Original article:

Study of anterior pituitary function in patients of cerebrovascular accident: an observational study from eastern India

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Abstract:

Aims and Objectives: To determine the prevalence of anterior pituitary hormone dysfunction in patients of cerebrovascular accident (CVA) and to evaluate the effects of this dysfunction in the prognosis of CVA.

Materials and Methods: Observational, longitudinal**,** hospital-based, single centered study included 300 patients treated under department of General Medicine at IPGME&R, Kolkata who were diagnosed with CVA or stroke. Blood investigations like complete blood count, urea, creatinine, fasting and post prandial glucose, lipid profile, serum sodium and potassium were done. Anterior pituitary hormone testing included FT3, FT4, TSH, FSH, LH, IGF1, Prolactin, Cortisol and ACTH. Other relevant investigations were done as indicated.

Results: Of 300 patients 109 patients were of hemorrhagic type of CVA (36%) and 191 patients had ischemic type of CVA (64%). At baseline IGF 1 ($p<0.0001$), FSH ($p=0.36$), FT3 ($p<0.0001$), FT4 ($p=0.11$) and TSH ($P<0.0001$) values were lower than normal range whereas ACTH ($p<0.0001$), cortisol ($p<0.0001$), LH ($p=0.03$) and PRL ($p<0.0001$) value were higher than normal range. After six-month IGF1, ACTH, cortisol, prolactin , FT4 , FT3 values were found to be within the normal range in majority of the patients.**Conclusion:** There was statistically significant difference in level of IGF1, LH, Free T3, cortisol, ACTH and prolactin at six month of evaluation. Further study are required to better understand pathophysiological relation between stoke and pituitary dysfunction.

Keywords: Cerebrovascular accident , Thyroid stimulating hormone

Introduction:

Cerebrovascular accident (CVA) or stroke happens to be one of the most common and devastating disorder. It includes ischemic stroke and hemorrhagic stroke. It is the second leading cause of death worldwide after coronary artery disease. Also it is the commonest cause of chronic adult disability. The lifetime risk of stroke after 55 years of age is 1 in 5 for women and 1 in 6 for men.[(1)] More than four-fifth of all strokes occur in developing countries. Atherosclerosis of intracranial arteries remains the commonest cause of ischemic stroke in India. Based on neuroimaging findings, recent studies have determined the stroke subtypes and the ratio of

cerebral infarct to hemorrhage range as 1.86:1-2.21:1.[2,3] Hence, cerebral hemorrhage is proportionately much higher in the Eastern Indian community than in Western countries where the ratio of infarct to hemorrhage is 5:1. Incidentally, the high incidence of cerebral hemorrhage also has been noted among Chinese population. [4]
Pituitary hormones are involved in for responding appropriately to stress and maintaining different vital body functions. The vasculature of the pituitary gland is complex. The anterior lobe and posterior lobe have the same venous drainage (anterior and posterior hypophyseal veins) whereas they have an individual arterial supply:
The anterior pituitary gland receives arterial supply from the superior hypophyseal artery (a branch of the internal carotid artery). This vessel first forms a capillary network around the hypothalamus and anterior pituitary known as the hypothalamo-hypophysial portal system. This system allows the hypothalamus to communicate with the anterior pituitary via the release of neurotransmitters into the bloodstream.
The infundibulum and posterior pituitary gland receive a rich blood supply from many arteries. Of these, the major vessels are the superior hypophyseal artery, infundibular artery and inferior hypophyseal artery.

Endocrine disorders contribute to the long-term morbidity of the stroke survivors and are often undiagnosed / underdiagnosed due to lack of significant symptoms attributable to the hormonal dysfunction(5). Endocrine disorders are reported to occur in 15–55% of stroke survivors(6). The blood supply of pituitary and hypothalamus get affected during the vascular insult in the brain. Basal hormone measurements are used in evaluating pituitary functions in addition to clinical findings [7, 8].The clinical findings of pituitary hormone deficiency [9] 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.. Here we have planned to observe the anterior pituitary function in our patients diagnosed with a stroke at the time of admission and follow up after 6 month.

