Depression and functional outcome after stroke: the effect of antidepressant therapy on functional recovery

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Aim. The optimal strategy to prevent post-stroke depression is an important but still-unresolved issue. This study examined the differences in functional recovery among post-stroke depressed patients (DP) compared to post-stroke non-depressed patients (NDP) over the course of six months after stroke.

Methods. On the basis of a semistructured psychiatric examination, DSM-IV diagnostic criteria and the Hamilton Depression score, a consecutive series of ischemic or hemorrhagic stroke patients were included in this study. They had suffered from first-time stroke, and did not have depression diagnosis before. During follow-up, treatment with 20 mg/day citalopram per os was initiated whenever a diagnosis of depression was established. Their functional recoveries were assessed using the Scandinavian Stroke Scale, the modified Rankin scale and the Barthel index during acute hospitalization, at the time of depression diagnosis and at the third and sixth month follow-up visits.

Results. Forty patients met the diagnostic criteria and 11 patients suffered from depression during the follow-up period. There were no differences in demographic variables, lesion characteristics and neurological symptoms between DP and NDP. Functional recovery in DP was impaired in comparison to NDP (P<0.05). All DP, whose mood improved after administration of citalopram, and improved daily functions living functions during the follow-up.

Conclusion. This study’s findings suggest that remission of post-stroke depression is associated with improvement in functional recovery. Early diagnosis and effective treatment of depression will help the rehabilitation outcome of stroke patients.

KEY WORDS: Stroke - Recovery of function - Depression, therapy - Antidepressive agents - Citalopram, therapeutic use.

Motor impairment is an important and common symptom of stroke. Functional recovery (FR) problems are common after stroke and may be related to the depression that develops after stroke.1-6 In other words, a depressed mood after stroke is associated with impaired FR and a poorer outcome during rehabilitation therapy.7, 8 Depression has a negative impact on FR in stroke patients and depressed patients (DP) have greater difficulties in returning to their prior social activities compared with nondepressed patients (NDP).9-11 In accordance, many studies have demonstrated that remission from post-stroke depression is associated with FR.1, 8, 12-15

A time-related therapeutic window should be considered, as well as the fact that the correlation between depression and FR is strongest during hospital admission and six months after stroke.1, 16 Both minor or major depression leads to impaired functional recovery.14, 17 Moreover, Morris et al. reported that this correlation was stronger for patients with milder forms of depres-
For the most part, depression and depression-related complications like impaired FR are neglected. This study investigated the development of depression and the differences in FR among DP and NDP within the six months after stroke.

Materials and methods

**Patient population**

Study samples were selected among all NDP affected by acute ischemic stroke or intracerebral hemorrhage from a consecutive series of patients admitted to the Department of Neurology at Kartal Education and Research Hospital in Istanbul between July 2001 and June 2003. Inclusion criteria included the following: 1) patients should have been affected by first-time stroke; 2) patients should not have been affected by depression starting within the first 15 days of the acute stroke period; 3) patients should not have been currently diagnosed with major or minor depression; 4) patients should not have currently been administered antidepressants; 5) subjects should have been between 45 and 85 years of age; 6) there should not be any medical contraindication to the administration of citalopram. In addition, they were required to have no severe comprehension deficit e.g. dysphasia or severe disarticulation, as demonstrated by their ability to correctly answer the questions. Thrombo-embolic stroke or intracerebral hemorrhage were verified by computed tomography or magnetic resonance imagining. Patients were included in the DP group if clinical evaluation, which was performed at each control by a clinical psychiatrist using DSM-IV, concluded depression diagnosis. The Hamilton Depression Scale (HDS) was used for follow-up. More than mild communication deficits and/or cognitive impairment (Mini-Mental State Status Examination Scale [MSSES] <24) was an exclusion criterion, as were relevant diseases of the central nervous system (subarachnoid bleeding, cerebral tumor, trauma; thrombosis of the venous sinus), or previous degenerative or expansive neurological disorders (e.g., hydrocephalus, multiple sclerosis, amyotrophic lateral sclerosis). Any type of abuse was another exclusion criterion.

The number of patients who met the inclusion criteria and agreed to participate in this treatment study was 46. During the study, two patients died and four patients missed the follow-up. Thus, a total of 40 patients were enrolled in this prophylactic treatment study. The study protocol was approved by the local Ethics Committee and informed consent was obtained from every patient before inclusion in the study.

