Association Between Family History of Affective Disorder and the Depressive Syndrome of Alzheimer’s Disease

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For each of 41 index patients with probable Alzheimer’s disease and a first episode of major depression and 71 nondepressed Alzheimer’s disease patients, two first-degree relatives were interviewed by a rater blind to presence or absence of depression in the proband. The depressed patients had significantly more first- and second-degree relatives with depression than did control subjects. The lifetime risk for major depression, adjusted for differences in age distribution, was significantly greater in first-degree relatives of index patients, suggesting that depression in Alzheimer’s disease is genetically related to primary affective disorder. Alzheimer’s disease may be useful for studying aspects of depressive pathophysiology. (Am J Psychiatry 1990; 147:452-456)

Depressive symptoms accompanying Alzheimer’s disease are not uncommon (1-7) and may be a significant cause of distress and excess disability for Alzheimer’s disease patients (8). Whether these symptoms represent major affective disorder is unclear. It is possible that depression is an understandable psychological response to the presence of dementia. However, when present, the depressive syndrome appears to respond to the usual somatic treatments for major depression, suggesting the importance of biologic components in its etiology (9-11).

Patients with primary depressive illness frequently have family histories of affective disorder (12-14). However, to our knowledge, family history of affective disorder has not been studied in Alzheimer’s disease patients with first-episode depression. We therefore conducted a family history study to ascertain whether Alzheimer’s disease probands experiencing their first episodes of major depression had more relatives with affective illness than did nondepressed Alzheimer’s disease control subjects.

METHOD

We selected index and comparison subjects from 400 consecutively referred patients who were evaluated at the Johns Hopkins Department of Psychiatry’s Dementia Research Clinic between January 1979 and January 1984 for symptoms of cognitive decline beginning in late life. We examined the charts of all such individuals to determine which of them had met criteria for a DSM-III diagnosis of primary degenerative dementia and a diagnosis of probable Alzheimer’s disease made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA) (15). At the time of assessment each patient was examined by an attending psychiatrist and underwent physical and neurological examinations and relevant blood testing; a detailed history was taken from one or more relatives. Patients with other causes of dementia, CT scans with focal findings, or Hachinski scores (16) higher than 4 were excluded from the study. Each patient’s score on the Mini-Mental State Examination (17) was recorded at the time of the initial visit.

We identified 41 patients who were diagnosed by the attending psychiatrist at the time of initial evaluation or at subsequent follow-up as suffering from a major depressive episode. These index patients were independently judged by two of us (G.D.P. and C.A.R.) both to have met the criteria for a major depressive episode according to a DSM-III checklist and to have no prior personal history of affective disorder. Negative personal history was initially determined by re-
view of relevant records and by questioning one or more informants from the patient's family and the referring physician. In addition, we identified, but excluded from study, 18 individuals with previous clear-cut episodes of affective disorder (all major depression) that predated the onset of the dementia syndrome by many years.

We selected a comparison group of 71 individuals who had been evaluated during the same time period as the index patients, had met the NINCDS/ADRDA criteria for a diagnosis of probable Alzheimer's disease, and were found to be free of any noncognitive psychiatric symptoms (depression, hallucinations, or delusions) at ascertainment and at all subsequent clinic follow-up visits. The index and comparison subjects were followed for a mean of 30 months after initial evaluation.

Of the 41 patients with depression, 29 (71%) were later treated with tricyclic antidepressants; the other patients received a variety of therapies, including ECT and neuroleptics. Subsequently, 23 patients have died (seven were index patients). The diagnosis of Alzheimer's disease was confirmed neuropathologically in 22 cases, and the other patient was found to have abnormalities due to both Alzheimer's disease and multiple infarcts.

A single trained rater, blind to the presence or absence of depression in the proband, attempted to interview at least two family members per proband by telephone. This was accomplished in 85% of the cases. Diagnoses of depression, suicide, and bipolar disorder in first- and second-degree relatives were made according to the Family History Research Diagnostic Criteria (FH-RDC) (18). In these interviews, the absence of previous episodes of affective disorder in the index patients was confirmed. Diagnoses of probable late-life primary degenerative dementia in the relatives were made by using a checklist that combined the FH-RDC with the DSM-III-R criteria for primary degenerative dementia.

