Occult endocrine dysfunction in patients of cerebrovascular accident

K. V. S. Hari Kumar, Sandeep Kumar[1], Faiz M. H. Ahmad[2]

Departments of Endocrinology, [1]Medicine, [2]Neurology, Command Hospital, Chandimandir, Panchkula, Haryana, India

Abstract

Background: Cerebrovascular disorders are common conditions leading to significant morbidity and mortality in the population. Occult endocrine disorders also contribute to the morbidity and we studied the prevalence of endocrine dysfunction in patients of cerebrovascular accident (CVA). **Materials and Methods:** We evaluated 30 patients of CVA (aged 18-75, admission within 72 h of symptoms and positive neuroimaging) in this prospective, observational study. All subjects were assessed clinically and biochemically for hormonal dysfunction at admission and for mortality at the end of 1 month. The patients were divided into two groups: Group 1 (infarct, $n = 20$) and Group 2 (hemorrhage, $n = 10$) and the data were analyzed with appropriate statistical tests using GraphPad Prism Software, version 6. **Results:** The study participants (24M:6F) had a mean age of 60.7 ± 11.4 years and body weight of 67.2 ± 11.4 kg. Fourteen out of 30 patients showed results consistent with an endocrine disorder, including sick euthyroid syndrome (SES) and central hypothyroidism ($n = 10$), secondary hypogonadism ($n = 3$), subclinical hypothyroidism ($n = 1$), and growth hormone (GH) deficiency in two patients. The endocrine conditions did not differ significantly between both the groups and nine out of 30 patients succumbed to their illness within 1 month. None of the hormonal parameters studied, could predict the 30 day mortality. **Conclusion:** Endocrine disorders are common in acute stage of CVA and commonest finding is a SES. Hormonal dysfunction did not differ based on the etiology of the CVA. Long-term follow-up is essential to understand the morbidity contributed by the hormonal alterations.

Key Words

Cerebrovascular accident, endocrine disorder, hypogonadism, hypothyroidism, sick euthyroid syndrome

For correspondence:
Dr. K. V. S. Hari Kumar, Department of Endocrinology, Command Hospital,
Chandimandir, Panchkula - 134 107, Haryana, India.
E-mail: hariendo@rediffmail.com

Introduction

The prevalence of cerebrovascular accident (CVA) or stroke is increasing in frequency amongst the general population due to increased prevalence of diabetes and hypertension.[1] Stroke poses the risk of immediate mortality and long-term morbidity in the survivors with residual disability. The commonest underlying etiology of the CVA is vascular occlusion leading to infarction of brain.[2] Hemorrhagic stroke is less frequent than ischemic stroke and is due to aneurysmal rupture or malignant hypertension.[3] The identification of underlying etiology is essential for the initial management and also helps in long-term prognostication of the patients. Patients with

hemorrhagic stroke have higher short-term mortality, but ischemic stroke patients have a significant long-term disability and morbidity.[4] Long-term rehabilitation of stroke survivors includes multidisciplinary care looking at neurological, physical, social, and emotional aspects.

Endocrine disorders contribute to the long-term morbidity of the stroke survivors and are often undiagnosed 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 affects during the vascular compromise in the brain. The most common endocrine disorders include alterations in thyroid and gonadal axes. Previous reports showed the ability of the hormonal parameters in the prediction of long-term disability.[7] Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) administration resulted in the neuroprotective effects in animal and human studies.[8] There is no significant research on the endocrine disabilities in the acute phase of stroke and also about the endocrine dysfunction with respect to the etiology of CVA. Hence, we conducted this study to assess the prevalence of occult endocrine dysfunction in patients of stroke during the

acute phase of illness and followed-up the patients till 1 month to identify the hormonal predictors of survival after stroke.

Materials and Methods

We conducted this prospective, observational study at a tertiary level referral hospital in India. All patients with a diagnosis of CVA (aged 18-75 years) presented to our hospital within 72 h of onset of symptoms were included in the study as shown in Figure 1. CVA was diagnosed based on the following criteria:
1. Sudden onset monoparesis or hemiparesis lasting for more than 24 h and
2. Neuroimaging reveals findings consistent with infarct or hemorrhage. Patients with neurological deficit and negative initial scan findings underwent a repeat scan after 72 h to confirm the diagnosis.

The patients with known thyroid or endocrine disorders, previous history of radiation exposure, intake of drugs like glucocorticoids, estrogen, or testosterone were excluded from the study. All patients who received thrombolytic therapy for the stroke are excluded from the study.