Materials and Methods:-

Observational, longitudinal**,** hospital-based, single center study conducted on patients diagnosed with CVA. The total number of patients under study was 300 with study period from February 2016 to October 2017.
During the first study visit, written informed consent was obtained from the patients or their relatives, as required. A detailed history taking and thorough clinical examination with special emphasis to neurological system were done on all patients. Investigations including complete blood count, fasting and post prandial blood glucose, serum urea, creatinine, lipid profile, LFT, sodium and potassium were done by collecting the blood samples at the time of admission. Special tests performed to identify anterior pituitary functions included IGF1, FSH, LH, TSH, FT3, FT4, ACTH, Cortisol and Prolactin at the time of admission and all tests were repeated after 6 months.

Statistical Analysis:-

Data will be summarized as mean ± standard deviation for numerical variable and counts & percentages for categorical variables. Data will be analyzed with appropriate statistical tests and methods to determine the significance and power of study. Software used in the study was SPSS 20.

P-value ≤ 0.05 was considered for statistically significant.

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Results:

Out of total 300 patients 31% were male and 69% were female with a mean age of 55.1 years (range: 18–88). 109 patients had hemorrhagic type of CVA (36%) and 191 patients had cerebral infarct (64%).

IGF1, FSH, LH, FT3, FT4, TSH, ACTH, Cortisol and Prolactin levels were checked in both the group at the time of admission and were followed up at 6 months.

The pituitary hormones in hemorrhagic type of CVA were shown in Table 1**.**

Table 1: Pituitary hormones levels in hemorrhagic type of CVA

Parameters	**Above Normal**	**Below Normal**	**Abnormal**	**Normal**	**P Value**
FSH					
Admission	-	16	-	93	**0.3660**
After 6 Months	1	11	-	97	
LH					
Admission	35	-	-	74	**0.2956**
After 6 Months	28	-	-	81	
Cortisol					
Admission	103	01	-	05	**<0.0001**
After 6 Months	1	-	-	108	
ACTH					
Admission	109	-	-	-	**<0.0001**
After 6 Months	03	-	-	106	
IGF 1					
Admission	189	-	-	02	**<0.0001**
After 6 Months	05	-	-	186	
TSH					
Admission	4	-	-	105	**<0.0001**
After 6 Months	28	8	-	73	
FT4					
Admission	-	20	-	89	**0.35629**
After 6 Months	-	15	-	94	
Prolactin					
Admission	37	04	-	68	**0.0092**
After 6 Months	23	-	-	86	
FT3					
Admission	-	54	-	55	**<0.0001**
After 6 Months	-	01	-	108	

(p-value ≤ 0.05 was considered for statistically significant)

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Thyroid-stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and adrenocorticotropic hormone (ACTH), IGF 1(Insulin like growth factor 1) and FT 4 (Free T4).

The pituitary hormones levels in infarct type of CVA were shown in Table 2.

Table-2: Pituitary hormones levels in infarct type of CVA

Parameters	Above Normal	Below Normal	Abnormal	Normal	P Value
FSH					
Admission	-	16	-	175	**0.4684**
After 6 Months	1	20	-	170	
LH					
Admission	77	-	-	114	**0.0544**
After 6 Months	59	-	-	132	
Cortisol					
Admission	182	-	-	09	**<0.0001**
After 6 Months	-	-	-	191	
ACTH					
Admission	191	-	-	-	**<0.0001**
After 6 Months	21	-	-	170	
IGF 1					
Admission	-	297	-	03	**0.0001**
After 6 Months	-	08	-	292	
TSH					
Admission	4	-	-	187	**<0.0001**
After 6 Months	46	17	-	128	
FT4					
Admission	-	35	-	156	**0.2087**
After 6 Months	-	26	-	165	
Prolactin					
Admission	63	12	-	116	**0.0001**
After 6 Months	44	-	-	147	
FT3					
Admission	-	107	-	84	**<0.0001**
After 6 Months	-	06	-	185	

Thyroid-stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), adrenocorticotropic hormone (ACTH), IGF 1(Insulin like growth factor 1) and FT 4 (Free T4).

