Evaluation of Estrogen Treatment in Female Patients with Dementia of the Alzheimer Type

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Abstract. This study was designed to investigate the therapeutic efficacy of estrogen in female patients with dementia of the Alzheimer type (DAT). Fifteen DAT patients with a mean age of (x ± SE) 71.9 ± 2.4 years were treated with 0.625 mg of conjugated equine estrogens orally twice a day for 6 weeks. Of the 15 DAT patients, 4 were diagnosed as mild, 7 as moderate and 4 as severe. The effects of estrogen on DAT patients were evaluated by psychometric assessments, behavior rating scales, regional cerebral blood flow (rCBF) measurement and quantitative EEG analysis. Psychometric assessments consisted of Mini-Mental State Examination (MMSE) and Hasegawa Dementia Scale (HDS). Dementia syndromes were evaluated by the GBS-Scale (GBSS) and Hamilton Depression Rating Scale (HDRS). During estrogen replacement therapy (ERT), the mean MMSE score (x ± SE) increased significantly from 11.6 ± 1.9 to 13.2 ± 2.0 at 3 weeks (P<0.01) and 13.8 ± 2.0 at 6 weeks (P<0.001). The mean HDS score increased significantly from 8.6 ± 2.1 to 11.5 ± 2.3 at 3 weeks (P<0.001) and 11.6 ± 2.6 at 6 weeks (P<0.01). Significant improvements in the mean scores of the GBSS and HDRS were also observed in the estrogen-treated group, but not in the untreated control group with a mean age of 71.2 ± 2.5 years (n=15). The rCBF was measured by single photon emission computed tomography (SPECT). ERT increased the mean rCBF significantly in the lower frontal region (P<0.01) and primary motor area (P<0.02) of the right hemisphere. The mean absolute power delta band values in both left and right frontal EEG (Fp1 and Fp2) (P<0.01) and theta1 band values in Fp2 (P<0.05) decreased significantly during ERT. It is inferred that ERT significantly improves cognitive functions, dementia symptoms, regional cerebral blood flow and EEG activity in female patients with DAT.

Key words: Dementia of the Alzheimer type, Estrogen, Neuropsychological test, Cerebral blood flow, EEG.

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with an increase in the activity of ChAT [10, 11, 12], and an increase in the binding sites of hypothalamic n-Ach-R in rats [13]. The effects of estrogen in rats, however, show sex differences: estradiol administration increased the activity of ChAT in the nucleus of the diagonal band in oophorectomized females, but caused decreases or had no effect in castrated males [14].

In postmenopausal women, estrogen administration has been associated with a positive effect on attention span, concentration and libido [15]. During estrogen replacement therapy (ERT), improvement in memory function has been noted in both pre- and postmenopausal estrogen-deficient women [15, 16] and in surgically menopausal women [17]. It has also been observed that in female DAT patients serum levels of estrone sulfate are lower than in normal senile women [18]. In the aging rat, the cessation of cyclic changes in circulating estrogen has been associated with suppression of hippocampal function; supplemental estradiol has been shown to restore hippocampal function [19]. Based upon these observations, we speculate that the decline in or cessation of cyclic changes in circulating estrogen in menopausal and postmenopausal women may be a contributing factor in the etiology of DAT.

Conversely, these observations suggest the utility of ERT in postmenopausal patients with DAT. In fact, Fillit et al. [20] and Honjo et al. [18] both reported improvement in the performance of psychometric assessments in estrogen-treated DAT patients in two separate studies. Their evaluations of therapeutic efficacy of estrogen in DAT patients were based only on the results of psychometric assessments. This study was designed to investigate the therapeutic efficacy of estrogen in female patients with DAT, and reports changes in psychometric assessments, behavior rating scales, regional cerebral blood flow (rCBF) and electroencephalogram (EEG) activity in DAT patients treated with ERT.

