Alteration of Serum Pituitary Hormone Levels in Postmenopausal Women With Stroke

Gary M. Pepper, MD; Robert Koenigsberg, DO; Joseph L. Zito, MD; and Stanley Deutsch, PhD

Background and Purpose: The aim of this study was to determine if circulating levels of pituitary hormones are altered by stroke and, if so, whether these alterations offer insight into specific neurochemical pathways in the region of the central nervous system injury.

Methods: Twenty-eight consecutive postmenopausal women undergoing computed tomographic imaging of the brain for evaluation of clinical evidence of stroke underwent blood sampling for determination of serum levels of luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, triiodothyronine, prolactin, estradiol, and sex hormone–binding globulin.

Results: In stroke involving the caudate, serum levels of luteinizing hormone and follicle-stimulating hormone were reduced to 16% and 24% of concentrations found in those with stroke outside of the basal ganglia ($p < 0.03$ and $p < 0.01$, respectively). Levels of estradiol, sex hormone–binding globulin, thyroid-stimulating hormone, and prolactin were similar in all stroke groups. Nonspecific biochemical effects of stress that might influence hormone concentrations were assessed by measurement of serum triiodothyronine, the level of which is a sensitive biochemical correlate of disease severity. These levels were not different between stroke groups.

Conclusions: Stroke involving the caudate nucleus may interrupt neurotransmitter pathways involved in control of secretion of gonadotropins. Peripheral levels of these hormones may serve as a marker for central neurochemical disturbances associated with stroke in specific brain regions. (Stroke 1993;24:805–808)

KEY WORDS • hormones • neurotransmitters • women

Ischemic damage to the brain has been shown in animals to alter regional brain catecholamine content.1 Catecholaminergic pathways projecting to the hypothalamus, in turn, play an important role in regulating the secretion of hypothalamic releasing hormones. Disruption of catecholaminergic pathways by ischemic brain injury in humans could therefore alter hypothalamic releasing hormone production. This, in turn, could result in disturbance of pituitary hormone secretion. A previous study provided evidence of abnormal neurotransmitter control of growth hormone secretion in men and women with stroke.2 Changes in serum pituitary hormone concentrations resulting from disruption of neurotransmitter pathways within the central nervous system (CNS) might then reflect the extent or location of ischemic brain injury. In this prospective study of 28 postmenopausal women undergoing computed tomographic (CT) studies of the brain for evaluation of clinical evidence of stroke, we sought to determine whether serum levels of several pituitary hormones could be correlated to parameters of brain injury. We chose to examine peripheral concentrations of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and prolactin as representative of pituitary hormones, the secretion of which is known to be influenced by catecholaminergic pathways, as well as thyrotropin (thyroid-stimulating hormone [TSH]), which is thought to be more autonomous of this class of neurotransmitter.3 The absence of sex hormone feedback inhibition in postmenopausal women creates a tonic stimulus for gonadotropin release, making gonadotropin levels in this group potentially more likely to exhibit evidence of secretory disruption caused by stroke.

Subjects and Methods

Twenty-eight consecutive postmenopausal women older than 55 years (mean±SEM age, 77.1±2.1 years; range, 58–91 years) undergoing CT imaging of the brain for diagnostic evaluation of recent neurological findings consistent with stroke, who consented to blood drawing, were studied. All scans were performed with the General Electric model 9800 scanner at the same facility within 24–48 hours of the onset of neurological symptoms (one follow-up scan was done 10 days after the onset of symptoms [see below]). Blood for study was drawn within 24 hours of the scan. Scans were inter-
preted within 24 hours after being performed and without prior knowledge of the hormone data. Two neuroradiologists concurred on the extent and location of all findings. Women receiving steroid medication, sex hormones, or dopamine were excluded. Three women who had no CT evidence of stroke were excluded from the stroke group. One woman had biochemical evidence of thyrotoxicosis and was also excluded. Thirteen healthy age-matched postmenopausal women (mean age, 70.9±2.6 years; range, 56–83 years) provided normative data.