Overall in the CVA patients, at baseline IGF 1 ($p<0.0001$), FSH ($p=0.36$), F T3 ($p<0.0001$), FT4 ($p=0.11$), TSH ($P<0.0001$) values were lower than normal range and ACTH ($p<0.0001$), cortisol ($p<0.0001$) , LH($p=0.03$) and PRL ($p<0.0001$) value are higher than normal range.

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After six-months IGF1, ACTH, cortisol, prolactin, FT4, FT3 values were found to be in normal range in majority of the patients.

Discussion:

We conducted the study over a period of about 18 months on patient of CVA. Total 300 patients were included, out of which 117 were male patients (31%) and 183 were female(69%) with a mean age of 55.1 years (range: 18-88 years).

The pituitary dysfunction at the time of admission were decrease in IGF1 in 297 patients (99 %) , increase in ACTH in 291 patients (97%), increase in cortisol in 285 patients(95%), low Free T3 in 161 patients (53%), increase in prolactin in 100 patients (38%), increase in LH in 112 patients (37%) with minor change as low Free T4 in 55 patients (18.3%), low FSH in 32 patients (10.6%) and increase TSH in 8 patients (2.6%).

An examination of the prevalence of pituitary gland dysfunction showed that the dysfunction of the somatotropic axis was found in 99% of patients, corticotropic axis in 97%, thyrotropic axis in 53%, gonadotropic axis in 37% of cases. Gender was found to have no correlation with the incidence of pituitary dysfunction. Both infract and hemorrhage group showed similar incidence of pituitary dysfunction. The key findings of the study are that significant numbers of these patients had pituitary hormonal dysfunction at the time of diagnosis, low IGF1 (47%) being most common, followed by low FSH (35%) being the 2nd most common, followed by hyperprolactinemia (32%) & cortisol deficiency (19%). Almost all patients had high ACTH (99%) value probably stress related. 7 patients had low TSH and FT4 value.

At 6 month evaluation pituitary dysfunction was present in 37 % of CVA patients of which major finding being dysfunction of TSH in 33 % of patients where 74 patients had above normal range of TSH and below normal range of TSH was observed in 25 patients. LH level remained elevated in 87 patients (29%), Prolactin level remained persistently elevated in 67 patients (22.3%). FSH dysfunction present in 11% of the patients of which 31 patients remained below normal as in baseline and 2 patients newly developed elevated FSH value. ACTH value remain elevated in 24 patients(8%) , IGF1 remains below normal in 8 patients(2.6%) and cortisol value remain elevated in only 1 patient and in the remaining patients cortisol value normalized after 6 months of follow up. There is no significant difference in prevalence of hormone dysfunction in infarct and hemorrhagic type of CVA. One had central hypothyroidism and seven (23.3) showed low levels of LH and/or FSH.

This study demonstrated that most common hormone dysfunction in acute stage of CVA is low IGF1 followed by ACTH followed by cortisol which normalized in most of the patients within 6 month following the CVA episode. In the late phase, (i.e. after 6 month) new TSH abnormality detected in the form of either increase or decrease from the normal value. In most of the patients following CVA two or more dysfunctional axis is evident.

