Schizophrenia and Alzheimer's Disease: Clinical and Pathophysiologic Analogies

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Psychotic symptoms are prominent in schizophrenia and a frequent neuropsychiatric manifestation of Alzheimer's disease (AD), occurring in approximately 50% of patients affected. The shared psychiatric symptoms suggest common cerebral pathophysiologies. Radiologic and pathologic findings indicate a predilection toward limbic involvement, with structural and atrophic changes of the medial temporal region predominating in both disorders. Neurochemical alterations affecting the dopaminergic/cholinergic axis appear to be central to both schizophrenia and AD. The basic pathologies of the two disorders are different, but they have similarities in the pattern of regional brain dysfunction, biochemical dysfunction, and symptomatology. We represent a selective review of these similarities. Insights drawn from these observations enrich the understanding of each disorder.

SCHIZOPHRENIA is the most common psychotic illness, affecting approximately 1% of the population. It has long served as the prototype psychosis with its classic symptoms of delusions, hallucinations, illogical thinking, and formal thought disorder.[1] However, psychosis is not unique to schizophrenia. A broad range of neurological disorders and toxic-metabolic disturbances exhibit psychosis as one manifestation of brain dysfunction.[2]

Alzheimer's disease (AD) is a degenerative brain disorder characterized by both cognitive and noncognitive neuropsychiatric symptoms. AD is the most common of the dementias, accounting for approximately 60% of all cases of dementia in patients over age 65 years.[3] It is estimated that 2% to 4% of the population over age 65 years have AD, with prevalence rates increasing to 40% or more over age 85 years.[4] AD is characterized by acquired and persistent deficits in memory, language, visuospatial skills, personality organization, and cognition.[2] Psychiatric symptoms are common in AD, with psychosis—as evidenced by hallucinations and delusions—present in approximately 50% of affected patients.[5,6] This propensity toward psychosis coupled with the prevalence of AD in the population renders it second only to schizophrenia as a source of psychotic symptomatology.

The purpose of this article is to examine pathophysiologic analogies between schizophrenia and AD. There are many clinical, radiologic, and neurochemical similarities between schizophrenia and AD; increased appreciation of these analogies may enhance understanding and stimulate new research questions for both disorders. Their major clinical similarities, as well as shared radiologic, pathologic, and neurochemical findings, are discussed (Table 1).

CLINICAL FEATURES

Dementia is characterized by the development of multiple cognitive deficits that include memory impairment, as well as aphasia, apraxia, agnosia, or disturbances in executive functioning.[7] Although memory and cognitive changes are the cardinal features of AD, psychotic symptoms are common.[8,9] The neuropsychiatric manifestations of AD are the most burdensome for caregivers, often serve as the primary cause of institutionalization, and are a clinical marker of a more rapid cognitive decline.[6,9-11]

Schizophrenia is characterized by delusions, hallucinations, illogical thinking, and disorganized behavior. Alterations in affect, productivity of thought and speech, and volition are also common.[7] The clinical diversity of schizophrenia has prompted numerous efforts to define specific subtypes of the disorder. One recent classification system shown to have prognostic significance distinguishes patients with predominately positive symptoms from those with symptoms that are predominately negative in charac-

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Supported by the Department of Veterans Affairs and a National Institute on Aging Alzheimer's Disease Core Center Grant (A610123).

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0010-440X/96/3703-0005$03.00/0