Blood for hormone analyses was drawn between 8 AM and 4 PM by venipuncture. To account for the pulsatile nature of the secretion of gonadotropins, two peripheral blood samples were drawn for gonadotropin determinations, at an interval of 20 minutes or more, from each subject. Gonadotropin assays were performed on these two samples, and the arithmetic mean was used in subsequent calculations. A determination was performed at a single time point for all other hormone analyses. Assays for each of the hormones studied in those with stroke were performed only after all subjects had completed CT scan examination.

Determination of LH, FSH, prolactin, and TSH concentrations in serum were made in duplicate using radioimmunoassay kits (Diagnostic Products, Los Angeles, Calif.). Estradiol assay was performed with a nonextraction method (Radioassay Systems, Los Angeles, Calif.), triiodothyronine (T3) by a solid-phase component system (Becton Dickinson, Orangeburg, N.Y.), and sex hormone–binding globulin (SHBG) by immuno- noradiometric methodology (Diagnostic Products). Normal ranges of these hormones for postmenopausal women and assay sensitivity, respectively, are as follows: LH, >21 IU/mL; 2 IU/mL; FSH, >40 IU/mL, 1.2 IU/mL; prolactin, 0–20 μg/L, 1.4 μg/L; estradiol, 0–14 pg/mL, 8 pg/mL; SHBG, 16–120 nmol/L, 0.04 nmol/L; T3, 1.53–2.91 nmol/L, 0.075 nmol/L; TSH, 0.5–4.8 mU/L, 0.3 mU/L. Interassay and intraassay coefficients of variation were <13% for all assays.

All data are presented as mean±SEM. Data were analyzed by one-way analysis of variance followed by Tukey's honestly significant difference pairwise comparisons of means or by Kruskal-Wallis nonparametric analysis of variance if variances were significantly different by Bartlett’s test. F values are given for comparisons made by one-way analysis of variance. STATISTIX 3.5 software package (Analytical Software, St. Paul, Minn.) was used for these analyses.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>n</th>
<th>LH (IU/L)</th>
<th>FSH (IU/L)</th>
<th>Estradiol (nmol/L)</th>
<th>SHBG (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>70±3</td>
<td>13</td>
<td>68.1±10.0</td>
<td>90.1±9.0</td>
<td>0.7±0.2</td>
<td>72.3±14.3</td>
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<td>1</td>
<td>76±3</td>
<td>14</td>
<td>63.0±7.0</td>
<td>96.1±10.1</td>
<td>0.5±0.1</td>
<td>55.3±5.8</td>
</tr>
<tr>
<td>2</td>
<td>73±4</td>
<td>6</td>
<td>51.8±16.3</td>
<td>70.3±12.0</td>
<td>1.9±1.3</td>
<td>54.2±13.2</td>
</tr>
<tr>
<td>3</td>
<td>88±1</td>
<td>4</td>
<td>10.0±7.0*</td>
<td>23.1±12.0†</td>
<td>1.2±0.8</td>
<td>58.3±9.4</td>
</tr>
</tbody>
</table>

Values are mean±SEM. LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone–binding globulin. Group 1, stroke outside of basal ganglia; group 2, stroke involving basal ganglia excluding caudate; group 3, stroke involving but not limited to caudate.

*p<0.02 compared with normal, and p<0.03 compared with group 1.

†p<0.01 compared with normal and group 1.

Results

Strokes involving, but not necessarily limited to, the following areas were observed by CT imaging. The number in parentheses is the number of individuals with positive findings in the area. An individual may have findings in several areas: right middle cerebral (10); left middle cerebral (4); right posterior cerebral (2); right thalamus (2); left internal capsule (3); basal ganglia excluding the caudate (putamen and globus pallidus) (6); basal ganglia including the caudate (4); white matter (2).