All the patients were admitted to the intensive care unit initially and were given standard management as per the clinical condition. The control of blood pressure, glycemic status, and ventilator care was as per the standard management protocol of an acute stroke patient. All the patients were followed-up for a period of 1 month after the admission to determine the all-cause mortality rate. The patients were subdivided into two groups based on the etiology of CVA: Group 1 (infarct) and Group 2 (hemorrhage). The division into the groups was based on the findings of neuroimaging and patients with hemorrhagic transformation of an infarct were included in Group 1 only. The local ethics committee approved the trial protocol and verbal informed consent was obtained from all the patients or their relatives as applicable.

A fasting blood sample was collected from each patient at 0800 h in fasting state on the next day after admission. The

Figure 1: CONSORT diagram of the study. CONSORT = Consolidated standards of reporting trials

serum was separated and stored at −80°C for simultaneous analysis. All the samples were analyzed for pituitary profile (GH, IGF-1, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), and adrenocorticotrophic hormone (ACTH)), thyroid profile (free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (T3), total thyroxine (T4), and thyroid stimulating hormone (TSH)), and adrenogonadal profile (cortisol, total testosterone, estradiol (E2), dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS)). Patients with morning cortisol less than 200 nmol/L were subjected to modified ACTH stimulation test.[9] We did not do dynamic testing for the evaluation of somatotropic, gonadal, and thyroid axes involvement. The entire hormonal panel was evaluated using electrochemiluminescence assay barring IGF-1 and testosterone, which were measured by the enzyme immunoassay (EIA) method.

Primary hypothyroidism is defined as low FT4 (normal, 0.8-2.1 ng/ml) with elevated TSH (normal, 0.5-5.5 µIU/ml) and subclinical hypothyroidism as normal FT4 with raised TSH. Sick euthyroid syndrome (SES) is defined by the presence of low T3 or low T4 along with normal TSH levels. Secondary hypothyroidism is defined as low FT4 or FT3 with normal or low TSH levels. In this study, we combined the SES and secondary hypothyroidism into a single group, as we did not measure the reverse T3 to differentiate between these two entities. Primary hyperthyroidism is defined as elevated FT4 with low TSH and subclinical hyperthyroidism as normal FT4 with suppressed TSH. Hypogonadism is defined in males with testosterone less than 300 ng/dL (normal 310-1,200 ng/dL) and amenorrhea along with E2 <30 pg/ mL in females. The hypogonadism was termed as primary (elevated LH and FSH) or secondary (low or normal LH/ FSH). Adrenal insufficiency is diagnosed when 8AM cortisol is less than 100nmol/L and stimulated cortisol is below 500 nmol/L. We did not study the relative adrenal insufficiency in the subjects and a total of nine patients underwent the ACTH stimulation test. The concept of the "critical illness related corticosteroid insufficiency" is controversial with no consensus about the definition and diagnostic criteria. Hence, we used the standard cut-off values to define the adrenal insufficiency. An IGF-1 level below the age specific range is considered as diagnostic of GH deficiency (GHD). Complete hypopituitarism was diagnosed in the presence of dysfunction of three or more hormonal axes and partial hypopituitarism in cases with two hormonal axes dysfunction.

Data are presented as mean ± standard deviation (SD) and a comparison between the groups was done using nonparametric (Mann-Whitney U test) and Fisher's exact tests. The ideal method of comparison between the groups of small sample size is using the median and interquartile range instead of mean ± SD. However, Mann-Whitney U test may also be used for analyzing the means, when the normality assumption is not violated. Logistic regression analyses were conducted to analyze the association between the 30-day mortality and all hormonal parameters. The statistical analysis was done using the GraphPad Prism Software, version 6 (GraphPad Software, San Diego, CA, USA).
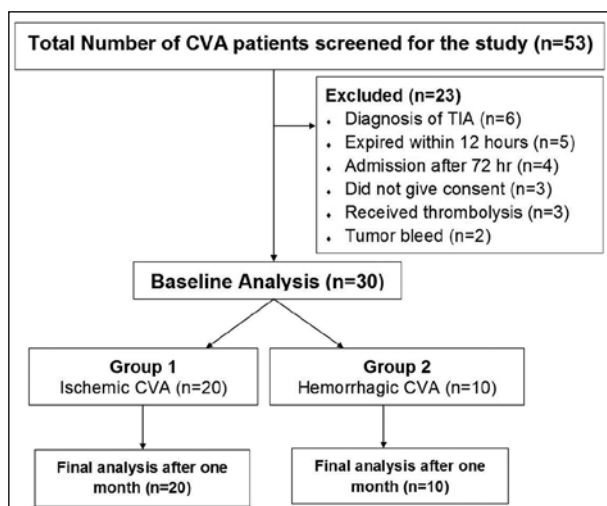
Results

The study participants consist of 24 males and six females with a mean age of 60.7 ± 11.4 yearsand body weight of 67.2 ± 11.4 kg. Twenty patients had an ischemic stroke and the remaining 10 had a hemorrhagic stroke. The CVA involved right-sided deficit in 17 patients and 13 patients had left-side involvement. Nine out of 30 patients succumbed to their illness within 1 month of observation. The individual causes of mortality were not analyzed in the study as the numbers were small in comparison.