**Assessment**

Personal variables were obtained at the initial evaluation. Follow-up visits were conducted in the Kartal Education and Research Hospital. Neurological and psychiatric assessments included the below-mentioned measurements. NDP were treated with standard follow-up therapy (secondary prevention protocols and rehabilitation) for stroke. DP were treated with citalopram for six months in addition to the standard stroke protocol. The neurological FR was evaluated for each patient at each follow-up.

**Measures and follow-up**

A neurological examination was performed at the beginning of the study, assessing the Barthel-Index (BI), the Scandinavian Stroke Scale (SSS) and the Rankin Scale (RS). Patients were assessed two weeks after admission and again at follow-up periods i.e. one month, three months and six months after inclusion. The examinations were undertaken through MSSE and HDS. Impairment of liver or renal function was excluded by biochemical analysis at each examination.

**Drug protocol**

The treatment period lasted six months and medication was given in a single morning dose. All 11 patients affected by depression were assigned to citalopram treatment (20 mg/day per os) whenever they revealed the symptoms of depression. The outcome of treatment was measured after four weeks from its beginning. In case the patient did not respond to treatment (HDS>13), the dose was doubled. The outcome of treatment was measured at each controls at first, third and sixth months). Afterwards, patients were offered continued antidepressant treatment for six months.

**Statistical analysis**

Statistical analyses were performed by mean and standard deviation. The student’s t test was used for the parametric data and intergroup comparisons. Frequency distributions were analyzed by means of chi-square tests. The primary outcome measure was the average change in FRs (BI, SSS, RS) after six
months of treatment. As a target of this study, the effects of antidepressant therapy on FR were evaluated by comparison of the two groups at each follow-up. A P value <0.05 was considered significant.

Results

Results concerning the 40 patients who met the inclusion criteria and finished the six-month treatment, were finally evaluated. Of the 40 patients considered who finished the study per protocol, 27 (67.5%) were males and 13 were (32.5%) females. At the time of inclusion, disability scores in DP and NDP were similar, as shown in Table I. Within several weeks after stroke, seven patients developed depression. At the third month control, four new patients suffered from depression. One patient affected by previously diagnosed depression did not return for the third month control visit, and was thus excluded from the sixth month analysis. At the sixth month control, all 10 patients were found to be normal upon psychiatric examination.

After the development of depression, the velocity of improvement of physical disability related to stroke decreased in each DP. At the beginning of the study, the mean HDS score was 2.73±3.26, and then increased to 14.5±0.58 (Table II). Mean HDS scores significantly decreased within six months after citalo-

Table I.—Comparison of sociodemographic and follow-up variables of the study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke patients affected by depression</th>
<th>Stroke patients not affected by depression</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The number of patients affected by</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>8 (25.8%)</td>
<td>23 (74.2%)</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>3 (33.3%)</td>
<td>6 (66.6%)</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (53.9%)</td>
<td>6 (46.1%)</td>
<td>13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>4 (14.8%)</td>
<td>23 (85.2%)</td>
<td>27</td>
<td>NS</td>
</tr>
<tr>
<td>Age mean (years±SD)</td>
<td>62.27±10.14</td>
<td>64.45±8.89</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SSS scale mean at acute stroke</td>
<td>3.60±2.46</td>
<td>3.13±2.24</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BI scale mean at acute stroke</td>
<td>11.90±7.25</td>
<td>12.70±5.71</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>RS scale mean at acute stroke</td>
<td>3.20±1.32</td>
<td>3.20±0.89</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SSS scale mean at diagnosis</td>
<td>3.20±2.30</td>
<td>1.77±1.43</td>
<td>NS</td>
<td>0.02</td>
</tr>
<tr>
<td>BI scale mean at diagnosis</td>
<td>14.60±6.52</td>
<td>15.93±4.36</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>RS scale mean at diagnosis</td>
<td>5.00±0.94</td>
<td>2.57±1.10</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SSS scale mean at 3rd month</td>
<td>2.67±2.00</td>
<td>1.50±1.17</td>
<td>NS</td>
<td>0.03</td>
</tr>
<tr>
<td>BI scale mean at 3rd month</td>
<td>15.78±5.67</td>
<td>18.00±3.02</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>RS scale mean at 3rd month</td>
<td>2.33±1.22</td>
<td>2.00±0.95</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SSS scale mean at 6th month</td>
<td>1.56±1.42</td>
<td>1.27±1.01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BI scale mean at 6th month</td>
<td>16.44±4.69</td>
<td>18.83±2.38</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>RS scale mean at 6th month</td>
<td>2.00±1.22</td>
<td>1.73±0.94</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS: not significant; SD: standard deviation; SSS: Scandinavian Stroke Scale; BI: Barthel Index; RS: Rankin Scale.