Subjects and Methods

Subjects

This protocol was approved by the Ethical Committee of Tokyo Metropolitan Institute of Gerontology. Informed consent was obtained from all participants and their spouses or guardians. Fifteen female patients with DAT in Tokyo Metropolitan Tama Geriatric Hospital were identified and enrolled in the study in order of application for the estrogen therapy (EST group). The other 15 patients with DAT were recruited as an untreated control (CON) group. The patients in both groups were matched for age and the severity of dementia. The mean age (\(\bar{x} \pm SE\)) was 71.9 ± 2.4 years in the EST group and 71.2 ± 2.5 years in the CON group. In the EST group, the mean scores (\(\bar{x} \pm SE\)) of Mini-Mental State Examination (MMSE) [21] and Hasegawa Dementia Scale (HDS) [22] were 11.6 ± 1.9 and 8.6 ± 2.1, respectively. In the CON group, they were 11.3 ± 1.5 and 8.0 ± 1.7, respectively. The mean number of years of education (\(\bar{x} \pm SE\)) were 8.4 ± 0.6 in the EST group and 9.1 ± 0.5 in the CON group. No significant differences between the EST and CON groups in the mean MMSE and HDS scores or the number of years of education were observed (unpaired \(t\)-test). Out of the 15 patients in the EST group, 4 were diagnosed as mild, 7 as moderate and 4 as severe. Out of the 15 patients in the CON group, 4 mild, 7 moderate and 4 severe patients were selected. In the EST group, 5 DAT patients were inpatients and the remaining 10 were outpatients. All in the CON group were outpatients. The mean durations (\(\bar{x} \pm SE\)) of illness in the EST and CON groups were 5.7 ± 0.9 years and 5.3 ± 0.4 years, respectively. DSM III-R [23] criteria were used to establish DAT diagnosis and the severity of dementia. In our study, multi-farct dementia was examined by using the Hachinsky Ischemic Score [24], and patients with a Hachinsky score above 4 were excluded.

Eleven patients out of the 15 EST group received the minimal required doses of the psychotropic drug sulpiride 30–50 mg/d (common doses: 150–300 mg/d). Seven patients in the 15 EST group received mianserin hydrochloride 10–20 mg/d (common doses: 30–60 mg/d). Eleven patients in the 15 CON group received sulpiride 30–50 mg/d and 8 received mianserin 5–30 mg/d. All of the EST group underwent a pre-treatment gynecologic examination including vaginal, cervical and endometrial Papanicolaou’s smears. Gynecologic follow-up examinations were also performed during and after ERT to evaluate side effects.
Estrogen administration protocol

ERT consisted of 0.625 mg of conjugated equine estrogens (CEE: Premarin®, Asahi Chemical Industry Co. Ltd., Japan) administered orally twice a day, continually for six weeks. Premarin is comprised of at least 10 estrogens; the estrogens present in the greatest amount are the sodium salts of estrone sulfate, equilin sulfate and 17α-dihydroequilin sulfate. This study was performed as an open trial.

Psychometric assessment and behavior rating scale

Psychometric assessments consisted of MMSE [21] and HDS [22]. Dementia syndromes were evaluated by behavior rating scales, the GBS-Scale (GBSS) [25] and Hamilton Depression Rating Scale (HDRS) [26]. Psychometric assessments and behavior rating scales were performed on all patients by T. Ohkura, M.D., K. Isse, M.D. and Katsuo Yamanaka, M.A., a postgraduate student of special education, Tsukuba University. The MMSE and HDS scores are inversely related to the degree of dementia: the higher the score the lower the degree of dementia. The full score in each test is 30 for the MMSE and 32.5 for the HDS. The GBSS and HDRS scores are directly related to the degree of dementia (GBSS) and the degree of depression (HDRS).

Psychometric assessments for MMSE and HDS in the EST group were performed just before ERT was initiated (0 week). During ERT, the assessment was performed twice at 3 weeks and 6 weeks after the initial administration. The last assessment was performed once 3 weeks after the termination of ERT. The MMSE and HDS in the CON group were performed at 3 week intervals in 9 consecutive weeks. In the EST group, the GBSS and HDRS were performed once during each of 3 periods: just before ERT, during the 4th to 6th weeks of ERT, and 3 weeks after the termination of ERT. In the CON group, the GBSS and HDRS were performed at 0 week, 4 to 6 weeks and 9 weeks. The GBSS scores were evaluated by reference to the nurses’ opinions of inpatients and the families’ opinions of outpatients.