The comparison between the groups regarding the clinical profile and hormonal parametersis given in Table 1. Fourteen out of 30 patients showed results consistent with an endocrine disorder, includingSES and central hypothyroidism (n = 10), secondary hypogonadism (n = 3), subclinical hypothyroidism (n = 1), and GHD in two patients. Two patients had partial hypopituitarism and none of the participants showed features of complete hypopituitarism. The endocrine conditions did not differ significantly between the individual groups. None of the patients had primary hypothyroidism, hyperthyroidism, hypocortisolism, and primary hypogonadism.

The comparison between the groups regarding the hormonal profile is also given in Table 1. Briefly, the findings include low levels of IGF-1 and DHEAS in patients with infarct when compared to patients with hemorrhagic CVA. Thyroid panel and other hormones did not show any alteration between both the groups. We also analyzed the data as per the side of the stroke (right vs left) and the survival status of the patient (data not shown). This subanalysis did not reveal any significant difference between the groups in the hormonal abnormalities. None of the evaluated parameters showed any statistically significant independent association with the 30-day mortality as shown in Table 2.

Discussion

Our study results suggest that occult endocrine dysfunction is seen in the majority (47%) of stroke patients in the acute phase. Fortunately, the major contributor is the SES, which is a self-limiting illness.[10] Acute stress induces physiological and hormonal alterations in the body and SES is a common response observed in these critically-ill patients. The occurrence of central hypothyroidism is also seen frequently during the 1st week after an ischemic stroke.[11] Previous reports also suggest suppressed thyroid function and failure of TSH stimulation during acute stroke.[12] Subclinical hypothyroidism may be an incidental finding in one of our patients and appears unrelated to the underlying stroke.

Table 1: Comparison between two groups regarding their clinical and hormonal profiles

Feature	Units	Group 1 (Infarct) n = 20	Group 2 (Hemorrhage) n = 10	*P* - value
Age	Years	60.9 (13.4)	60.4 (6.1)	0.5288
Sex	M:F	16:4	8:2	0.9684
Duration of CVA	Days	1.5 (0.8)	1.7 (0.8)	0.6243
Duration of hospital stay	Days	8.4 (4.4)	10.7 (3.1)	0.1516
Side of weakness	Right:Left	12:8	5:5	0.7055
Survival status	Living: Dead	14:6	7:3	0.6696
Pituitary Profile				
Growth hormone	ng/mL	4.7 (6.2)	2.8 (2.8)	0.3672
IGF-1	µg/L	182.4 (65.6)	252.2 (94.1)	0.0252
LH	IU/L	20.2 (17.6)	12.7 (7.1)	0.2128
FSH	IU/L	19.3 (15.7)	18.6 (10.1)	0.7134
Prolactin	mIU/L	391.1 (138.3)	437.4 (138.5)	0.3268
ACTH	pmol/L	4.3 (3.1)	4.3 (2.9)	0.8279
Thyroid profile				
Total triiodothyronine	nmol/L	0.73 (0.26)	0.79 (0.2)	0.5295
Total thyroxine	µg/dL	7.6 (2.1)	7.4 (1.2)	0.9032
Free triiodothyronine	pmol/L	2.1 (0.7)	2.5 (0.8)	0.2926
Free thyroxine	ng/dL	0.86 (0.17)	0.92 (0.14)	0.5957
Thyroid stimulating hormone	mIU/L	2.9 (3.2)	3.1 (5.2)	0.3563
Adrenogonadal profile				
Cortisol (8AM)	nmol/L	219 (83.8)	258.9 (86.5)	0.2335
DHEA	ng/dL	356.3 (197.9)	431.6 (300)	0.4163
DHEAS	µg/dL	103.7 (45.2)	176.3 (71.7)	0.0134
Total testosterone (males)	ng/dL	321.9 (108.9)	314.5 (92.2)	0.7678
Total testosterone (females)	ng/dL	24.2 (19.5)	14.5 (22.1)	0.6643
Estradiol (males)	pmol/L	36.8 (15.5)	26.7 (16.4)	0.2318
Estradiol (females)	pmol/L	91.8 (25.5)	79.7 (19.6)	0.1127