Gonadotropin, Estradiol, Sex Hormone–Binding Globulin

Serum LH and FSH concentrations in women with evidence of CNS lesions were stratified by location of the stroke (Table 1). The lowest gonadotropin levels were seen in those with stroke including the caudate nucleus (group 3), intermediate levels were found in those with lesions involving the basal ganglia excluding the caudate (group 2), and the highest levels were observed in the group with lesions outside of these two areas (group 1). Mean LH concentration in group 3 was reduced to 15% of that in normal postmenopausal women and 16% of that in group 1 (F=3.69, p<0.02 and p<0.03, respectively). Mean FSH concentration in group 3 was reduced to 25% of that in normal subjects and 24% of that in group 1 (F=5.60, p<0.01 and p<0.01, respectively) (Table 1). Comparing each of the stroke groups independently with the normal control group yielded similar statistical relations. There was no correlation of these findings to the number of infarcts per patient, as seen by CT examination.

Serum estradiol (by Kruskal-Wallis) and SHBG (F=0.02) concentrations were similar in all groups (Table 1).

Prolactin, Triiodothyronine, and Thyroid-Stimulating Hormone

Serum levels of prolactin (F=1.34) and TSH (by Kruskal-Wallis) were similar in all groups (Table 2). The composite mean value of prolactin for the three stroke groups, 12.3±2.2 μg/L, tended to be greater than normal (6.2±1.8 μg/L), but this relation did not reach statistical significance (F=3.44, p=0.07). T3 levels were similar in the three stroke groups (Table 2) (F=1.36); values in group 2 were less than normal (F=5.81, p<0.01).
Table 2. Prolactin, Thyroid-Stimulating Hormone, and Triiodothyronine Levels in Normal Postmenopausal Women and Those With Stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Prolactin (µg/L)</th>
<th>TSH (mU/L)</th>
<th>T3 (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13</td>
<td>6.2±1.8</td>
<td>3.1±1.0</td>
<td>1.83±0.10</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>11.1±2.8</td>
<td>2.9±1.3</td>
<td>1.35±0.15</td>
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<tr>
<td>2</td>
<td>6</td>
<td>13.1±3.6</td>
<td>2.2±0.5</td>
<td>0.95±0.25*</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>16.0±10.3</td>
<td>2.5±0.6</td>
<td>1.0±0.25</td>
</tr>
</tbody>
</table>

Values are mean±SEM. TSH, thyroid-stimulating hormone; T3, triiodothyronine. Group 1, stroke outside of basal ganglia; group 2, stroke involving basal ganglia excluding caudate; group 3, stroke involving but not limited to caudate.

*p<0.01 compared with normal.

The ages of patients in group 3 are clustered in the eighth decade (Table 1). However, the mean ages of our patient subgroups are not significantly different from each other. Also, we found that normal aging in postmenopausal women in the age range of 56–83 years is not correlated with changes in levels of LH, FSH, estradiol, TSH, T3, or SHBG. Calculation of the statistics of this study excluding those younger than 79 years reveals similar statistical relationships for all hormone measurements. Specifically, mean LH is less in group 3 (caudate stroke) compared with normal subjects (p<0.05) and group 1 (stroke not involving the basal ganglia) (p<0.04); mean FSH is less in group 3 (caudate stroke) compared with normal subjects (p<0.02) and group 1 (stroke not involving the basal ganglion) (p<0.03).

Discussion

In this study, postmenopausal women whose stroke included basal ganglia structures, which here specifically refers to the corpus striatum (the caudate nucleus, globus pallidus, and putamen) plus the amygdaloid nuclear complex, exhibited evidence of disruption of pituitary hormone secretion. In particular, women with stroke involving the caudate nucleus exhibited striking reductions of serum gonadotropin concentrations. Reduced gonadotropin levels were also observed in those with stroke of the basal ganglia structures excluding the caudate, although this did not reach statistically significant levels. Changes in serum concentrations of estradiol or SHBG, which could account for this stratification, were not found.

