Cognitive Impairment in Elderly Schizophrenia: A Dementia (Still) Lacking Distinctive Histopathology

by Steven E. Arnold and John Q. Trojanowski

Abstract

Recent clinical and neuropsychological studies have shown that severe deterioration in cognitive and functional capacities is prevalent in elderly, chronically hospitalized patients with schizophrenia. Postmortem studies of tissue from patients who were clinically well characterized have found notably little neurodegenerative or other pathology to explain the dementia. In contrast, several large studies using archival material have reported an unexpectedly high occurrence of Alzheimer's disease pathology in patients with schizophrenia irrespective of clinical status. Reasons for conflicting results likely include inaccuracies in psychiatric diagnoses but also could be due to differences in sample selection, treatment histories, and environmental influences. Thus, the neurobiological substrates for dementia in late-life schizophrenia remain uncertain. Further studies should incorporate standard diagnostic procedures with community-based and institutionalized schizophrenia patients as well as psychiatric control patients with similar treatment histories. These should apply sensitive neuropathological methods to assess disease-specific and nonspecific markers of neurodegeneration and dementia.

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Since E. Bleuler (1924) and Kraepelin (1919/1971) first described the disease, theories about the nature of cognitive impairment in schizophrenia, as well as predictions of the disease's course and outcome have been controversial. Bleuler characterized thought processes in schizophrenia as disordered and loose and argued that deterioration was not necessarily a feature. In contrast, Kraepelin emphasized the progressive deterioration of cognition, although he noted that memory, a cognitive domain central to current definitions of dementia, was spared. Though critical to addressing the issue of deterioration and possible neurodegeneration in schizophrenia, longitudinal studies extending into late life have been markedly few (Belitsky and McGlashan 1993; Jeste 1993). Ciompi (1980) described evaluations of the 289 mostly elderly probands surviving from a sample of 1,642 patients. He estimated that 25 percent suffered moderate to severe cognitive deficits, including memory disturbance and disorientation. Forty-nine percent were considered to have had a good outcome, with 27 percent having a complete social remission. Winokur et al. (1987) reevaluated a cohort of hebephrenic and catatonic schizophrenia subjects from the Iowa 500 study after 40 years, 17 of whom were elderly. They found that the elderly subgroup was significantly more likely to have worsened orientation and memory, more restricted affective range, and paucity of speech, along with decreased persecutory delusions and auditory hallucinations. Other long-term followup studies with few elderly patients have also had significantly heterogeneous outcomes (M. Bleuler 1968; Huber et al. 1980; Harding

et al. 1987a, 1987b; Carpenter and Kirkpatrick 1988). This heterogeneity could reflect differing pathological processes among the patients, or differences in treatment and environmental influences that modified the course of the disease.

There are also relatively few cross-sectional studies of symptomatology and cognition in elderly patients whose schizophrenia had an early onset. Recently, two independent groups have focused on more chronically ill, institutionalized elderly patients. Both groups found a high degree of severe cognitive impairment and negative symptoms and moderate to low degrees of positive symptoms. Davidson et al. (1995) have reported that negative symptomatology increases with age while positive symptomatology declines but does not "burn out." Furthermore, when they stratified their population into age groups by decade they found a slow decline in cognitive function on the Mini-Mental State Examination (MMSE; Folstein et al. 1975). This decline ranged from 1.2 to 4.6 points per decade, culminating in severe dementia in the oldest patients (Harvey et al. 1992; Davidson et al. 1995). Current neuroleptic use and history of somatic treatments such as electroconvulsive therapy, insulin coma, and leukotomy appeared to have had no effect on cognitive performance. Notably, after retesting a subgroup of these patients 1 to 2 years later, the investigators observed no significant further deterioration in cognitive impairment (Harvey et al. 1995). They interpreted this finding as inconsistent with a neurodegenerative disease like Alzheimer's disease (AD) and more consistent with a neurodevelopmental involution.

In a demographically similar population of elderly schizophrenia patients participating in a prospective clinicopathological studies program, Arnold et al. (1995) reported severe illness on the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), severe cognitive impairment on the MMSE, severe negative symptomatology on the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984a), and severe functional impairment on the Physical Self-Maintenance Scale (Lawton and Brody 1969), all of which correlated with age. Mild to negligible positive symptomatology observed on the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984b) did not correlate with age. While longitudinal data has not yet been gathered, psychometric study of this group (compared to a sample of AD patients matched in age and severity of global dementia) revealed a neuropsychological profile of dementia that shared a number of similarities with the profile seen in patients with AD (Gibney et al. 1993). In contrast, one study of community-based, "elderly" (mean age ■ 62 years) patients with early-onset schizophrenia admitted to an acute geriatric psychiatry unit for decompensation found moderate positive symptomatology and only mild cognitive impairment (Mulsant et al. 1993).

