HYPOTHALAMUS-ANTERIOR PITUITARY AXIS DYSFUNCTION IN STROKE: TSH RESPONSES TO ADMINISTRATION OF IV TRH

N. Taşdemir1, K. Haspolat2, M. Taşdemir3
Dicle University, Medical School, Department of Neurology, Diyarbakir, Turkey1
Dicle University, Medical School, Department of Pediatrics, Diyarbakir, Turkey2
Dicle University, Medical School, Department of Histology and Embriyology, Diyarbakir, Turkey3

ABSTRACT
We aimed to determine whether the lesion affected hypothalamus-anterior pituitary axis in 38 patients with cerebrovascular hemorrhage and infarct who did not have a thyroid disorder. For this purpose, we measured levels of serum thyroid hormones; T3 (triiodothyronin), T4 (tyroxin), FT3 (free T3), FT4 (free T4) and TSH (thyroid stimulating hormone) at 0 minute and TSH hormones were measured by RIA (radioimmunoassay) at 20 and 60 minutes after administering IV 500 μg TRH at 8:00 am. Results were compared with the control group comprising 17 euthyroidic subjects. In stroke patients, responses of TSH to TRH were variable and 28.9% had low response (n=11), 5.3% extremely delayed response (n=2) and 65.8% normal responses (n=25). TSH parameters of 25 patients with stroke and 13 patients with axis dysfunction (case group) were compared with normal control group parameters. TSH values were found to be significantly lower in stroke patients compared to the control group (p<0.001, p<0.001 respectively).

Introduction
Thyrotropin-releasing hormone (TRH) is a tripeptide that stimulates release of prolactin (PRL) and thyroid stimulating hormone (TSH) from anterior pituitary gland. TRH is found in extrahypothalamic sites at substantial levels in humans and experimental animals (1). In humans, TSH secretion is maintained under dopaminergic control. Dopamine agonists suppress TSH secretion, while its antagonists stimulate it (2).

For several years, TRH has been successfully used for treatment of amyotrophic lateral sclerosis, spinal cord injury, ataxic symptoms of spinocerebellar ataxia, endogenous depression and epilepsy due to its neuromodulator and neurotropic effects (3-8).

Impaired TSH to TRH may be seen in pituitary disorders, depression, Cushing’s syndrome, chronic renal failure and during treatment with some drugs. Among neurologic disorders, dysfunction may be possible in cerebrovascular diseases (CVD) (9-12). In addition, systemic disorders, surgical stress, fasting and hepatic disease might alter thyroid function tests in euthyroidic patients (13).

It is known that TSH response increases in the presence of hypothyroidism. In CVD patients, after excluding this condition, determining whether the lesion affects the hypothalamus-anterior pituitary axis by administering the test has been subject to many research (10, 13). Especially in early stages of stroke and severe cases remarkably variable responses have been obtained (9,10).

In this study, our objective was to determine whether there was a relationship bet-
ween TSH responses obtained at various timepoints and lesion level in stroke patients by administering intravenous TRH.

**Materials and Methods**

A total of 38 euthyroidic patients, of which 24 had intrahemispheric hemorrhage and 14 had thromboembolism, who have been hospitalized in Dicle University Medical Faculty, Department of Neurology were enrolled in this study. Their diagnoses have been made by cranial –MR imaging.

Our patients were administered IV 500 μg TRH at 8:00 am (Thypinone, Abbott). At 0 minute, T3, T4, FT3, FT4 and TSH levels were measured and at 20 and 60 minutes only TSH (thyroid stimulating hormone) was measured by RIA (radioimmunoassay) technique in blood samples obtained. Informed consent was taken from the participants of the study. Thyroid hormone levels of control group and patients were measured at Dicle University Medical Faculty, Laboratory of Department of Nuclear Medicine. T3 and T4 were measured by using Amerlex kit, FT3 by Amerlex MAB FT3 kit, FT4 by Amerlex free T4 RIA kit and TSH values by RIA technique with the use of coated tube assay in <KB 1275 gamma counter instrument with hs TSH RIA kit. With this technique normal ranges of thyroid hormones were accepted as " T3: 0.8-2.7 nmol/L; T4: 62-165 nmol/L; FT3: 4.3-6.1 pmol/L; FT4: 11.8-23.4 pmol/L; and TSH: 0.32-4.1 μIU/mL)"

In our subjects, the lesion was considered as “close to axis” if the lesion level was at periaquaductal gray matter and basal ganglia and lobar and cerebellar lesions were considered as “distant from axis”. Diagnosis of hypothyroidism was considered as primary, secondary and tertiary hypothyroidism or normal according to reduced levels of basal T3, T4, FT3 and levels of TSH responses. Euthyroid sick syndrome was enrolled based on reduced levels of T3 (14). Extreme increase was observed in TSH values already high in primary hypothyroidism (14). In secondary hypothyroidism (ie. pituitary hypothyroidism) no increase was observed in TSH value at 20 and 60 minutes (14-15). In tertiary hypothyroidism (ie. hypothalamic hypothyroidism) TSH response was found to be late and extreme (15).