Other studies also demonstrated low IGF 1 is the most common hormone dysfunction in their in the acute stage(10,11). This could be explained by the nature of underlying illness, presence of cerebral edema, coexisting atherosclerotic damage in major organs, and biological variation in the hormonal levels (12). Increased activity of the hypothalamic-pituitary-adrenal (HPA) axis is common early after stroke. Hypercortisolism is a prominent manifestation. Normally the secretion of cortisol is regulated by adrenocorticotrophic hormone (ACTH), but ACTH/cortisol dissociation after stroke was reported in several recent studies. Cytokines may influence the HPA axis, and plasma IL-6 levels are elevated following stroke(13). The adrenal glucocorticoid stress response

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in humans causes catabolism, increasing blood glucose and heart rate, and possibly potentiates ischaemic damage to neurons. These effects could induce secondary brain damage in acute stroke.(14)

Limitations: Our study has several limitations. Dynamic tests like dexamethasone suppression test, GHRH and GnRH stimulation test could not be performed. A control group of appropriate age and sex could not be included. Study does not contain data of pituitary dysfunction in long term.

Conclusion:

At 6 month of evaluation IGF1, FSH, Free T3,Free T4 value were higher than the basal value and cortisol, ACTH, prolactin and LH value ware lower than the basal value in majority of the patients. However such values ware statistically significant for IGF1, LH, Free T3, cortisol, ACTH and prolactin. Further study are required to better understand pathophysiological relation between stoke and pituitary dysfunction.

Reference:-

1. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, et al. The lifetime risk of stroke: Estimates from the Framinham Study. Stroke 2006;37:345-50
2. Banerjee TK, Mukherjee CS, Sarkhel A. Stroke in the urban population of Calcutta: An epidemiological study. Neuroepidemiology 2001;20:201-7.
3. Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Mukherjee CS, et al. A prospective community-based study of stroke in Kolkata, India. Stroke 2007;38:906-10.
4. Jiang B, Wang WZ, Chen H, Hong Z, Yang QD, Wu SP, et al. Incidence and trends of stroke and its subtypes in China: Results from three large cities. Stroke 2006;37:63-8.
5. Bondanelli M, Ambrosio MR, Zatelli MC, Basaglia N, Degli Uberti EC. Prevalence of hypopituitarism in patients with cerebrovascular diseases. J Endocrinol Invest. 2008;31:16–20.
6. Urban RJ. Hypopituitarism after acute brain injury. Growth Horm IGF Res. 2006;16:S25–9.
7. Singh S. Pituitary tuberculoma: Magnetic resonance imaging. Neuro India 2003;51:548-50
8. Ahmad FU, Sarat Chandra P, Sanyal S, Garg A, Mehta VS. Sellar tuberculoma: An unusual infection. Indian J Tuberc 2005;52:215-7.
9. Schaefer S, Hypothalamic-pituitary insufficiency following infectious diseases of the central nervous system. Eur J Endocrinol 2008;158:3–9.
10. Ioanna Dimopoulou ,Andreas T. Kouyialis, Stylianos Orfanos,Apostolos Armaganidis,,Marinella Tzanela, Nikolaos Thalassinos ,Stylianos Tsagarakis Neurocritical Care December 2005, Volume 3, Issue 3, pp 224-229 Endocrine alterations in critically III patients with stroke during the early recovery period.
11. Boehncke S. Ackermann H. Badenhoop K. Sitzer M. Pituitary Function and IGF-I Levels following Ischemic Stroke, Cerebrovasc Dis 2011; 31: 163–169
12. Maes M, Mommen K, Hendrickx D, Peeters D, D'Hondt P, Ranjan R, et al. Components of biological variation, including seasonality, in blood concentrations of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers. Clin Endocrinol (Oxf) 1997;46:587–98.
13. Åsa Johansson[a, b], Tommy Olsson[a], Bo Carlberg[a], Kurt Karlsson[b], Markku Fagerlund[c] Journal of the Neurological SciencesVolume 147, Issue 1, 20 March 1997, Pages 43–47 Hypercortisolism after stroke — partly cytokine-mediated?
14. Hanne Christensen, Gudrun Boysen, Helle Hjorth Johannesen Journal of the Neurological SciencesVolume 217, Issue 2, 15 February 2004, Pages 175–180