Regional Cerebral Blood Flow (rCBF) measurements

The rCBF was measured only in the EST group. The SPECT was performed 15 min after 6 mCi 123I-IMP intravenous injection, with a rolling gamma camera GE400-AC. Box regions of interest (ROI) 12 × 12 mm² were set in 8 mm-thick horizontal slices parallel to the orbitomeatal line (OM-line) to count ROI activity in each cortex and basal nucleus. According to Johnson et al. [27], relative 123I-IMP uptake was calculated as the ratio of each cortical ROI activity to the mean (right and left) cerebellar ROI counts (cortico-cerebellar ratio: CCR). The measurement was performed in 13 regions in each hemisphere at the levels of OM-20 (20 mm above the OM-line), OM-50 (approximately 50 mm above OM-0) and OM-70 (approximately 70 mm above OM-0). The SPECT was performed once within one month before the initiation of ERT and used as a control value. Repeat SPECT was performed on all patients during the 4th to 6th weeks of ERT.

Quantitative EEG

EEG activity from 21 channels (10–20 International Electrode System) was simultaneously recorded on paper and magnetic tape. After an inspective judgement by EEG specialists, artifact-free resting records from Fp₁ (left frontal pole), Fp₂ (right frontal pole), F₃ (left frontal), F₄ (right frontal), C₃ (left central), C₄ (right central), P₃ (left parietal), P₄ (right parietal), O₁ (left occipital) and O₂ (right occipital) (ipsilateral ear reference) were quantified by fast Fourier transformation (FFT) analysis. EEG epochs (1024 points, sampling interval 5 msec) were average-accumulated 10 times with a Signal Processor (San-Ei, 7T 18). The mean absolute power values for 6 frequency bands of each subject before and during ERT were calculated. Six frequency bands are defined as follows: delta, 2.0–3.8 Hz; theta₁, 4.0–5.8 Hz; theta₂, 6.0–7.8 Hz; alpha₁, 8.0–9.8 Hz; alpha₂, 10.0–13.8 Hz; and beta, 14.0–20.0 Hz. EEG analysis was performed once within one month before estrogen administration for a control value and performed again during the 4th to 6th weeks of ERT. No EEG study was performed on the CON group.
Determination of serum levels of steroids and pituitary hormones

Blood samples were taken from all patients in the EST group before and 3 weeks after the initiation of ERT to determine serum levels of estradiol (E₂), testosterone (T), androstenedione (ASD), dehydroepiandrosterone sulfate (DHEA-S), LH, FSH and prolactin (PRL). Estriol (E₃) was determined in 10 outpatients before and during ERT. The samples were measured by radioimmunoassay (RIA) at Mitsubishi Yuka Bio-Clinical Laboratories, Inc. (MBC). Using the MBC assay kit (DIRIA-ESTRK, Sorin Biomedica, Italy), the sensitivity of RIA for serum E₂ was 10 pg/ml and E₂ levels less than 10 pg/ml were calculated as 10 pg/ml. Serum E₃ levels less than 2 pg/ml were calculated as 2 pg/ml. The mean serum E₂ value (x± SE) during the mid-follicular phase (days 6-9) of 15 women with a normal menstrual cycle in Koshigaya Hospital was 38.1 ± 3.9 pg/ml, which was lower than that measured by other kits.

Statistical analysis

Statistical analyses were performed by paired t-test.

Results

Psychometric assessment and behavior rating scale

1) MMSE: The mean score (x ± SE) of the EST group increased significantly from 11.6 ± 1.9 to 13.2 ± 2.0 at 3 weeks (P<0.01) and 13.8 ± 2.0 at 6 weeks (P<0.001), and returned to the pre-treatment level at 3 weeks after the termination of ERT. In contrast, the mean score of the CON group did not show any significant changes (Fig. 1). During ERT, 11 patients out of the 15 in the EST group showed an increase in HDS scores at both 3 and 6 weeks. Two out of the 4 severe DAT patients, one out of the 7 moderate DAT patients and one out of the 4 mild DAT patients showed no increase in HDS scores during ERT.