Severe systemic illness itself is associated with diminished serum gonadotropin levels in both women and men, with the lowest values in the most critically ill. Because individuals with stroke can be expected to exhibit this endocrine manifestation of general illness, we examined our groups for differences attributable solely to variation in disease severity. Serum T3 levels are a well-known and sensitive correlate of disease severity. We therefore used serum T3 concentrations as a quantitative measure of degree of illness, having excluded individuals with evidence of intrinsic thyroid disease from study. The mean T3 level in stroke subgroup 2 (basal ganglia infarct excluding the caudate) was less than normal. However, there were no significant differences of T3 concentrations between the three stroke subgroups. Despite the similarity of T3 levels in the stroke subgroups, gonadotropin levels were markedly lower in subgroup 3. We therefore conclude that it is the differential effects of the CNS lesions themselves that offer the best explanation for the observed stratification of gonadotropin levels, rather than influences related to disease severity. Longitudinal data help to support this conclusion. In a single case of stroke involving the caudate nucleus so studied, serum LH concentration fell from 67.2 IU/L to 3.7 IU/L and serum FSH concentration fell from 104.9 IU/L to 9.3 IU/L during a 10-day period from acute onset of neurological deficit to follow-up study. During this same period, serum T3 levels rose slightly from 0.95 nmol/L to 1.2 nmol/L, indicative of the lack of relation between alteration of gonadotropin concentration and of underlying biochemical effects attributable to disease severity. Additional studies of this type would add valuable information about the genesis of gonadotropin disruption after stroke.

Serum TSH levels were normal in all stroke subgroups. This finding is consistent with the report by Olsson et al of a group of elderly men and women with stroke in unspecified locations. Direct pituitary damage due to stroke is therefore an unlikely explanation of our results. Likewise, the normal prolactin levels in those with stroke reported here would be against nonspecific hypothalamic-pituitary damage as the explanation of the observed reductions in gonadotropin levels. It can be noted, however, that the mean prolactin level in those with caudate stroke is higher than that in the other groups. Such a finding would support the postulation that catechol pathways, in this case dopaminergic, are compromised by stroke in this region.

In a recent study of gonadotropin regulation in postmenopausal women with basal ganglia disease caused by Parkinson's disease, significant reductions of serum LH levels in those with Parkinson's disease compared with normal subjects were found. Evidence of abnormal opioid regulation of LH secretion in this disease was also presented, suggesting that such neurotransmitter disturbance could account for these findings. Other lesions in basal ganglionic structures, such as infarcts, might then be posited to evoke disruption of gonadotropin secretion through a similar mechanism.

Other investigators studying poststroke depression have suggested that strokes involving the caudate may interrupt ascending catecholaminergic input from the brainstem. Catecholaminergic input to the hypothalamus is important for regulation of gonadotropin secretion, as we have noted. Although the corpus striatum itself is not a hypothalamic afferent, the amygdala, a portion of the basal ganglia, is an afferent. Damage to this pathway (amygdalo-hypothalamic) either directly or indirectly can result in alteration of hypothalamic regulation of gonadotropin secretion. Direct tracts interconnecting the caudate with the amygdala are not known. However, the two are contiguous at the tail of the caudate, making it feasible that damage to the caudate could influence amygdaloid function.

One method by which damage to a neighboring but noncommunicating brain region could influence local neural activity is through substances released by injured brain tissue or by inflammatory hematogenous cells that have infiltrated the area. It has been demonstrated that the inflammatory neuropeptide substance P can selectively inhibit pituitary secretion of LH, and interleu-

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kin-1 α and β and tumor necrosis factor-α, when injected intracerebroventricularly, can impair LH secretion in gonadectomized rats. The release of these substances at critical CNS locations after stroke may provide another explanation of our findings.

In conclusion, in a prospective study of postmenopausal women with stroke, we have documented markedly diminished serum gonadotropin levels in those with stroke involving the caudate nucleus. This finding does not appear to be a nonspecific outcome of illness or aging. Although the number of cases studied with caudate involvement was relatively small, the differences noted were of sufficient magnitude to be highly significant. Further confirmation of these findings is required, however. Based on our observations, alterations in gonadotropin secretion could potentially serve as a marker for disturbances in CNS biochemistry after stroke, as well as an indication of location of the lesion.

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References

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