In the seven cases where family members gave conflicting information, we contacted further relatives, and an attending psychiatrist blind to the presence or absence of depression in the proband was called on to make the final judgment. Completed suicides and cases of bipolar illness were also tabulated separately.

Significance levels were set at p<0.05, continuous variables were analyzed with Student's two-tailed t test, and discontinuous variables were analyzed with the chi-square test (with Yates' correction where needed).

RESULTS

The index (depressed) and comparison probands were not significantly different in age at onset of dementia (mean±SD=68.5±8.3 versus 69.3±8.5 years), age at initial clinic evaluation for Alzheimer's disease (72.3±7.6 versus 73.1±8.1 years), percentage of female patients (70.7% versus 67.6%), or Mini-Mental State score at initial evaluation (16.7±7.3 versus 16.0±6.8).

For the index group, the time (mean±SD) from the first symptoms of cognitive decline (as noted by their families) to the onset of clinically documented depression was 17.9±19.3 months; depression occurred within 12 months of cognitive decline in 48% of the cases.

The number of informants interviewed per case, numbers of currently living and total first- and second-degree relatives, and age of these relatives are displayed in table 1. There was no significant difference between groups in the number of informants interviewed per case, total number of first-degree relatives, or number of first-degree relatives currently living. Both the total number of second-degree relatives and the number of them currently alive was significantly higher for the index patients. The relatives' mean ages were not significantly different.

As shown in table 2, a positive family history of dementia occurring in late life was present in approximately half of both the index and comparison families, and there were no between-group differences in percentages of affected first-degree, second-degree, or total relatives.

In contrast, a positive family history of major depression was present in significantly more families of

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**TABLE 1. Numbers and Ages of First- and Second-Degree Relatives of Depressed and Nondepressed Probands With Alzheimer's Disease**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alzheimer's Disease Plus Depression (N=41)</th>
<th>Alzheimer’s Disease (N=71)</th>
<th>Analysis (df=110)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>t</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of informants interviewed per case</td>
<td>2.0±1.3</td>
<td>1.9±1.1</td>
<td>0.30</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of first-degree relatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8.8±4.5</td>
<td>8.0±3.0</td>
<td>1.08</td>
<td>n.s.</td>
</tr>
<tr>
<td>Living</td>
<td>4.9±3.8</td>
<td>4.1±2.3</td>
<td>1.30</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of second-degree relatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11.1±9.6</td>
<td>5.3±7.0</td>
<td>3.70</td>
<td>0.001</td>
</tr>
<tr>
<td>Living</td>
<td>7.6±8.2</td>
<td>3.4±5.0</td>
<td>3.34</td>
<td>0.001</td>
</tr>
<tr>
<td>Age of all relatives (years)</td>
<td>52.1±15.5</td>
<td>51.4±15.6</td>
<td>0.21</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Alzheimer's disease patients with depression than in the families of the nondepressed probands. Positive family histories of major depression or suicide were found in more than 50% of the index patients. Both the first- and second-degree relatives of the depressed probands had higher rates of depression, excluding suicide, than the relatives of the control probands. Separate analysis of completed suicides revealed a similar and significant association with depression in the proband.

As shown in table 3, there was no significant difference in the age at onset of either dementia or depression between the relatives of the index and comparison groups, either between the total groups or between just the first- or second-degree relatives.

Using a modified life-table method (19), we compared the lifetime risks for major depression in the first-degree relatives of the two groups, estimated by means of the Kaplan-Meier statistic adjusted for differences in age distribution. The lifetime risk was higher in the first-degree relatives of the index patients than in the first-degree relatives of the comparison patients (17.1% versus 7.7%). This difference was statistically significant ($\chi^2 = 4.5$, df = 1, $p < 0.05$, generalized Savage test).

**DISCUSSION**

The major finding of the current study was the association between major depression occurring for the first time in patients with Alzheimer's disease and a high risk of affective disorder in their relatives. Almost half of 41 Alzheimer's disease patients with depression had at least one first-degree relative with major depression, compared with only 11% of nondepressed Alzheimer's disease patients. The lifetime risk for depression in the first-degree relatives of the index patients was over two times as high as in the comparison group, which in turn had a rate comparable to that of the general population (12-14, 20). The contrast between the proportion of probands with affected first-
degree relatives (46%) and their lifetime risk estimate (17%) stems from the counting procedure. If, for example, a proband had six first-degree relatives and only one of them was affected, it would count as a positive finding in determining the number of probands with affected relatives, but in estimating lifetime risk the fraction affected would be taken into account.

