

# Alzheimer Disease and Related Neurodegenerative Diseases in Elderly Patients With Schizophrenia

## A Postmortem Neuropathologic Study of 100 Cases

Dushyant P. Purohit, MD; Daniel P. Perl, MD; Vahram Haroutunian, PhD; Peter Powchik, MD; Michael Davidson, MD; Kenneth L. Davis, MD

**Background:** Clinical studies suggest that severe cognitive impairment is common among elderly patients with schizophrenia who reside in long-stay psychiatric institutions; however, previous autopsy-based neuropathologic investigations have provided conflicting results about the occurrence of Alzheimer disease (AD) in elderly patients with schizophrenia. We report the results of a comprehensive neuropathologic study performed to identify AD and other dementing neurodegenerative diseases in elderly patients with schizophrenia.

**Methods:** A neuropathologic examination was performed on 100 consecutive autopsy brain specimens of patients aged 52 to 101 years (mean, 76.5 years). A cognitive assessment of these cases was also done by employing the Clinical Dementia Rating Scale. For comparison, we included 47 patients with nonschizophrenic psychiatric disorders from the same psychiatric hospital and 50 age-matched control subjects.

**Results:** Although 72% of the patients with schizophrenia showed cognitive impairment, AD was diagnosed in only 9% of the patients and other dementing diseases were diagnosed in only 4% of the patients. The degree of se-

nile plaques or neurofibrillary tangles was not different in the group with schizophrenia compared with the age-matched controls or the group with nonschizophrenic psychiatric disorders. The higher Clinical Dementia Rating Scale scores lacked correlation with neuropathologic evidence of dementing disorders. In the 87 cases lacking a neuropathologic diagnosis of AD or other dementing disorders, the mean ( $\pm$ SD) Clinical Dementia Rating Scale score was 2.21 ( $\pm$ 1.14), with 43 of the cases scoring 3 or higher (indicating severe, profound, or terminal cognitive impairment).

**Conclusions:** This study provides evidence that elderly patients with schizophrenia are not inordinately prone to the development of AD or to increased senile plaques or neurofibrillary tangle formation in the brain. Other dementing neurodegenerative disorders are also uncommon. The cognitive impairment in elderly patients with schizophrenia must, therefore, be related to some alternative mechanisms.

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**S**EVERAL CLINICAL studies have reported that relatively severe cognitive impairment is seen in a high proportion of elderly patients with schizophrenia who reside in long-stay psychiatric institutions.<sup>1-6</sup> It has also been suggested that the cognitive impairment seen in these patients is progressive<sup>6</sup> and is not attributable to a lack of cooperation, attention, or motivation or to exposure to neuroleptic medications.<sup>6-9</sup> These observations raise questions about whether cognitive impairment represents a late outcome of schizophrenia itself or whether elderly patients with schizophrenia are more susceptible than the general population to the development of Alzheimer disease (AD) or other recognized dementing neurodegenerative diseases. Postmortem neuropathologic studies in elderly patients with schizophrenia have provided conflicting findings<sup>9-13</sup> about

the frequency of AD or AD-related lesions. These varying findings may have resulted from several limiting factors, including a small sample size examined, a limited neuropathologic evaluation, absence of a properly age-matched control group, or reliance on archival postmortem reports.

A further shortcoming of these studies was a lack of correlative clinicopathologic assessments comparing the cognitive impairment during life with the extent of neuropathologic lesions in the brain specimens. We previously reported the results of a preliminary clinicopathologic study based on 13 cases<sup>13</sup> and addressed this and some previously mentioned shortcomings. The results

From the Neuropathology Division, Departments of Pathology (Drs Purohit and Perl) and Psychiatry (Drs Haroutunian, Powchik, Davidson, and Davis), Mount Sinai Medical Center, New York, NY.