Table 1. Characteristics of Schizophrenia and AD

Schizophrenia	AD
Clinical features	
Delusions: persecutory, referential, bizarre	Delusions: persecutory, theft, infidelity
Hallucinations: auditory > visual	Hallucinations: visual > auditory
Flattened affect, avolition, apathy, poverty of speech and thought	Disengagement Apathy
Neuroimaging	
Lateral/third-ventricular enlargement	Pronounced lateral/third-ventricular enlargement
Regional atrophy: temporal lobes, hippocampus	Diffuse cortical atrophy: marked involvement of temporal lobes, hippocampus
Reduced glucose metabolism in frontal lobes	Reduced glucose metabolism in frontal lobes as the illness progresses Prominent temporal/parietal hypometabolism
Pathology	
Regional atrophy of medial limbic structures	Generalized atrophy: medial limbic and parietal structures > frontal cortex
Hippocampus: atrophy, neuronal loss, gliosis, pyramidal cell disarray	Hippocampus: senile plaques, NFTs, granulovacuolar degeneration
Substantia innominata: cell degeneration	Substantia innominata: neurofibrillary degeneration
Neurochemistry	
Overactivity central dopaminergic systems (disturbed dopamine/acetylcholine balance)	Under activity presynaptic cholinergic systems (disturbed dopamine/acetylcholine balance)
Treatment	
Dopamine-blocking agents	Dopamine-blocking agents and cholinergic enhancement

Abbreviations: NFTs, neurofibrillary tangles.

ter.[12,13] Crow[14] has proposed that the underlying process of positive symptoms of schizophrenia is a disturbance in dopaminergic transmission, whereas negative symptoms of schizophrenia are more likely a result of cell loss and structural changes in the brain. Some patients manifest both types of symptoms, and many have both types of pathological change.

Positive symptoms of schizophrenia are characterized by delusions, hallucinations, formal thought disorder, and bizarre behavior. Although delusional content is variable, persecutory and referential delusions are most common. Hallucinations may involve any sensory modality, but auditory hallucinations are most characteristic of the disorder. Disorganized speech and behavior represent distortions or exaggerations of language, communication, and behavioral monitoring.[7]

Positive psychotic symptoms are common in AD. The frequency with which these symptoms are reported varies among studies from 10% to 73%.[15] Delusions occur more frequently than hallucinations.[9,16] The delusions of dementia tend to be unsystematized and loosely held,[17] with the majority being of a simple, persecutory type involving theft of one's property, personal harm, or fears regarding infidelity of one's spouse. However, delusions of imposters, phantom boarders, amorous involvement, and parasitic infestation have also been reported.[9] Hallucinations are predominately visual or auditory in nature. Visual hallucinations are most common and frequently involve people or animals.[16,18] Auditory experiences range from hearing distinct voices or conversations to perceiving indistinguishable sounds.[16] The occurrence of positive symptoms in AD has been correlated with a more rapid rate of cognitive decline.[9,10,19] Delusions in AD are not correlated with severity of dementia and are an independent manifestation of brain dysfunction.[20]

Negative symptoms of schizophrenia include marked poverty of speech and thought content, flattened affect, and a generalized avolition characterized by apathy and a reluctance to initiate goal-directed behavior. A predominance of negative symptoms correlates with the presence of neuropsychological deficits, poor premorbid adjustment, limited response to somatic intervention, and a more deteriorative prognostic course.[12,21]

AD also has prominent negative symptoms. Disengagement, apathy, diminished emotional responsiveness, loss of volition, and decreased initiative occur in nearly all patients.[22,23] Affective blunting, poverty of speech, and decreased spontaneous movement may also be seen late in the disease course.[24] This symptom profile closely resembles the deficit state in schizophrenia.

Schizophrenia and AD share many common clinical characteristics. Positive and negative symptom complexes are apparent in both disorders. The positive symptoms of AD resemble those seen in schizophrenia and consist predominately of delusions and hallucinations. Persecutory content is common to the delusions of both

illnesses. Auditory hallucinations are characteristic of schizophrenia, whereas visual hallucinations are more pronounced in AD. Negative symptoms, including avolition, apathy, and decreased emotional responsiveness, are observed in both disorders.