The improvements in the MMS and HDS scores were often observed in the questions regarding orientation in time and space (MMS and HDS), recent and remote events (HDS), calculation (MMSE and HDS), and repeating digits in reverse order (HDS).

3) GBSS: The GBSS is divided into four subscales measuring motor, intellectual and emotional functions and different symptoms characteristic of dementia. All the mean scores of the four subscales decreased significantly during ERT as level at 3 weeks after the termination of ERT. In contrast, the mean score of the CON group did not show any significant changes (Fig. 2). During ERT, 11 patients out of the 15 in the EST group showed an increase in HDS scores at both 3 and 6 weeks. Two out of the 4 severe DAT patients, one out of the 7 moderate DAT patients and one out of the 4 mild DAT patients showed no increase in HDS scores during ERT.

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Fig. 1. Changes in the scores in the Mini-Mental State Examination (MMSE) in estrogen-treated (EST) and untreated control (CON) groups.
In contrast, the mean scores of the four subscales in the CON group did not show any significant changes (Table 1). Two out of the 4 severe DAT patients and one out of the 4 mild DAT patients did not show any changes during ERT. All the remaining 13 patients showed a decrease in the GBSS score during ERT. The improvements in the GBSS scores were often observed in the following items: intellectual functions, such as impaired orientation in space and time, impaired recent and distant memory, absent-mindedness, and long-windedness; motor functions, such as motor insufficiency in taking food, deficiency of spontaneous activity, and motor insufficiency in managing personal hygiene; emotional functions, such as emotional blunting and lability; different symptoms common in dementia, such as anxiety and restlessness. The mean scores of the CON group did not show any significant changes. Daily activities of 13 patients out of the 15 EST group were also improved, which were reflected in decreases in the GBSS scores.

4) HDRS: No significant difference was observed between the EST and CON groups in the mean scores at 0 week (unpaired t-test). The mean score (± SE) of the EST group decreased significantly from 3.9 ± 0.8 to 1.3 ± 0.7 during ERT (P<0.001) and the decrease in the HDRS score remained lower at 3 weeks after the termination of ERT (P<0.001). The mean score of the CON group did not show any significant changes (Fig. 3). Two out of the 4 severe DAT patients and one out of the 7 moderate DAT patients had an HDRS score of 0 before ERT. One out of the 4 mild DAT patients had an HDRS shown in Table 1. In contrast, the mean scores of the four subscales in the CON group did not show any significant changes (Table 1). Two out of the 4 severe DAT patients and one out of the 4 mild DAT patients did not show any changes during ERT. All the remaining 13 patients showed a decrease in the GBSS score during ERT. The improvements in the GBSS scores were often observed in the following items: intellectual functions, such as impaired orientation in space and time, impaired recent and distant memory, absent-mindedness, and long-windedness; motor functions, such as motor insufficiency in taking food, deficiency of spontaneous activity, and motor insufficiency in managing personal hygiene; emotional functions, such as emotional blunting and lability; different symptoms common in dementia, such as anxiety and restlessness. The mean scores of the CON group did not show any significant changes. Daily activities of 13 patients out of the 15 EST group were also improved, which were reflected in decreases in the GBSS scores.

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Table 1. Changes in the four subscale scores on the GBS-Scale (GBSS) in estrogen-treated (EST) and untreated control (CON) groups