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## PARTICIPANTS AND METHODS

### CASE SELECTION

Institutional review board approval was granted for this study by Mount Sinai Medical Center, New York, NY, and Pilgrim Psychiatric Center, Brentwood, NY. One hundred cases of chronic schizophrenia (of patients aged 52-101 years; mean [ $\pm$ SD], 78.5 $\pm$ 10.5 years) made up a consecutive autopsy series at the Pilgrim Psychiatric Center, a large, state-run, long-term care psychiatric hospital situated in metropolitan New York. Selection bias in this study was avoided by recruiting the subjects irrespective of their cognitive status or severity of psychiatric illness, during the clinical assessment and for the autopsy. The age of the subjects at autopsy (>50 years) was the only selection criteria. Sixty-nine cases were clinically assessed by a research team of clinicians (led by P.P. and M.D.) within 18 months prior to death. The remaining 31 cases were assessed by the same team from retrospective medical record reviews. All cases included in the study met the *DSM-III-R* criteria for a clinical diagnosis of schizophrenia. In addition, the research team assessed the cognitive status of the cases by using the CDR,<sup>15</sup> based on multiple information sources, including the patient examination (available for 69 cases), interviews with the caregivers, and medical record reviews. Harvey et al,<sup>8</sup> in a study on methods of cognitive assessment in elderly patients with schizophrenia, found that standard cognitive rating scales provided reliable ratings and also that cognitive assessments achieved a higher degree of reliability when multiple information sources were employed. Accordingly, multiple information sources were employed in the CDR assessments. The CDR scores were expressed numerically with increasing grades of cognitive impairment as follows: 0, cognitively intact; 0.5, minimal impairment; 1, mild impairment; 2, moderate impairment; 3, severe impairment; 4, profound impairment; and 5, terminal state of cognitive impairment.

of that study indicated that AD-related changes were no more prevalent in elderly patients with schizophrenia than in an age-matched elderly population without schizophrenia, despite the occurrence of severe cognitive impairment in the group with a psychiatric disorder. We report the comprehensive neuropathologic findings of 100 consecutive autopsies performed on elderly patients with chronic schizophrenia who resided in a large, long-stay psychiatric institution. The clinical diagnosis of schizophrenia was confirmed by a research team of clinicians (led by P.P. and M.D.) who followed the *DSM-III-R*<sup>14</sup> diagnostic criteria. The same research team performed a cognitive assessment of these cases using the Clinical Dementia Rating Scale (CDR).<sup>15</sup> Neuropathologic evaluations of these cases were based on a complete and uniform examination of the postmortem brain specimens, designed to document changes related to AD and other dementing neurodegenerative diseases and to provide a neuropathologic diagnosis.

### RESULTS

The mean CDR score of the 100 elderly patients with schizophrenia was 2.33, with 52 of the patients scoring

For the comparison of the neuropathologic lesions, 47 consecutive autopsy cases (of patients aged 53-106 years; mean [ $\pm$ SD], 76.9 $\pm$ 11.4 years) with clinical diagnoses of non-schizophrenic psychiatric disorders were obtained from the same hospital. We also selected, from the general hospital autopsy service (at Mount Sinai Hospital), 50 control cases lacking a clinical history of dementia or any psychiatric disorders. These cases were age matched to the schizophrenia series (range, 52-99 years; mean [ $\pm$ SD], 76.5 $\pm$ 11.0 years).

### NEUROPATHOLOGIC METHODS

The brain specimens were received in 10% buffered formalin fixative and usually consisted of the entire right half of the brain. All specimens were examined to identify and document the extent and distribution of neuropathologic lesions of AD and related neurodegenerative diseases using a protocol standardized for the Alzheimer's Disease Research Center at the Mount Sinai/Bronx Veterans Administration Medical Centers. This protocol was adopted from the neuropathologic procedures devised by the Consortium to Establish a Registry for Alzheimer's Disease.<sup>16</sup>

According to this protocol, tissue blocks were obtained for paraffin sections from 5 areas of the neocortex and from the rostral and caudal hippocampus, the basal nucleus of Meynert, the amygdala, the mesencephalon, the pons, the medulla, and the cerebellum (see Purohit et al<sup>13</sup> for full details). The paraffin sections were stained with hematoxylin and eosin, thioflavin S, and modified Bielschowsky stains. Additionally, we performed immunohistological testing for ubiquitin to identify Lewy body formation in the substantia nigra and neocortex.

An assessment of the presence and degree of AD-related changes was performed blind to clinical information by 2 experienced neuropathologists (D.P.P. and D.P.P.). This assessment (employing a 4-point scale: absent, sparse, moderate, and severe) included estimates for the density of senile plaques (SPs) containing neuritic change and amyloid cores and neurofibrillary tangles (NFTs) at a magni-

3 (severe cognitive impairment) or higher and 72 of the patients scoring 2 (moderate cognitive impairment) or higher. The postmortem neuropathologic examination findings revealed that only 9 of the 100 patients met the neuropathologic criteria for a diagnosis of AD. Other, more uncommon, dementing neurodegenerative diseases included 2 cases of Parkinson disease and 1 case of multi-infarct dementia. There was also 1 case of multiple sclerosis. Diffuse cortical Lewy body disease was found in 1 case, actually mixed with AD. There were 39 cases with assorted neuropathologic diagnoses (either clinically manifest or as incidental findings) (**Table 1**). The cases of ischemic cerebrovascular disease were mild to moderate, and there were several cases of acute infarctive or hemorrhagic lesions. As shown in Table 1, the mean CDR scores and the percentages of cases in the different neuropathologic diagnostic categories with mean CDR scores of 3 or higher did not differ significantly ( $P > .05$ ). The group of 11 cases with evidence of frontal leukotomy did not show any greater degree of cognitive impairment.