NEUROIMAGING

Computed tomography reveals abnormalities in many but not all schizophrenic patients. The most consistent findings include lateral- and third-ventricular enlargement and enlarged cortical sulci.[25-29] These atrophic changes are independent of age, chronicity, and amount or type of treatment received.[30] Atrophy has been shown to correlate with substandard performance on neuropsychological tests, the presence of negative symptoms, and poor treatment response.[21,25,31-33]

Structural abnormalities of the limbic system are also apparent on magnetic resonance imaging scans of schizophrenics. Decreased size of the hippocampus has been reported in the affected member of monozygotic twin pairs discordant for schizophrenia.[34] In addition, schizophrenics have been reported to show enlargement of the temporal horn of the lateral ventricles and decreased volume of temporal lobe tissue relative to controls.[35-37]

Computed tomographic and magnetic resonance imaging scans of AD typically show pronounced atrophy and ventriculomegaly.[38] Cortical atrophy with enlargement of both lateral and third ventricles becomes more striking as the disease progresses.[2] Although mild generalized atrophy is consistent with the aging process, the pronounced regional atrophy of the temporal lobes distinguishes AD subjects from age-matched controls.[39,40] In addition, hippocampal volumes are reduced in AD, a finding that is often marked even in the early stages of the disease.[40] Thus, atrophy of temporal structures contributes significantly to the ventricular enlargement observed in both AD and schizophrenia.

Positron emission tomography has been used to assess regional cerebral metabolism in both schizophrenia and AD. The most consistent finding in studies comparing schizophrenics with normals has been a relative reduction in frontal lobe activity among schizophrenics. This finding has been widely reproduced and is independent of neuroleptic treatment.[41-45] Precise correlations between this hypofrontal pattern and particular clinical characteristics have yet to be fully elucidated, but reduced activity in this region has been postulated to relate to the psychomotor retardation and lack of goal-directed behavior observed in some schizophrenics.[41]

Positron emission tomography studies reveal markedly reduced rates of cerebral glucose metabolism in AD, with mean cortical rates reduced by as much as 30% to 49% in AD subjects compared with normal age-matched controls.[46,47] Numerous studies show a pattern of bilateral hypometabolism in the parietal and temporal cortex of patients with mild to moderate AD, and frontal cortical hypometabolism becomes evident as the disease progresses.[40,48,49] Reduced metabolic activity is more severe and extensive in AD than in schizophrenia. Reduced frontal lobe metabolism is present in both disorders.[40]

Neuroimaging reveals structural and metabolic abnormalities in both schizophrenia and AD. Atrophy, as evidenced by ventricular and sulcal enlargement, is common in both disorders. Regional atrophy is most pronounced in medial temporal structures. Functional imaging reveals reduced frontal lobe metabolism in schizophrenia. Temporoparietal hypometabolism is most prominent in AD, with reduced frontal metabolism occurring as the disease progresses.

PATHOLOGY

Postmortem investigations reveal that pathological changes of the limbic system are common in both schizophrenia and AD. Ventriculomegaly is frequently observed in schizophrenia and is associated with volume loss in medial limbic structures of the temporal lobe, including the amygdala, hippocampal formation, and parahippocampal gyrus.[50] Analysis of brains in AD also reveals atrophic changes and ventriculomegaly. Although more severe than the alterations observed in schizophrenia, the atrophic changes of AD also exhibit a regional predilection for structures of the temporal lobe, particularly the medial limbic portions containing the hippocampi and amygdaloid nuclei.[2,51]

The most consistent histopathological aberrations reported in schizophrenia are neuronal loss and gliosis. These changes have been observed to varying degrees in the reticular formation, hypothalamus, periaquaductal gray regions, and the hippocampus.[52] In addition, various types of cell degeneration, including vacuolated cytoplasm and peripherally displaced nuclei, have been described in the substantia innominata of schizophrenic patients. Portions of this structure (the nucleus basalis of Meynert) provide cholinergic innervation to the cortex and have shown morphological alterations in AD.[53,54]

Hippocampal pathology is also evident in schizophrenia. Several types of changes of the hippocampus have been reported in investigations of postmortem tissue from schizophrenic patients. These include gliosis,[52] decreased volume,[50] decreased pyramidal cell number,[55] reduced pyramidal cell density,[56] and disarray of pyramidal cell orientation.[57,58]