The finding was no artifact due to inclusion of patients with preexisting affective disorder, since such patients (who would be expected to have family histories of depression) were excluded from the study. Other factors that might influence the presence of depression, such as gender, age at onset of dementia, age, or Mini-Mental State score at initial evaluation for dementia, were not different in the index and comparison groups. There was a difference between the groups in total number of second-degree relatives, but we do not believe this affected our finding. The lifetime risk for depression was clearly higher in the first-degree relatives of the index patients, and the number of these relatives did not differ between groups.

The prevalence of major depression in the first- and second-degree relatives of our index patients is similar to expected prevalences in relatives of nondemented probands with major depressive diagnoses (12–14). Despite the exclusion of 18 Alzheimer’s disease patients with preexisting major depression, there were still high numbers of both first- and second-degree relatives with major depression in the index group. This enabled us to address specifically the issue of depression first manifesting itself after the onset of Alzheimer’s disease. The percentages of relatives with late-life dementia in both the index and comparison groups were consistent with previous estimates (21–23).

Our diagnoses of major depression were made by using a DSM-III checklist. More recently, specific scales for assessment of depressed mood in demented patients have been published (24, 25). The use of such scales would have been important had our patients been more severely cognitively impaired. A subsample of index and comparison patients was independently examined in another recent study (8). In that study (in which the diagnosis of depression was based on concurrent examination with a standardized psychiatric rating instrument), the diagnoses were in close agreement: seven of eight index patients were diagnosed as suffering from major depression, and all of 26 comparison patients were judged not to be depressed. The one index patient not diagnosed as depressed had met the criteria for depression according to chart review but was no longer depressed at the time of re-examination.

The relatively high prevalence of major depression detected in our Alzheimer’s disease patients (41 of 400 initial referrals, after patients with prior major depression were eliminated) likely reflects a bias toward referral to a psychiatry-based dementia clinic. If the 18 excluded patients are added to the sample of 41, the total prevalence would be approximately 15%, similar to the 17% obtained by Rovner et al. (8), whose patient sample partially overlapped ours. In two previous studies on major depressive disorder in Alzheimer’s disease that used the DSM-III criteria (26, 27) the prevalence rates were 19% and 0%, respectively. In general, the rate we report is in agreement with those from previous similar studies, which have been summarized by Wragg andJeste (7).

Dementia and affective disorder can coexist in two separate circumstances (6, 28–30). First, depression can occur in the context of a dementing illness, such as Alzheimer’s disease; Reifler (6) termed this a “type 2” mixed cognitive-affective disturbance, and Feinberg and Goodman (28) described it as a “dementia with secondary depression.” Second, reversible cognitive impairment may occur in the context of major affective disorder (“dementia syndrome of depression” or “pseudodementia”) (31–38). We feel confident that our depressed patients did not have this latter syndrome, since the onset of their dementia preceded that of their affective symptoms and their Mini-Mental State scores were still abnormal after standard treatment of the depression, which was successful in more than 80% of the cases. Their dementia continued to progress as they were followed within the dementia clinic (their Mini-Mental State scores fell by a mean of 3.7 points per 12 months). Finally, the diagnosis of Alzheimer’s disease was pathologically confirmed in a subset of cases.

The neuropathologic basis of secondary depression in Alzheimer’s disease is unknown. Cognitive symptoms in Alzheimer’s disease are closely associated with deficits in the cholinergic system (39). Cholinergic mechanisms may also play a role in affective disorders (40). As it evolves, Alzheimer’s disease also affects noncholinergic neurotransmitter systems in the brainstem, including locus coeruleus noradrenergic and raphe serotonergic systems (41–45). It is possible that monoamine systems are involved in the genesis of non-cognitive symptoms (46, 47).

Our results suggest that depression in Alzheimer’s disease is related by family history to the depression of primary affective disorder. Alzheimer’s disease as it evolves may interact with an existing genetic vulnerability to affective disorder, which is not expressed until the degenerative changes of Alzheimer’s disease unfold. This may make Alzheimer’s disease a useful model system for studying aspects of depression.

REFERENCES
DEPRESSIVE SYNDROME IN ALZHEIMER’S DISEASE