Of the 47 cases in the nonschizophrenic psychiatric disorders group, neuropathologic evidence of diseases causing or likely to cause dementia was found in 12 cases, a

fication of 250, using the density estimation guidelines devised by the Consortium to Establish a Registry for Alzheimer's Disease.<sup>16</sup> Other histological changes were also assessed, including congophilic angiopathy; neocortical neuronal loss; neuropil degeneration and gliosis; hippocampal degeneration, including neuronal loss, granulovacuolar degeneration, and Hirano bodies; and neuronal loss and SP and NFT formation in the subcortical and brainstem nuclei. A further assessment of the SP density in the neocortex was performed by employing the following quantitative method: the neocortical SPs (plaques with neuritic change and an amyloid core but not the diffuse plaques) were counted in 5 different neocortical areas. First, areas with a high SP density were identified using low-power scanning of the thioflavin S-stained slides. Five such areas were selected on each of the 5 sections of the neocortex to perform an SP count at a medium-high power magnification ( $\times 250$ ), giving a calculated visual field of 0.5 mm<sup>2</sup>. From these results, a mean neocortical SP count for each case was calculated per centimeter, squared, area. The evaluation of the NFT formation was compiled as follows: the density of the NFT formation was scored for the extent of the lesions on a 4-point scale, as previously mentioned, in 4 specific neuroanatomical regions, namely, the neocortex (5 areas), the hippocampus, the entorhinal cortex, and the subcortical nuclei (including the amygdala, the basal nucleus of Meynert, the locus ceruleus, the dorsal raphe, and the dorsal vagal nucleus). The mean NFT scores for each of the 4 regions were added to arrive at the total NFT score (ranging from 0 to a possible maximum of 12) for each case.

For the neuropathologic diagnosis of AD, we followed the diagnostic criteria based on the age-related SP count in the neocortex (the so-called Khachaturian criteria<sup>17</sup>).

The neuropathologic examination also included documentation of cerebrovascular arteriosclerotic changes, infarcts, neoplasms, and other morphological abnormalities. We also sought histological lesions associated with other dementing neurodegenerative disorders, such as Parkin-

son disease, diffuse Lewy body disease, Creutzfeldt-Jakob disease, and Pick disease. The level of ischemic cerebrovascular disease was evaluated as mild, moderate, and severe based on the size and number of infarcts in the brain.<sup>18</sup>

## STATISTICAL METHODS

To compare the degree of SP with NFT formation, we employed analyses of variance (ANOVAs) using a software package (Statistica for Windows, Statsoft Inc, Tulsa, Okla).<sup>19</sup> The  $\alpha$  level was set at .05 for all statistical tests. The analysis of SP and NFT formation in the cases with schizophrenia, in the cases with nonschizophrenic psychiatric disorders, and in the age-matched controls was performed using the Kruskal-Wallis test, which was appropriate for this study because of a lack of normal distribution of SPs and NFTs. Additionally, the effect of age on SP and NFT formation was evaluated using the following age groupings: 65 years and younger, 66 to 72 years, 73 to 79 years, 80 to 86 years, and 87 years and older. For this analysis, a 2-factor ANOVA was employed. The effect of SP and NFT formation on cognitive function was evaluated by grouping the cases according to the levels of cognitive status, as expressed in the following groups of CDR scores: 0 to 0.5, cognitively intact; 1 to 2, mild to moderate cognitive impairment; and 3 to 5, severe to profound cognitive impairment to the terminal stage of cognitive impairment. Because the age-matched controls were cognitively intact, an isolated control group ANOVA strategy was employed with the groups with diagnoses of schizophrenia and nonschizophrenic psychiatric disorders entered as independent factors and the age-matched controls entered as an isolated (hanging) factor. In this way, we compared SP and NFT formation in the cases with schizophrenia, in the cases with nonschizophrenic psychiatric disorders, and in the age-matched controls as a function of cognitive status.

