Schizophrenia, Alzheimer’s Disease, and Anti-inflammatory Agents

by Robert J. Oken and Patrick L. McGeer

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Abstract

Some recent postmortem reports raise the possibility that Alzheimer-type pathology may be 6 to 12 times higher in elderly schizophrenia patients than in the general population. One study indicates that neuroleptic treatment may be an important contributor. Other reports, however, suggest that cognitive impairment in elderly schizophrenia patients is seldom due to Alzheimer-type pathology, indicating that more detailed follow-up studies are needed. Since multiple epidemiological studies show that Alzheimer's disease is less prevalent in patients with medical conditions requiring anti-inflammatory drugs than in the general population, anti-inflammatory medication might be considered as an adjuvant to chronic neuroleptic treatment in elderly schizophrenia patients showing early signs of Alzheimer-type memory deficits.


Some recent postmortem studies have suggested that there is a remarkable prevalence of Alzheimer's disease (AD) pathology among hospitalized schizophrenia patients. In a study of 225 chronic schizophrenia patients who died between the years of 1975 and 1985, Soustek (1989) found that the risk of developing AD among such patients was at least six times higher than in the general population. Prohovnik et al. (1993), examining all autopsy cases conducted at the New York State Psychiatric Institute between 1977 and 1988, found that of 544 schizophrenia patients, 28 percent were diagnosed as having AD. Further, the researchers reported a 32 percent rate of AD in the over-65 age group, compared with the 2 to 6 percent rate observed in the general population in various epidemiological studies. Again, the rate was 4 to 12 times higher than anticipated. Such pathology has not been predicted from clinical findings. Three explanations are possible. One is that relevant neuropsychological assessments are not being carried out on elderly schizophrenia patients. A second is that these assessments are not appropriate for this population. A third is that the pathological data do not truly reflect the elderly schizophrenia population.

Buhl and Bojesen-Moller (1988) studied 100 consecutive patients who died in psychiatric departments and concluded that a significant percentage of undiagnosed AD was concealed by other psychiatric disorders. Wisniewski et al. (1994) examined the brains of 102 schizophrenia patients who died at age 72 or older. Forty-one died between 1932 and 1952, before the era of neuroleptics. The remaining

Reprint requests should be sent to Dr. R.J. Oken, P.O. Box 412, Hopatcong, NJ 07843.
61, who died between 1954 and 1990, had all received neuroleptics. Finding that schizophrenia patients dying in the neuroleptic era had significantly higher neurofibrillary changes than those who died in the preneuroleptic era, Wisniewski and colleagues concluded that chronic treatment with neuroleptics, and not schizophrenia itself, significantly increased the risk of more frequent, earlier, and accelerated development of neurofibrillary pathology in the brains of elderly schizophrenia patients.

However, reports of an unusually low AD pathology in cognitively impaired schizophrenia subjects contradict this conclusion. Haroutunian et al. (1994) found no decrease in cholinergic marker activity in the postmortem brains of a series of cognitively impaired elderly schizophrenia patients. Arnold et al. (1994) reported that, in a cohort of 10 elderly patients with both schizophrenia and dementia, the plaque and tangle count was normal in all cases. Similarly, Purohit et al. (1993) examined the brains of 12 elderly schizophrenia patients with severe cognitive impairment and found that none met the neuropathological criteria for AD. Casanova et al. (1993) had comparable results examining the hippocampi of 10 cognitively impaired schizophrenia patients.

It is not clear whether the schizophrenia patients examined in these studies had definite AD-type clinical findings. Assessing neuropsychological impairment in schizophrenia is not as straightforward as it is in AD. For example, Heaton et al. (1994) gave schizophrenia patients a battery of tests and found that cognitive impairment was unrelated to current age, age at onset, or duration of the mental illness. Tests that can clearly identify the progressive memory deficits characteristic of AD need to be incorporated into the clinical assessment of elderly schizophrenia patients.

Clearly, further autopsy and neuropsychological assessment work needs to be done to clarify to what extent, if any, elderly schizophrenia patients are at increased risk for AD, and what specific factors might lead to cognitive impairment in the absence of AD. In the meantime, available knowledge suggests a practical approach to treating those elderly schizophrenia patients showing AD-type mental deficits. For example, epidemiological studies have established that AD is less prevalent among people taking anti-inflammatory drugs, or suffering from disorders such as arthritis for which taking such drugs is routine (Jenkinson et al. 1989; Broe et al. 1990; Li et al. 1992; Lindsay 1994; Lucca et al. 1994; Myllykangas-Luusuviary and Isomaki 1994; Andersen et al. 1995; Breitner et al. 1995; Rich et al. 1995). In the largest study, McGeer et al. (1990) evaluated 7,490 hospital separation records in the 65 and older population for concomitant diagnoses of rheumatoid arthritis and AD and found that the combined rate was 0.39 percent, or 6 to 12 times lower than the rate recorded in several general population studies. The possibility that genetics was a factor seemed to be ruled out by Breitner et al. (1994), who reported in a study of 50 elderly twin pairs with the onset of AD separated by 3 or more years, that administering anti-inflammatory drugs prevented or delayed the onset of AD pathology.

These findings are in line with observations of postmortem specimens in which numerous inflammatory changes have been documented in association with AD lesions (McGeer et al. 1989, 1993; McGeer and Rogers 1992). In a pilot clinical trial of indomethacin, a powerful nonsteroidal anti-inflammatory drug (NSAID) that crosses the blood-brain barrier, Rogers et al. (1993) found the progression of AD to be arrested. The epidemiological data thus suggest that taking anti-inflammatory drugs can prevent or delay the onset of AD, while the pilot clinical trial of indomethacin indicates that it might also be effective.

The Breitner et al. (1994) twin study suggested that adrenocorticotropic hormone or steroids might likewise be effective in preventing or delaying dementia onset. However, it is important to consider steroids' negative effects. Steroids are notorious, for example, for their adverse psychogenic effects. Moreover, prednisone, even at low doses, can produce electrolyte disturbances that induce congestive heart failure, osteoporosis leading to bone fractures, vulnerability to infection, cataracts, and ulcers leading to gastrointestinal bleeding (Haynes 1990). In animal experiments, steroids have been shown to be neurotoxic to hippocampal pyramidal neurons, a class of cells already vulnerable in AD (Sapolsky 1985). There are no agents to protect against these side effects. NSAIDs cause side effects as well. The most serious is gastrointestinal ulceration, although gastroprotective agents such as misoprostol (Graham et al. 1988) have been found to protect against it.

Taken together, the above con-
siderations support the adjuvant administration of anti-inflammatory agents to schizophrenia patients who are receiving neuroleptics and show clinical evidence of concomitant AD.

References


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**The Authors**

Robert J. Oken, Ph.D., is Molecular Biologist (retired), formerly consultant to Director, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY. Patrick L. McGeer, M.D., Ph.D., F.R.C.P.(C), is Professor Emeritus, Department of Psychiatry, Kinsmen Laboratory of Neurological Research, University of British Columbia, Vancouver, B.C., Canada.

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**Erratum**

In the article entitled “Prodromal Symptoms and Relapse Prevention in Schizophrenia” by Marvin I. Herz and J. Steven Lambert (Schizophrenia Bulletin, Vol. 21, No. 4, 1995), the following sentence on page 547 (second paragraph) should read: “However, the low 2-year relapse rates achieved by both groups (30% for the intermittent group and 16% for the maintenance group, a nonsignificant difference) suggest that monitoring for prodromal symptoms with early intervention could significantly reduce relapse rates among many outpatients with schizophrenia.”