
Blue color: Values measured above normal levels
Red color: Values measured below normal levels

Table 3. Comparison of basal and month ay hormone levels of CVE patients

Hormones	CVE Group Basal (n: 47)	CVE Group Month six (n: 47)	p*
TSH	1,14± 0,78	1,99±2,59	**0,001**
GH	0,51±0,69	0,42±0,63	0,158
FSH	28,8±30,5	32,1±36,2	**0,041**
LH	13,25±14,07	14,98±19,28	0,392
PRL	16,64±13,83	17,7±15,17	0,197
ACTH	24,83±19,3	21,25±23,5	**0,002**

*p:Wilcoxon test

Discussion

Cerebrovascular event is a focal disorder of cerebral functions that can be attributed to no factors other than vascular factors, that can result in death, and that last longer than 24 hours. Primary risk factors include old age, sex (10), genetic (11,12), hypertension (13), diabetes mellitus (14,15), hyperlipidemia (16), cardiac diseases (17–20), smoking (21), alcohol consumption (22), lifestyle (23), carotid artery atherosclerosis (24), aortic atheroma (25), hemostatic factors (26,27), use of oral contraceptives (28,29), and infections (30). The literature contains limited number of studies studying the relationship between CVE and anterior pituitary hormones.

The study of Boehncke et al. (31) about post-ischemic stroke pituitary function offers significant findings about this subject matter. The mean age of 46 patients who suffered ischemic strokes (27 males and 19 females) was found to be 61,3. Thirteen patients had IV thrombolysis treatment. Combined growth hormone-releasing hormone tests (GHRH, CRH) were made on 41 and 39 patients, respectively. And basal hormone tests could be made on 5 patients due to contraindications. Pituitary dysfunction was found to an extent in 82% of the patients, with the major finding being GH-R (79,5%) and secondary finding being adrenal failure (14,6%). The GH value was below 4 µg/l in 35,9% of patients, 4–9 µg/l in 43,6% of patients, and over 10 µg/l in 20% of patients. The study found a dysfunctional axis in 26 patients, 2 dysfunctional axes in 5 patients, and one dysfunctional axis in one patient. An

examination of the prevalence of pituitary gland dysfunction showed that the dysfunction of the somatotropic axis was 79,5%, gonadotropic axis 4,3% and corticotropic axis 14,6%. While secondary hypogonadism was seen in two patients and corticotropic deficiency was found in six patients; no patients had thyrotropic deficiency. There were no significant correlations between the time after stroke and hormone levels. Gender was found to have no correlation with the incidence of pituitary dysfunction.

Bondanelli et al. (32) have conducted a study on 56 patients who had ischemic stroke. They have made their initial evaluations at month 1-3, and their second evaluations 12-15 months later. 10 patients have been lost in the first three months. Initial evaluation have shown GH deficiency in 36,95% and hypogonadism in 13,04% of the patients, and ACTH deficiency in one patient. General evaluation has found at least one anterior pituitary hormone to be deficient in 32,7% of patients. Second evaluation has, again, found at least one hormone deficiency in 35,5% of the patients. Three patients have shown newly emerging GH deficiency. Initial and second evaluations have found no TSH deficiency. This study has also demonstrated that GH and gonadotropins had the most common post-CVE hormone deficiency.

And, this study, which was conducted on 47 ischemic stroke patients, TSH was found to be below the normal level (0,01–0,28 µg/dL) in 13,0% of the all-male patients in the initial evaluation. Low TSH levels (0,04–0,28 µg/dL) prevailed in three (6,4%) of them at month six. And TSH was over the normal level (>12,55 µg/dL) in two patients. GH values were below the normal level (0,05 ng/mL) only in three patients (6,4%) (1 female, 2 male) in the initial 24 hours of ischemia. Control evaluation at month six found GH values to be below normal values (0,01–0,05 ng/mL) in 25,53% (58,3% male, 41,7% female) of the patients. However, these low values were not statistically significant. GH was not measured above normal values in any of the patients. FSH values were found to be below the normal level (2,4–18,05 mIU/ml) in two patients in the initial evaluation, and in four female (8,51%) patients at month six. Initial measurements were above the normal level in 17,02% of the patients, and FSH measurements at month six were above the normal level in 23,40% of the patients. LH was below normal values (2,17-9,12 mIU/ml) in initial measurements in four patients, and at month six measurements in 10,63% of patients. At month six, LH was found to be over the normal values in 23,40% of the patients. Six month evaluation found that

ACTH values were under normal level (p=0.002) in 17,02% (4 female, 4 male) of the patients. No PRL deficiency was found in any patient at month six.

Study limitations

Combined growth hormone-releasing hormone tests (GHRH, CRH) could not be performed. A control group in the appropriate age range could not be included. The study contains no data about the condition of the post-stroke long-term pituitary function.

In conclusion, TSH, PRL, GH, ACTH, FSH and LH control values measured at month six were found higher than basal values in our study. However, such high values were statistically significant for TSH, ACTH and LH. Our study contains no data about the condition of the post-stroke (> 6 ay) long-term pituitary function. Further studies are needed in order to better understand the pathophysiology of the causal relationship between pituitary dysfunction and stroke.

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