We also analyzed the proportions of the cases with or without SP formation, comparing them with those in the age-matched controls. A  $\chi^2$  test was used for this analysis.<sup>20</sup>

considerably greater proportion than in the schizophrenic group. However, they included just 2 cases of AD, while the remaining diagnoses were 3 cases of multi-infarct dementia and 1 case each of Parkinson disease, post-encephalitic parkinsonism, Wernicke-Korsakoff syndrome, alcoholic cerebellar degeneration, metastatic carcinoma in the brain, meningovascular syphilis, cortical dysplasia, and a cerebral malformation with hemiatrophy of the cerebrum. Furthermore, 12 cases had a mild to moderate degree of ischemic cerebrovascular disease. The remaining 22 cases were free from any notable neuropathologic abnormalities.

## AD-RELATED NEUROPATHOLOGIC CHANGES

### Senile Plaques

Quantitative assessments of the neocortical SP density in the 2 groups, namely, the elderly patients with schizophrenia and the elderly patients with clinical diagnoses of psychiatric disorders other than schizophrenia, along with SP assessments in the age-matched controls, are provided in **Table 2** and **Table 3** and charted in **Figure 1**.

Neocortical SP formation in both groups (the elderly patients with schizophrenia and the elderly patients with nonschizophrenic psychiatric disorders) was found to be nominally greater than in the age-matched controls; however, neocortical SP formation was considered sparse in extent overall and comparable in all groups.

Statistical analysis of SP formation in both groups (the elderly patients with schizophrenia and the elderly patients with nonschizophrenic psychiatric disorders) and in the age-matched controls showed that the difference in SP formation was not quite significant ( $P=.05$ , Kruskal-Wallis nonparametric ANOVA test), whereas the Dunn multiple comparison test performed for the 2 groups and the age-matched controls revealed a nonsignificant result ( $P>.05$ ). Further statistical analysis among the groups of cases, which were subdivided according to the age at death (Table 3), revealed no significant difference in SP formation. In this analysis (a 2-factor ANOVA), a strong age effect was observed:  $F_{\text{age}}(6, 176)=4.0$  ( $P<.05$ ). However, the effect of the 3 diagnostic groups themselves (ie, the elderly patients with schizophrenia, the elderly patients with nonschizophrenic psychiatric disorders, and the age-matched controls) was nonsignificant:  $F_{\text{diagnostic}}(2, 176)$

**Table 1. Postmortem Neuropathologic Characteristics of the Brain Specimens of 100 Elderly Patients With Schizophrenia\***

| Neuropathologic Diagnosis                                    | No. of Cases | Mean CDR Score                  | Cases With CDR Scores $\geq 3$ , % |
|--|--------------|---------------------------------|------------------------------------|
| <b>All Cases</b>   | <b>100</b>   | <b>2.33<math>\pm</math>1.16</b> | <b>52.0</b>                        |
| All dementing neurodegenerative diseases                     | <b>13</b>    | <b>2.70<math>\pm</math>1.05</b> | <b>69.2</b>                        |
| Alzheimer disease†   | <b>9</b>     | <b>2.50<math>\pm</math>1.00</b> | <b>55.6</b>                        |
| Other diagnoses  | <b>4</b>     | <b>2.85</b>                     | <b>73.3</b>                        |
| Parkinson disease  | 2            | ...                             | ...                                |
| Multi-infarct dementia                                       | 1            | ...                             | ...                                |
| Multiple sclerosis   | 1            | ...                             | ...                                |
| All diagnoses excluding dementing neurodegenerative diseases | <b>87</b>    | <b>2.21<math>\pm</math>1.14</b> | <b>48.8</b>                        |
| Ischemic cerebrovascular disease                             | 23           | 2.42 $\pm$ 1.02                 | 65.2                               |
| Secondary neoplasms in brain                                 | 3            | ...                             | ...                                |
| Brainstem hemorrhage   | 1            | ...                             | ...                                |
| Hemangioma in parietal lobe                                  | 1            | ...                             | ...                                |
| Frontal leukotomy  | 11           | 2.05 $\pm$ 1.00                 | 45.5                               |
| No significant pathologic finding                            | 48           | ...                             | ...                                |

\*Also included are the mean ( $\pm$ SD) Clinical Dementia Rating Scale (CDR) score and the percentage of cases with a CDR score of 3 or more (severe, profound, or terminal degree of dementia) in all cases and in the major diagnostic categories (from Hughes et al<sup>15</sup>). Ellipses indicate data not applicable.

†The group with Alzheimer disease includes 1 case with mixed features of Alzheimer disease and diffuse Lewy body disease.