Values are presented as mean (SD). CVA = Cerebrovascular accident, IGF-1 = insulin-like growth factor-1, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotrophic hormone, DHEA = dehydroepiandrosterone, DHEAS = DHEA sulfate, SD = standard deviation

Table 2: Multiple logistic regression model for survival status

Independent variable	Coefficient	Standard error	Oddsratio	*P* - value
Growth hormone	2.88226	5,842.31707	17.8546	0.9996
IGF-1	0.18106	256.30238	1.1985	0.9994
LH	−0.50983	2,038.90051	0.6006	0.9998
FSH	1.11982	1,851.34809	3.0643	0.9995
Prolactin	0.11956	244.75253	1.1270	0.9996
ACTH	4.06779	3,193.86059	58.4279	0.9990
Total T3	13.91172	118,469.97317	1.10E + 006	0.9999
Total T4	−3.26497	6,602.52788	0.0382	0.9996
Free T3	−7.37054	84,563.60331	0.0006	0.9999
Free T4	−74.15894	143,429.87246	6.21E-033	0.9996
TSH	4.06532	4,231.19549	58.2834	0.9992
Cortisol	−0.23930	551.43246	0.7872	0.9997
DHEA	0.019339	43.17903	1.0195	0.9996
DHEAS	0.15335	123.78587	1.1657	0.9990
Testosterone	−0.061180	40.03271	0.9407	0.9988
Estradiol	−0.48194	215.12418	0.6176	0.9982

IGF-1 = Insulin-like growth factor-1, LH = luteinizing hormone, FSH = follicle stimulating hormone, ACTH = adrenocorticotrophic hormone, T3 = triiodothyronine, T4 = thyroxine, DHEA = dehydroepiandrosterone, DHEAS = DHEA sulfate

Prevalence of hypopituitarism is seen in 17% (five out of 30) of acute stroke patients in our study. Previous reports suggest the prevalence of hypopituitarism in 15-45% of patients in the 1st week of the stroke.[13] PRL values were not altered in our study; whereas, previous reports suggest subnormal secretion of PRL after stroke.[14] This discrepancy could be due to the difference in the population and the single point estimation of PRL in our study. Hypopituitarism may persist in the majority of cases and is associated with aggravation of the functional disability.[13] Unfortunately, we did not observe these patients long-term to assess for the persistence of hypopituitarism. Two patients had evidence of GHD and the same contributes in increasing the cardiovascular mortality in the stroke survivors. GH has protective effect in limiting the hypoxic ischemic damage and GHD may adversely affect the functional recovery in these patients.[15]

Few studies have assessed the risk factor profile separately for the ischemic and hemorrhagic stroke patients. The evaluated parameters include microalbuminuria, glycemic load, and many other risk factors.[16,17] Our data suggest that IGF-1 and DHEAS are severely affected due to ischemic stroke when compared to hemorrhagic stroke. 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.[18] Previous reports gave conflicting evidence regarding the hormonal parameters as prognostic markers. Cortisol level helped in predicting the death and functional outcome after 1 year and other studies could not identify any hormonal parameter as a predictor of mortality.[12,13] Our study also did not show the predictive capability of any hormonal parameter on the 30-day mortality rate.

The strengths of our study include assessment of all hormonal axes in the acute phase of CVA and 100% follow-up for 1 month. Another novel finding of our study includes the assessment of endocrine dysfunction based on the etiology of the stroke. The limitations include small sample size; short follow-up period;

failure to measure free testosterone, sex hormone binding globulin, and reverse T3 to identify the SES. We did not perform dynamic testing for GHD and the diagnosis of GHD is further complicated due to the GH resistance during acute phase of critical illness and the delayed fall of IGF-1 despite GHD.[19] Our study is also limited by the lack of recovery data based on the underlying endocrine dysfunction and inability to assess the long-term hypopituitarism in stroke survivors.

Conclusion

To conclude, occult endocrine dysfunction is common in patients of CVA. The SES is the commonest abnormality followed by the involvement of somatotropic and gonadal axes. The endocrine dysfunction is not different between the ischemic and hemorrhagic stroke, even though minor differences exist in the hormonal changes based on the etiology. Further, large-scale studies with more number of patients are required to confirm the findings observed in our study.

Acknowledgements

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