Table II.—The Hamilton Depression Scale of patients during the follow-up period.

<table>
<thead>
<tr>
<th>Evaluation time</th>
<th>Patients affected by depression</th>
<th>Patients not affected by depression</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDS Mean±SD N</td>
<td>HDS Mean±SD N</td>
<td></td>
</tr>
<tr>
<td>At acute stroke period</td>
<td>2.73±3.26 11</td>
<td>1.69±2.63 29</td>
<td>NS*</td>
</tr>
<tr>
<td>At the diagnosis of depression</td>
<td>12.63±3.50 8</td>
<td>2.34±2.10 32</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>At the 3rd month evaluation</td>
<td>14.50±2.58 4</td>
<td>3.29±2.48 36</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>At the 6th month evaluation</td>
<td>4.42±2.59 10</td>
<td>2.62±2.54 29</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: not significant; SD: standard deviation; HDS: Hamilton Depression Scale.
Bilge

EFFECT OF ANTIDEPRESSANT THERAPY ON FUNCTIONAL RECOVERY AFTER STROKE

Pram use (P<0.00). At the sixth month control, the HDS scores were similar between DP and NDP. Parallel with recovery from depression, physical disabilities also diminished: BI score increased, RS and SSS score decreased significantly in the citalopram group (Figures 1, 2, 3). At six months after the beginning of the study, all scales revealed similar FRs in DP and NDP. No serious side effects related to citalopram were detected, except some minor side effects like dizziness and nausea. No patient left the study owing to side effects of antidepressant medication. All patients were administered a 20 mg/day dose citalopram. They did not require any overdose.

Discussion

Depression following stroke is seen in 20-50% of patients, and the risk is higher during the first three months.23 Similar to previous reports, the ratio of depression in this study was 27.5%, and no new depression diagnosis was made at the six-month examination. There was no relationship between depression and stroke types, and the prevalence of depression in female patients was higher than in previous reports.24-27 In this study, two groups of post-stroke patients were compared in terms of FR: in the first group depression was treated with selective serotonin reuptake inhibitor (SSRI)-citalopram, the second group included NDP instead. Results showed that DP who had a remission from their post-stroke depression over the first few months after stroke also rehabilitated well and demonstrated an FR similar to NDP at the sixth month examination. In other words, the present study confirmed the negative role of depression on the outcome of post-stroke patients. But, it important to also acknowledge the socio-demographical and methodological limitations of this study. First, the patients examined belonged predominantly to the lower education class, and it is uncertain whether these findings pertain to other populations of stroke patients. Second, the patients were seen only four times during follow-up, so a false positive diagnosis of depression was possible. Third, there was no placebo group but, because depression is an important issue with a negative effect on FR, as shown in previous reports, an antidepressant was administered to all DP because of ethical reasons.2, 3, 7, 9-11, 12, 28, 29 On the other hand, none of the NDP developed depression and used any SSRI dur-
ing follow-up. This supported the negative effect of depression on FR more than the use of SSRI in the study.

Conclusions

Post-stroke emotional incontinence or anger is related to serotonergic dysfunction in the brain. In addition, post-stroke depression seems to be associated with multiple neurotransmitter dysfunctions, including the adrenergic system, as well as with patients' psychogenic reaction related to physical or social/environmental difficulties. Depression and emotional disturbances are associated with a less successful rehabilitation therapy outcome after stroke. This study demonstrated that patients who had a remission from their post-stroke depression over the first few months after stroke also showed significantly greater improvement in their functions.

The need for early recognition and treatment of post-stroke DP has often been emphasized. In fact, there are many antidepressives used for depression after stroke. Recent studies demonstrated that citalopram may be a promising approach, due to its safety and tolerability in DP patients after stroke. Supporting these reports, repeated measurements in the present study showed that FR increased after administration of citalopram. As citalopram was administered to all DP, questions could be raised regarding the prognosis of patients without treatment. Although this study did not include any control group, the increase in FR after therapy suggests the potential utility of the antidepressant. In fact, remission from depression led to an improved FR over the first few months after stroke. In contrast, a high level of depression resulted in decreased concentration and energy, leading to poor recovery.

This study sample may have been too small, but this is the result of the above-mentioned selection criteria. The patients were required to have no severe comprehension deficit and be first-ever stroke patients with depression independent of the ischemia.

In conclusion, depression is a common problem independent of the stroke type that affects FR, even in cases of first stroke. Therefore, it is clear that patients affected by depression needed to be treated with antidepressants after stroke, not only in order to improve their psychiatric status, but also their FR.

References


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