**Table 2. Neocortical Senile Plaque (SP) and Neurofibrillary Tangle (NFT) Formation in the Brain Specimens of Elderly Patients With Schizophrenia Compared With Patients With Nonschizophrenic Psychiatric Disorders and With Age-Matched Controls\***

| Group  | Patient Age, y  | SP Count, cm <sup>2</sup> | NFT Formation Scores | P†     |                   |
|--|-----------------|---------------------------|----------------------|--------|-------------------|
|  |                 |                           |                      | For SP | For NFT Formation |
| All cases  |                 |                           |                      |        |                   |
| Patients with schizophrenia‡ (n=100)             | 78.5 $\pm$ 10.5 | 364.8 $\pm$ 426.7         | 3.20 $\pm$ 2.6       | .05    | >.05              |
| Patients with other psychiatric diseases‡ (n=47) | 76.9 $\pm$ 11.4 | 275.2 $\pm$ 444.5         | 3.10 $\pm$ 2.40      |        |                   |
| Age-matched controls (n=50)                      | 76.5 $\pm$ 11.0 | 192.6 $\pm$ 315.4         | 2.34 $\pm$ 1.97      |        |                   |
| Cognitively intact (CDR=0-0.5)§                  |                 |                           |                      |        |                   |
| Patients with schizophrenia (n=13)               | 70.3 $\pm$ 5.3  | 183.3 $\pm$ 421.8         | 2.42 $\pm$ 1.68      | >.05   | >.05              |
| Patients with other psychiatric diseases (n=6)   | 70.2 $\pm$ 5.3  | 158.7 $\pm$ 258.0         | 1.33 $\pm$ 1.37      |        |                   |
| Mild or moderate dementia (CDR=1-2)              |                 |                           |                      |        |                   |
| Patients with schizophrenia‡ (n=36)              | 78.4 $\pm$ 10.5 | 419.0 $\pm$ 399.3         | 3.09 $\pm$ 3.01      | >.05   | >.05              |
| Patients with other psychiatric diseases (n=19)  | 76.1 $\pm$ 10.5 | 284.7 $\pm$ 404.5         | 2.47 $\pm$ 1.96      |        |                   |
| Severe to terminal states of dementia (CDR=3-5)  |                 |                           |                      |        |                   |
| Patients with schizophrenia‡ (n=51)              | 80.5 $\pm$ 10.0 | 369.3 $\pm$ 441.5         | 3.44 $\pm$ 2.55      | >.05   | <.05              |
| Patients with other psychiatric diseases‡ (n=22) | 77.0 $\pm$ 11.4 | 179.0 $\pm$ 344.7         | 3.22 $\pm$ 2.02      |        |                   |

\*Values are expressed as the mean ( $\pm$ SD) unless otherwise indicated.

†Calculated using the Kruskal-Wallis nonparametric analysis of variance for differences between groups and age-matched controls.

‡These groups also include cases with a neuropathologic diagnosis of superimposed Alzheimer disease or other dementing disorders.

§CDR indicates Clinical Dementia Rating Scale score based on Hughes et al.<sup>15</sup>

=1.83 ( $P>.05$ ). The interaction of age by the diagnostic group was as follows:  $F_{\text{age} \times \text{diagnostic}}(12, 176)=0.94$ . Statistical analysis (isolated control group strategy) (see the "Statistical Methods" subsection of the "Participants and Methods" section) of SP formation within the categories based on cognitive impairment in both groups and the age-matched controls also failed to reveal significant differences:  $F(2, 190)=2.26$  ( $P>.05$ ).

Some degree of SP formation in the neocortex was identified in 47%, 43%, and 40% of the cases of schizophrenia, the cases of nonschizophrenic psychiatric disorders, and the age-matched controls, respectively. The prevalence of SP formation was greater in the older cases; nevertheless, it was comparable among all 3 groups (Figure 1). With the use of the  $\chi^2$  test, a group comparison of the cases with and without SP formation in the neocortex of all 3 groups in different age ranges showed no significant difference among the 3 groups ( $\chi^2=0.59$ ,  $df=8$ ,  $P>.05$ ).

## Neurofibrillary Tangles

The findings of NFT formation, as compiled in the total NFT scores (see the "Neuropathologic Methods" subsection of the "Participants and Methods" section), are provided in Table 2 and Table 3 and in **Figure 2**. Similar to the findings for SP formation, NFT formation in the groups with schizophrenia and with nonschizophrenic psychiatric disorders was nominally higher than in the age-matched controls. As shown in Table 2, further comparisons for the total NFT scores (by the Kruskal-Wallis nonparametric ANOVA test) showed no significant difference when a comparison was made for all cases among the 2 groups and controls ( $P>.05$ ). However, when the 2 groups and the controls were similarly compared among the cases with cognitive impairment of a mild or moderate degree (CDR score of 1 or 2) and of a severe or higher degree (CDR score  $\geq 3$ ), the difference was statistically significant ( $P<.05$ ).