In community-based geriatric populations, 50 to 60 percent of all dementias are due to AD, 20 to 30 percent to cerebrovascular disease, and 10 to 20 percent to a wide variety of reversible, nonreversible, or unexplained etiologies (Freemon 1976; Larson et al. 1984, 1985; Cunha 1990; Arnold and Kumar

1993). Postmortem studies have attempted to determine the neuropathological basis for the dementia in late-life schizophrenia. Arnold et al. (1994) and Purohit et al. (1993) conducted autopsy examinations in well-characterized patients and found no recognized neuropathological abnormalities to explain the severe dementia. Of particular interest was the minimal neurofibrillary tangle and senile plaque formation. Further studies failed to identify excess AD-related protein abnormalities (Powchik et al. 1993), decreased cholinergic activity (Haroutunian et al. 1994), or abnormal apolipoprotein E genotype distribution (Martinoli et al. 1995). These findings agreed with those of two other studies of carefully diagnosed patients (Bruton et al. 1990; el-Mallakh et al. 1991).

In contrast, several other large studies have reported an increased prevalence of AD lesions in patients with schizophrenia (Corsellis 1962; Soustek 1989; Prohovnik et al. 1993; Wisniewski et al. 1994). The study by Wisniewski et al. (1994) was especially provocative in that patients who had been treated with antipsychotic medication exhibited significantly greater neurofibrillary pathology than those who had died in the preneuroleptic era. The investigators theorized that the increased prevalence of AD-related pathology in this group reflected a neuroleptic effect on neurofibrillary tangle maturation rather than an aspect of the schizophrenic disease process.

The conflicting findings of these studies might be explained in a number of ways. Chief among them is the possibility of misdiagnosis. In gathering elderly patients for their clinicopathological studies,

Arnold et al. (1995) found that of 528 patients with a chart diagnosis of schizophrenia, 248 had to be excluded because they were misdiagnosed or because their medical histories were insufficient to allow application of modern diagnostic criteria. This extraordinarily high proportion of inaccurate diagnoses not only highlights the need for applying established diagnostic criteria in postmortem studies of schizophrenia but calls into question the validity of the findings of large survey studies, as many as half of whose subjects may not have had schizophrenia. Alternatively, the discrepant results could reflect a sampling selection effect, where different subtypes of schizophrenia were examined. Other explanations include differences in treatment or environmental histories that influenced the development of AD pathology.

Obviously, continued and better designed studies are needed. In addition to mandatory application of standard diagnostic and assessment instruments, studies should incorporate both community-based and institutionalized patients, longitudinal followup, use of psychiatric control groups with similar treatment histories, and sensitive, specific neuropathological methods to assess AD-related pathology, Lewy bodies, and other neurodegenerative disease markers.

If the dementia of schizophrenia in late life is not due to AD or other known neurodegenerative disease processes, as studies using rigorously diagnosed subjects indicate, then the mechanisms underlying the severe cognitive impairments in elderly schizophrenia patients remain to be elucidated. Numerous postmortem studies have indicated subtle cytoarchitec-

tural, morphometric, synaptic, and neuroreceptor abnormalities in schizophrenia that have been interpreted as reflecting aberrant neurodevelopment (for reviews, see Bogerts 1993; Pilowski et al. 1993; Shapiro 1993). Abnormalities in the hippocampal region, a critical anatomical substrate for cognition, have been described most often. Perhaps small accumulations of neurodegenerative pathology (e.g., neurofibrillary tangles and senile plaques that would not qualify for a neuropathological diagnosis of AD) cause cognitive deterioration when they are superimposed on a marginally functioning, developmentally abnormal region like the hippocampus. Quantitative studies that correlate neuropathological findings with antemortem cognitive and functional measures will be necessary to test this hypothesis. In addition to disease-specific markers such as neurofibrillary tangles and senile plaques, many other less specific marker possibilities correlating neurodegeneration and dementia are worth examining. Among these are neuron loss, astrogliosis, microglia proliferation, and synapse-related proteins (e.g., synaptophysin, synapsin, and chromogranin), as well as metabolic markers such as cytochrome oxidase and protein kinase activity, neurochemical markers such as choline acetyl transferase and somatostatin-like immunoreactivity, and programmed cell death markers. While none of these are disease-specific, an abnormality in the expression or metabolism of one or more of these could guide further investigations of the molecular mechanisms underlying dementia in schizophrenia in late life and in the schizophrenic disease process.

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