Results between the patients and the control group were compared. “Student-t” test was used for statistical analysis.

**Results and Discussion**

Age and gender distribution of a total of 38 patients (24 with intrahemispheric hemorrhage (63.15%) and 14 with thromboembolism (36.84%)) is shown in [Table 1](#), serum thyroid hormone levels in [Table 2](#) and TSH responses to TRH in [Table 3](#). In the TRH test minimum increase compared to baseline was 1-2 μU/mL and normal response showed 5-10 fold increase compared to baseline.

In the light of these results and CBT findings, 6 patients out of 38 with cerebrovascular pathology were consistent with euthyroid sick syndrome. In five patients lesion was close to hypothalamus-pituitary axis and at periventricular and basal ganglia level and in 1 patient lesion was a cerebellar haematoma distant from the axis.

Pituitary hypothyroidism was seen in 11 cases, of which 8 had basal ganglia and periventricular hemorrhage and other 3 cases including 2 with frontal cortex infarct and 1 with cerebellar infarct.

Two cases with hypothalamic hypothyroidism were marked by late and extreme responses at 20 and 60 minutes. In both cases, lesion was an infarct distant to hypothalamus-pituitary axis.

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Males Females</td>
<td>Range Mean ± SD</td>
</tr>
<tr>
<td>Stroke 38 22 16</td>
<td>12-76 54.4 ± 14.0</td>
</tr>
<tr>
<td>Control 17 10 7</td>
<td>52-70 58.8 ± 3.5</td>
</tr>
</tbody>
</table>

**TABLE 1**

<table>
<thead>
<tr>
<th>Age and gender distribution of patients</th>
<th>Number of Subjects</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Males Females</td>
<td>Range Mean ± SD</td>
</tr>
<tr>
<td>Stroke 38 22 16</td>
<td>12-76 54.4 ± 14.0</td>
<td></td>
</tr>
<tr>
<td>Control 17 10 7</td>
<td>52-70 58.8 ± 3.5</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2

Baseline serum thyroid hormone levels of patients and controls (P>0.05)

<table>
<thead>
<tr>
<th></th>
<th>T3 (nmol/L)</th>
<th>T4 (nmol/L)</th>
<th>FT3 (pmol/L)</th>
<th>FT4 (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke patients</td>
<td>1.136 ± 0.088</td>
<td>102.9 ± 9.6</td>
<td>4.62 ± 0.20</td>
<td>16.77 ± 1.2</td>
</tr>
<tr>
<td>Control</td>
<td>1.65 ± 0.031</td>
<td>100.5 ± 17.0</td>
<td>4.98 ± 0.20</td>
<td>15.59 ± 1.2</td>
</tr>
<tr>
<td>Reference values</td>
<td>0.8-2.7</td>
<td>62-165</td>
<td>4.3-6.1</td>
<td>11.8-23.4</td>
</tr>
</tbody>
</table>

TABLE 3

TSH responses to TRH

<table>
<thead>
<tr>
<th>Time</th>
<th>Stroke</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>1.42±1.66</td>
<td>3.27±1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20 min</td>
<td>3.23±2.89</td>
<td>8.65±4.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60 min</td>
<td>3.20±2.68</td>
<td>5.54±2.84</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Among our cases, 25 had TSH values within normal range. In these 25 patients, lesion was basal ganglia and thalamic haematoma in 12, cerebellar infarct in 3 and cortical infarct and haematoma in 10 patients.

TSH responses to TRH were reduced by advanced age. This association was statistically significantly low at 20 and 60 minutes (r=0.514, r=0.410 and r=0.485 respectively; p<0.001).

When the association between distance of lesion site to the axis and thyroid hormone levels and TSH responses to TRH were evaluated, only FT3 level was found to be lower in lesions close to axis (p<0.05) and no association was observed between T3, T4, FT4 and TSH and lesion’s proximity to the axis (p>0.05). No association was found between TSH responses to TRH among men and women (p>0.05).