**Table 3. Mean Neocortical Senile Plaque (SP) and Total Neurofibrillary Tangle (NFT) Formation in the Brain Specimens of Elderly Patients With Schizophrenia\***

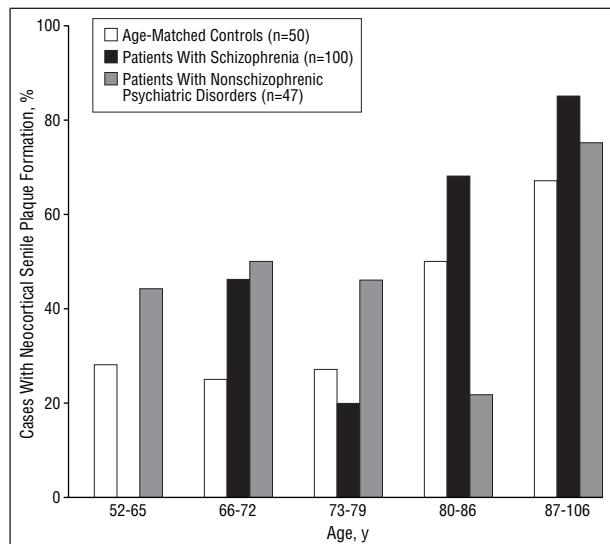
| Group  | Age Range, y     |                  |                  |                 |                  |
|--|------------------|------------------|------------------|-----------------|------------------|
|  | <66              | 66-72            | 73-79            | 80-86           | >86              |
| <b>SP Formation in the Neocortex, cm<sup>2</sup>†</b>                |                  |                  |                  |                 |                  |
| Patients with schizophrenia‡ (n=100)                                 | 0 (n=14)         | 264±356 (n=14)   | 167±33 (n=14)    | 449±395 (n=38)  | 670±483 (n=20)   |
| Patients with psychiatric disorders other than schizophrenia‡ (n=47) | 145±368 (n=9)    | 292±35 (n=8)     | 309±444 (n=13)   | 156±278 (n=9)   | 485±660 (n=8)    |
| Age-matched controls (n=50)  | 117±242 (n=7)    | 79±172 (n=12)    | 111±257 (n=11)   | 186±227 (n=8)   | 429±451 (n=12)   |
| <b>Total NFT Formation Scores§</b>                                   |                  |                  |                  |                 |                  |
| Patients with schizophrenia‡ (n=100)                                 | 1.29±1.59 (n=14) | 2.64±2.41 (n=14) | 2.43±2.85 (n=14) | 3.35±2.2 (n=38) | 4.95±3.05 (n=20) |
| Patients with psychiatric diseases other than schizophrenia‡ (n=47)  | 2.10±1.9 (n=9)   | 1.5±1.07 (n=8)   | 3.46±2.4 (n=13)  | 3.22±2.33 (n=9) | 4.88±3.04 (n=8)  |
| Age-matched controls (n=50)  | 1.43±1.9 (n=7)   | 1.41±1.83 (n=12) | 2.55±2.16 (n=11) | 3.75±2.06 (n=8) | 2.67±1.37 (n=12) |

\* Values are expressed as the mean (±SD) unless otherwise indicated.

† Compared with patients who suffered chronic psychiatric disorders other than schizophrenia and with age-matched controls (cases subgrouped according to the age at death).

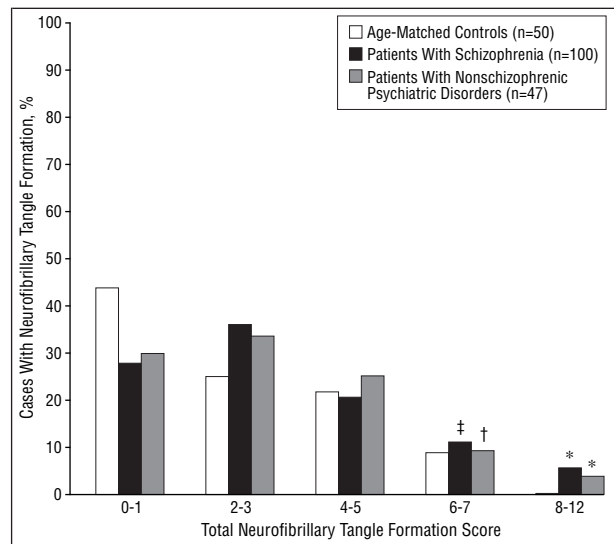
‡ These groups also include cases with a neuropathologic diagnosis of superimposed Alzheimer disease and other dementing disorders.