<table>
<thead>
<tr>
<th>Subscales</th>
<th>Groups</th>
<th>Before (0 week)</th>
<th>During (4-6 weeks)</th>
<th>After (9 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor functions</td>
<td>EST</td>
<td>8.5 ± 2.5</td>
<td>7.7 ± 2.4*</td>
<td>8.8 ± 2.6</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>9.3 ± 1.8</td>
<td>10.3 ± 2.0</td>
<td>10.4 ± 2.0</td>
</tr>
<tr>
<td>Intellectual functions</td>
<td>EST</td>
<td>30.6 ± 4.3</td>
<td>26.8 ± 4.8**</td>
<td>30.5 ± 4.6</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>32.1 ± 3.2</td>
<td>32.3 ± 3.3</td>
<td>32.9 ± 3.4</td>
</tr>
<tr>
<td>Emotional functions</td>
<td>EST</td>
<td>6.7 ± 1.2</td>
<td>5.1 ± 1.4**</td>
<td>6.7 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>6.6 ± 1.2</td>
<td>6.7 ± 1.2</td>
<td>6.9 ± 1.2</td>
</tr>
<tr>
<td>Different symptoms</td>
<td>EST</td>
<td>3.3 ± 0.9</td>
<td>1.2 ± 0.5**</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>CON</td>
<td>2.9 ± 1.0</td>
<td>2.7 ± 1.0</td>
<td>2.9 ± 1.0</td>
</tr>
</tbody>
</table>

Scores are the mean ± SE. No significant differences were observed between the EST and CON groups in the mean scores at 0 week (unpaired t-test). * P<0.02 vs. before; ** P<0.01 vs. before.
score of 1 before ERT. Out of the remaining 11 patients in the EST group, only one mild DAT patient did not respond to ERT.

**Regional Cerebral Blood Flow (rCBF)**

The mean values ($\bar{x} \pm SD$) for rCBF during ERT significantly increased from $0.471 \pm 0.126$ to $0.594 \pm 0.138$ in the right lower frontal region at OM-20 (R-LFR) ($P<0.01$) and from $0.837 \pm 0.083$ to $0.882 \pm 0.084$ in the primary motor area at OM-70 (R-PMA) ($P<0.02$) (Fig. 4, Fig. 5). The increase rates were 26.3% and 5.4%, respectively. However, 2 out of the 15 patients showed a decrease in rCBF in the R-LFR, and the decrease rates were 19.3% and 19.8%, respectively. One out of the 15 patients showed a decrease in rCBF in the R-PMA, and the decrease rate was 11.9%. No significant changes in rCBF were observed in the other regions of the brain during ERT.

**Electroencephalogram (EEG)**

The mean absolute power values ($\bar{x} \pm SD$) for the delta band significantly decreased from $16.2 \pm 8.1 \mu V$ to $12.2 \pm 4.9 \mu V$ in Fp1 and from $15.8 \pm 8.0 \mu V$ to $11.6 \pm 4.8 \mu V$ in Fp2 during ERT ($P<0.01$). The decrease rates were 24.7% and 26.6%, respectively. The mean values for the theta band also decreased significantly from $11.7 \pm 5.4 \mu V$ to $9.1 \pm 3.2 \mu V$ in Fp2 during ERT ($P<0.05$) (Fig. 6). The decrease rate was 22.2%. However, 3 out of the 15 patients showed an increase in the delta band in Fp1, and the increase rates were 8.8%, 23.6% and 12.3%, respectively. Two patients showed an increase in the
delta band in Fp2, and the increase rates were 11.5% and 24.9%. Three patients showed an increase in the theta1 band in Fp2, and the increase rates were 23.3%, 8.4% and 37.6%. No significant changes in EEG were observed in the other regions and bands during ERT.

Serum levels of steroids and pituitary hormones

During ERT, the mean serum E2 (x ± SE) increased significantly from 10.9 ± 0.6 pg/ml to 39.6 ± 4.7 pg/ml (P<0.001) and the mean serum E3 increased significantly from 2.1 ± 0.1 pg/ml to 6.1 ± 1.1 pg/ml (P<0.02). The other serum levels of steroid hormones (T, ASD and DHEA-S) did not show any significant changes. ERT significantly suppressed serum LH and FSH (P<0.001) and significantly increased PRL (P<0.01). The mean PRL level before ERT exceeded the normal PRL level (normal range of PRL is less than 14.6 ng/ml). Table 2 shows a summary of statistics for serum levels of hormones before and during ERT.