When TSH values of all our stroke patients were compared with the control group, they were significantly low at 0 and 20 minutes (p<0.001) and also at 60 minutes (p<0.01).

In recent years, it was observed that TSH responses obtained following intravenous TRH administration were found to be lower than normal values in patients with acute cerebrovascular pathology. Later, an association between TSH response and time elapsed after stroke initiation was assessed by many investigators (1, 11). A tendency to inverse relationship was reported between the degree of extremity paresis and TSH values. Low levels were sustained after regression or improvement in paresis or following mobilization of the patients. We did not find such a relation in our subjects.

TSH responses to intravenous TRH are low especially in men (9). TSH responses of our male and female patients were assessed at 0, 20 and 60 minutes. No statistically significant difference was found for gender. It has been reported that serum T3 concentration was low in many non-thyroidal disorders and CVD (10). Serum T3 levels were low in 44.7% of our study subjects. Wank et al. (16) observed transient increases in TSH levels in at least 4 patients among 95 patients with acute non-thyroidal disorder. Serum TSH and TSH responses to TRH are normal in the majority of non-thyroidal patients.

It is known that TSH responses show variability and decrease in the elderly. Thus, diagnosis of thyroid dysfunction is difficult in the elderly (11). In the study of Hagg et al (9) mean age of control and stroke patients was similar and depressed TSH parameters were apparent with advanced age in men.

In our patients it was observed that TSH responses to TRH were decreased remarkably due to aging. Our study was consistent with the literature from this aspect.

Burrows et al (2) did not report any change in TSH responses to TRH in one-third of 35 geriatric patients. However in some patients, they found an increase in the form of delayed response but could not
explain varied TSH responses in the geriatric patients. TSH responses to TRH are low in depressive patients (11). Depressive mood is frequently seen in stroke patients (11). However, none of our patients required psychiatric support or antidepressant treatment. Extremely delayed TSH response indicates hypothalamic dysfunction (15). Two of our subjects had extremely delayed response. In these patients the lesion was distant from hypothalamo-pituitary axis.

Faber (17) reported that severe non-thyroidal disorders lead to secondary hypothyroidism. Pituitary-thyroid axis was examined especially in patients with hepatic coma, cancer, respiratory failure and in patients receiving treatment for stroke and it was found that secondary hypothyroidism resulted from a marked decrease in T4, T3, FT3, FT4 and TSH concentrations. In our study, 28.94% of the subjects had pituitary hypothyroidism findings secondary to stroke. In 6 of our patients, euthyroid sick syndrome was considered. Euthyroid sick syndrome is seen in acute infections and metabolic and neoplastic disorders (18). Euthyroid sick syndrome seen in our patients was the result of non-neurologic complications secondary to stroke. Five of these patients had a vascular lesion at the periventricular basal ganglia (thus close to hypothalamo-pituitary axis) level but 1 of them had a cerebellar haematoma distant from the axis.

Hu (13) reported that in cerebral hemorrhage cases, changes in serum thyroid hormones were more remarkable compared to infarct patients and pointed out that they were correlated to the severity of acute cerebrovascular apoplexy. In our study, among 24 patients with haemorrhage and 14 patients with thromboembolism, 13 patients had dysfunction and our haemorrhagic and infarct findings (8 and 3 patients respectively) were consistent with the literature.

Liang et al (18) found that T3 abnormalities were more apparent during the acute phase and that there was a negative correlation between lesion size and T3 levels and a positive correlation with rT3 levels during the chronic phase. A positive correlation was reported between rT3 and a haemorrhage size more than 30 ml and infarct size more than 20 ml. As we were not be able to assess rT3, we could not be able to evaluate our subjects for that matter.

In summary, while TSH values were much lower than normal range in our 11 patients, 25 patients had TSH levels within normal laboratory range and 2 had greater than normal TSH values. Mean values of the stroke patients measured at 0, 20 and 60 minutes were significantly lower compared to the control group (p<0.001, p<0.01). Literature search revealed that our results were consistent with findings of Hagg (9).

However, since the lesion was located at periaqueductal region, the relation between thyroid hormone levels and TSH responses to TRH was observed only for FT3. No significant change was found for T3, T4, FT4 and TSH hormone levels.

In conclusion, while proximity of the lesion to hypothalamo-pituitary axis and reduced levels of TSH were directly related to the axis in stroke patients, in the majority of patients, it was the result of ischemic dysfunctional hormonal changes secondary to the edema which occurred due to a lesion distant from the axis.

REFERENCES