§ Compared with patients with nonschizophrenic psychiatric disorders and with age-matched controls (cases subgrouped according to the age at death).



**Figure 1.** The cases with the presence of senile plaque formation, charted for different age groups.

Further statistical analysis between the 2 groups and the age-matched controls, which were subdivided according to the age at death (Table 3), revealed no significant difference in the total NFT scores. In this analysis (a 2-factor ANOVA), a strong age effect was observed:  $F_{\text{age}}(6, 166)=1.40$  ( $P<.05$ ). However, the effect of the diagnostic groups (ie, the elderly patients with schizophrenia, the elderly patients with nonschizophrenic psychiatric disorders, and the age-matched controls) was nonsignificant:  $F_{\text{diagnostic}}(2, 166)=1.55$  ( $P>.05$ ). The interaction of age by diagnostic groups was nonsignificant:  $F_{\text{age} \times \text{diagnostic}}(12, 166)=1.44$  ( $P>.05$ ). Statistical analysis (ANOVA, isolated control group strategy) (see the “Statistical Methods” subsection of the “Participants and Methods” section) of the total NFT scores between the categories based on the cognitive impairment status of the 2 groups and the age-matched controls (Table 3) revealed a statistically significant difference for the total NFT scores:  $F(2,$



**Figure 2.** The cases showing different grades of neurofibrillary tangle (NFT) formation (expressed as the total NFT scores). Among the cases with high total NFT scores, a neuropathologic diagnosis of Alzheimer disease was made in all cases in the groups marked with an asterisk and in most cases in the group marked with a double dagger. One case of postencephalitic parkinsonism in the patients with nonschizophrenic psychiatric disorders was in the group marked with a dagger.

188)=3.22 ( $P=.02$ ). Subsequent contrast analysis revealed that it was due to the differences in the total NFT scores in the 2 groups with CDR scores of 3 or higher:  $F(1, 188)=6.46$  ( $P=.01$ ). Individual comparisons showed that the total NFT scores of both groups with CDR scores of 3 or higher were significantly greater than the total NFT scores of the age-matched controls:  $F_{\text{schizophrenia}}(1, 188)=4.0$  ( $P=.05$ ) and  $F_{\text{nonschizophrenic psychiatric disorders}}(1, 188)=5.31$  ( $P=.02$ ).

When the 2 groups and the age-matched controls were compared for the total NFT scores, the groups with schizophrenia and with nonschizophrenic psychiatric disorders showed similar trends for the grades of severity of NFT formation: the percentage of the cases was inversely related to the total NFT scores (Figure 2). In both

groups, all cases with the most severe NFT formation (total NFT scores between 8-12) were those with superimposed AD; among the patients with schizophrenia who had a total NFT score of 7, some had superimposed AD. Of the 2 patients with nonschizophrenic psychiatric disorders with a total NFT score of 7, 1 had postencephalitic parkinsonism.

#### OTHER AD-RELATED NEURODEGENERATIVE CHANGES

The extent of other AD-associated neuropathologic features in the groups with schizophrenia and with nonschizophrenic psychiatric disorders was not greater than in the age-matched controls (assessments by grades,<sup>18</sup> quantitative data not compiled). These features included amyloid angiopathy; neuronal depletion in the basal nucleus of Meynert, the amygdala, the locus ceruleus, the dorsal raphe, and the dorsal nucleus of the vagus; and hippocampal changes, including neuronal loss, granulovacuolar degeneration, and Hirano bodies in the pyramidal neurons.

#### COMMENT

This clinicopathologic study complements the findings of our earlier report<sup>13</sup> and reinforces the concept that while severe cognitive impairment is commonly observed in elderly patients with schizophrenia, it is only occasionally due to superimposed AD. Although 72% of the patients examined in this study showed moderate or severe degrees of cognitive impairment, only 9% met the neuropathologic criteria of AD. This small percentage of neuropathologic diagnoses of AD among elderly patients with schizophrenia is quite similar to that encountered in several autopsy-based studies of the general elderly population without psychiatric disorders.<sup>21-25</sup> Other forms of neurodegenerative disorders associated with cognitive impairment were encountered even less frequently. In most patients with schizophrenia, no notable neuropathologic abnormalities were identified that could be ascribed as the underlying cause of cognitive impairment.