Gynecological changes and side effects

In Papanicolaou’s smears, 1 patient’s diagnosis changed from a baseline class II (primarily vaginal and cervical) to class IIIa (vaginal, cervical and endometrial), but returned to class II (vaginal, cervical and endometrial) on a repeat smear following withdrawal bleeding caused by the termination of ERT. A follow-up endometrial biopsy showed no abnormal changes. In the other 14 patients, no abnormality in Pap smears before, during or after ERT was observed. Withdrawal bleeding occurred in 13 out of 15 patients. Redness of the papilla mammae and/or transient breast tenderness were observed in most cases.

Discussion

No pharmacologic treatment except tacrine, a cholinesterase inhibitor [28], has yet been proven effective in DAT patients. In order to modify the central cholinergic deficit, Fillit et al. [20] used 2 mg/d of micronized estradiol for 6 weeks in 7 female patients with DAT. Only 3 patients showed significant improvements in attention, orientation, mood and social interaction as measured by MMSE, HDRS, and Randt Memory Test [29]. They reported that response to estradiol therapy ap-
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appeared dependent on the initial cognitive status: patients with higher HDRS scores, higher MMSE scores, and higher Randt general information and repeating numbers scores were the ones who showed improvements with therapy. Honjo et al. [18] also reported that 5 out of the 7 female DAT patients treated with a dose of 1.25 mg/d CEE for 6 weeks showed a significant improvement in HDS scores, and 6 out of 7 showed an improvement in the scores in a new screening test for dementia developed by the Japanese National Institute of Mental Health. They noted the improvements particularly in memory, orientation and calculation.

In our study, 15 female DAT patients were evaluated before, during and after ERT with 0.625 mg of CEE orally twice a day. Evaluations in-

Fig. 6. Changes in absolute power values in quantitative EEG before and during estrogen replacement therapy. No significant changes were observed in any regions or bands other than those shown here. Fp1, left frontal pole; Fp2, right frontal pole.

Table 2. Serum hormone levels before and during estrogen replacement therapy

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
</tr>
</thead>
<tbody>
<tr>
<td>E₂ (pg/ml)</td>
<td>10.9 ± 0.6</td>
<td>39.6 ± 4.7***</td>
</tr>
<tr>
<td>E₃ (pg/ml)</td>
<td>2.1 ± 0.1</td>
<td>6.1 ± 1.1*</td>
</tr>
<tr>
<td>T (ng/ml)</td>
<td>0.51 ± 0.05</td>
<td>0.51 ± 0.04</td>
</tr>
<tr>
<td>ASD (ng/ml)</td>
<td>0.427 ± 0.039</td>
<td>0.401 ± 0.042</td>
</tr>
<tr>
<td>DHEA-S (ng/ml)</td>
<td>457 ± 75</td>
<td>396 ± 43</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>22.5 ± 2.9</td>
<td>20.0 ± 0.7***</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>86.9 ± 6.5</td>
<td>5.2 ± 1.4***</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>17.7 ± 4.3</td>
<td>51.4 ± 9.0**</td>
</tr>
</tbody>
</table>

Data are the mean ± SE. All hormone levels except estriol (E₃) were determined in 15 patients in the EST group. E₂ was determined in 10 outpatients. E₃, estradiol; T, testosterone; ASD, androstenedione; DHEA-S, dehydroepiandrosterone sulfate. *, P<0.02 vs. before; **, P<0.01 vs. before; ***, P<0.001 vs. before.
cluded psychometric assessments, behavior rating scales, rCBF measurement and EEG analysis. We used the GBSS [25] to measure changes in dementia symptoms during ERT. It is constructed for rating dementia syndromes. Improvement in the EST group was observed in 10 out of 15 patients with the MMSE scores and 11 out of 15 with HDS scores. Apparent improvement in the dementia symptoms in these patients was observed not only by the authors but also by the nurses of inpatients and by the families of outpatients whose observations were reflected in changes in the GBSS scores. The families of estrogen-responded patients described improvements in patients’ deeds in daily life and requested continuation of ERT long-term. The mean scores for MMSE, HDS and GBSS returned to the baseline levels after the termination of ERT, suggesting the therapeutic efficacy of ERT in these patients.