The presence of a limited degree of neocortical SP formation and of entorhinal and hippocampal NFT formation in most of the cases was consistent with age-related morphological changes commonly encountered in the nondemented elderly.<sup>24,26-29</sup> Furthermore, the degree of SP and NFT formation was not significantly increased when compared with nondemented age-matched controls or with the cases of nonschizophrenic psychiatric disorders derived from the same long-stay care institution ( $P > .05$ ). However, there was 1 exception: The extent of NFT formation was significantly greater in cases with severe degrees of cognitive impairment ( $P < .05$ ). This increase in NFT formation was seen in both groups (elderly patients with schizophrenia and elderly patients with nonschizophrenic psychiatric disorders), probably representing the effects of high NFT scores in a few patients, including the patients with a neuropathologic diagnosis of AD. One study has suggested a possible role of prolonged neuroleptic treatment in promoting NFT formation in the brains of patients with schizophre-

nia,<sup>30</sup> but a meta-analysis of 10 postmortem studies of AD-like neuropathologic characteristics in patients with schizophrenia concluded that SPs and NFTs were no more common in patients with schizophrenia who were treated with neuroleptic medications.<sup>31</sup>

Arnold et al<sup>10</sup> suggested that a developmentally abnormal hippocampal region in patients with schizophrenia could become functionally defective (leading to cognitive impairment), even with a minor accumulation of SPs and NFTs. Further studies<sup>32-37</sup> have suggested a developmentally defective prefrontal lobe and temporal lobe cortical circuitry, deficits in small interneurons, and an increase in vertical axon numbers in the cingulate gyrus in the brains of the patients with schizophrenia. While it is possible that further damage to such altered circuitry could underlie the cognitive impairment seen in many of our elderly patients with schizophrenia, this concept was beyond the scope of this study.

Of the 72 cases of schizophrenia with at least moderate cognitive impairment (CDR score  $\geq 2$ ), 53 (73.6%) of the cases failed to show neuropathologic evidence of AD or any other neuropathologic entity associated with cognitive impairment. On rare occasions, a neuropathologic examination of the brain specimens derived from demented (nonschizophrenic) elderly patients fails to reveal evidence of AD or any other neurodegenerative diseases to account for the cognitive impairment. Several studies<sup>16,38-40</sup> indicate that only 1.5% or less of clinically demented cases failed to show neuropathologic confirmation of AD or other dementing neurodegenerative disease. In contrast, cognitive impairment in 73.6% of the elderly patients with schizophrenia was without an identifiable neuropathologic explanation.

Our neuropathologic findings are also congruent with several neurochemical studies on cortical tissue showing that the neurochemical profile in elderly patients with schizophrenia is dissimilar from that of patients with AD. For example, cerebral cortical cholinergic activity was not reduced in the brain tissue of the cognitively impaired elderly patients with schizophrenia.<sup>41</sup> Additionally, immunoreactivity to Alz-50 (an AD-related monoclonal antibody marker) was found to be lacking in the homogenates of the cerebral cortex from the brain specimens of elderly patients with schizophrenia.<sup>42</sup> Furthermore, measurement of the levels of neuropeptides in 6 neocortical areas suggested a broad-based multiple peptide deficit syndrome in the elderly patients with schizophrenia.<sup>43</sup> However, comparative evaluation in that study showed that the neuropeptide deficit pattern in patients with schizophrenia contrasted with that in patients with AD in most findings: corticotropin releasing factor was reduced across the 6 regions in patients with AD but not in those with schizophrenia, whereas neuropeptide Y, cholecystokinin, and vasoactive intestinal peptide were reduced in patients with schizophrenia but not in those with AD. Only cortical somatostatin levels were decreased in patients with schizophrenia and in patients with AD.

Some studies have failed to confirm cognitive impairment in patients with schizophrenia; however, they were based on smaller samples, examined relatively younger individuals, or studied less severely affected community-dwelling patients.<sup>44-46</sup> Our group conducted clini-

cal studies in parallel with this study<sup>5,6,8</sup> and found that the cognitive decline was common in this population of institutionalized elderly patients with schizophrenia and that this cognitive decline was progressive in nature.<sup>6</sup>

Our detailed neuropathologic study provides evidence that elderly patients with schizophrenia are not inordinately prone to the development of AD or to show increased SP or NFT formation in the brain. This study also shows that other types of recognizable dementing neurodegenerative disorders are even more uncommon among elderly patients with schizophrenia. Therefore, AD must be related to other mechanisms that, to date, have eluded identification using routine morphological approaches.

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Reprints: Dushyant P. Purohit, MD, Neuropathology Division, Box 1134, Mount Sinai Medical Center, 1 Gustave L. Levy Pl, New York, NY 10029-6574.

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