Antidepressant effects of conjugated estrogens have been suggested by others [30, 31]. Fillit et al. [20] observed that a median baseline HDRS score was 21 in estrogen-responded patients compared with a median baseline HDRS score which was 9 in estrogen-non-responded patients. The median HDRS score in our study was 4. The low HDRS scores might be partly due to the chronic administration of low doses of sulpiride and/or mianserin. Therefore, the effect of ERT in DAT patients was not considered to be secondary to the improvement in depressive symptoms. However, although the baseline HDRS scores were low, they decreased further, and so a cognitive function-depressive symptoms link could not be dismissed.

Many investigators [15, 16, 17, 32] demonstrated the improvement in memory function in association with ERT. Ditkoff et al. [33] observed an overall improvement in mood and quality of life in postmenopausal women on ERT. However, the mechanism by which estrogen may affect cognitive and emotional functions in DAT has not yet been clarified, but the following possible explanations might be considered: links between estrogen and the synthesis of acetylcholine [9] and the activity of ChAT [10, 11, 12] and the effects of estrogen on neural cells [34]. Hagino [19] demonstrated that early-aging females exhibited a decrease in hippocampal function that was restored with supplemental E2 administration. E2 has been described as a trophic factor during neuronal development [35] and also appears to play a role in the reparative neuronal response to injury [36]. Arimatsu and Hatanaka [37] showed that estrogen enhanced survival of cultured amygdala neurons.

Goldman et al. [38] noted an effect of intravenous estradiol on the cerebral circulation in rats: within 10 min of estradiol injection, blood flow to most regions of the brain increased significantly in the frontal cortex (44%), hippocampus (36%), basal ganglia (33%) and cerebellum (27%). They reported that females were more affected than males. We did not use a quantitative method to measure rCBF. Relative 123I-IMP uptake (CCR) measured with SPECT in DAT patients reflects the severity of dementia [27, 39]. In our study, the increase in rCBF was observed in the right lower frontal region where it seemed to associate with the cholinergic neurons of the nucleus basalis of Meynert. These cholinergic neurons projected their axon terminals onto the cerebral cortex. These findings suggest that the increased 123I-IMP uptake observed in our study may be related to the increased activity of cholinergic neurons, and that ERT may improve, in part at least, the cerebral cortical function of DAT patients.

Quantitative EEG can be used to detect minor changes in brain function. It is non-invasive, provides a direct sample of brain activity in a numerical form, and is not influenced by motivational factors and practice effect as is a neuropsychological examination. An increase in theta power values was observed in mild DAT and a decrease in alpha power values was observed in moderate DAT, and when DAT became severe, an increase in delta power values was observed in addition to an increase in theta and decrease in alpha [40-42]. In our study, ERT resulted in a decrease in absolute power values for delta and theta4 bands. However, no significant increase in alpha power values was observed during ERT. The 4–6 week-treatment may have been too short to recover alpha power values, and may have affected pathological slow waves like delta and theta bands more easily than normal alpha waves in DAT brains. Two out of the 15 patients in the EST group showed an increase in delta and theta bands. The correlation between improvements in cognitive function and changes in EEG activity induced by ERT remains to be elucidated further.

ERT increased the mean serum E2 level to the values for the mid-follicular phase of the normal menstrual cycle in healthy women. The PRL level,
which was high prior to estrogen administration perhaps due to the chronic administration of small doses of sulpiride, increased further during ERT. The increase in PRL is considered to be one of the causes of slight breast tension.

In one patient, the changes in Pap smears from class II to class IIIa during ERT may be the result of improved surveillance. All patients in the EST group underwent vaginal, cervical and endometrial smear tests, but endometrial smears were often difficult to perform in the elderly whose uterine orifice was tightly closed. In this patient, after the initiation of ERT, the uterine orifice had become enlarged enough to allow a better endometrial smear sample to be taken. It is therefore possible that class IIIa tissue was present but remained undiagnosed before ERT. Adequate observation of the endometrium is necessary when estrogen is used for a long time.

In summary, estrogen treatment for 6 weeks significantly improved cognitive functions, dementia symptoms, regional cerebral blood flow and EEG activity in female patients with dementia of the Alzheimer type.

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