The histopathology of AD includes senile plaques, neurofibrillary tangles, and granulovacuolar degeneration involving limbic system structures and the association cortex. Senile plaques may be present throughout the cortex of affected individuals, but are particularly prevalent in the hippocampal region and the association cortex.[59,60] Neurofibrillary tangles share a predilection for medial temporal structures including the amygdaloid complex and the pyramidal cells of the hippocampus, where most neurons are involved.[59] Granulovacuolar degeneration is usually restricted to the hippocampal formation.[60]

AD-like neurohistological lesions have also been observed in the brains of elderly patients with schizophrenia. Corsellis[61] reported a higher incidence of both neurofibrillary tangles (23%) and neuritic plaques (42%) in the brains of elderly schizophrenics versus the general population, and the rate of AD pathology has been found to be significantly higher in patients with schizophrenia than in age-matched controls.[62] In a recent study by Wisniewski et al.,[63] the incidence of neurofibrillary tangles was found to be twice as high in elderly schizophrenics who did receive (74%) versus those who did not receive (36%) neuroleptics, suggesting that neuroleptic use may contribute to neurofibrillary pathology. These findings suggest a correlation between schizophrenia and acceleration of AD pathology. The degree to which medications influence this finding requires further study.

Thus, postmortem investigations demonstrate that the limbic system is the brain region most prominently affected in both schizophrenia and AD. While hippocampal pathology has long been linked with memory dysfunction,[64] increasing evidence suggests a role for amygdala and medial temporal dysfunction in the pathophysiology of psychotic symptoms,[65] and changes in these areas may contribute to positive symptoms in both disorders. Neurohistological lesions consistent with AD have been observed to be more numerous in elderly schizophrenics than in age-matched controls. These findings suggest a link between schizophrenia or its treatment and the presence of AD pathology.

NEUROCHEMISTRY

The most widely held neurochemical hypothesis for the pathophysiology of schizophrenia proposes that the symptoms reflect relative overactivity of central dopaminergic systems.[66] This hypothesis is derived largely from pharmacological evidence demonstrating that dopamimetic drugs (e.g., amphetamine) can produce many of the positive symptoms associated with schizophrenia, whereas drugs that reduce dopaminergic activity, primarily through dopamine receptor blockade, are efficacious in the treatment of these symptoms.[67,68]

The most striking neurochemical alteration in AD involves the presynaptic cholinergic system. Studies have consistently provided evidence for a central cholinergic deficit in AD characterized by markedly reduced concentrations of both choline acetyltransferase and acetylcholine in the cerebral cortex and hippocampus of patients with AD.[69-72] Reductions in choline acetyltransferase activity and acetylcholine synthesis correlate with loss of cholinergic nerve endings in these areas,[73] a finding consistent with reports of reduced choline uptake[74,75] and cholinergic neuron loss in the basal forebrain (nucleus of Meynert), from which these cortical projections arise.[76]

Neurochemical alterations in AD and schizophrenia may contribute to the shared psychotic symptomatology. Several lines of evidence indi-

cate that dopamine and acetylcholine exist in a dynamic balance essential to the optimal regulation of biologic processes in the corpus striatum and possibly in other cerebral regions (see Meltzer and Stahl[77] for a thorough review). A shift in the concentration of either neurotransmitter (increased dopamine activity in schizophrenia or decreased acetylcholine activity in AD) could distort a dopaminergic/cholinergic balance, resulting in psychotic behavior. Dopaminergic excess appears strongly correlated with the psychosis of schizophrenia. In AD, cholinergic levels are reduced while dopaminergic levels are maintained,[78] creating a relative dopamine predominance that may contribute to psychotic symptoms.[79] Both dopamine receptor-blocking agents and cholinergic therapies are efficacious in the treatment of AD-related psychosis.[79-81] Thus, the severe cholinergic deficiency found in AD may create a cholinergic/dopaminergic imbalance similar to that hypothesized as the underlying neurochemical disturbance in schizophrenia.

TREATMENT

The therapeutic efficacy of antipsychotic agents in the treatment of schizophrenia is well established.[82] However, investigation of the effects of these agents in AD has been limited. Petrie et al.[83] compared loxapine, haloperidol, and placebo treatments in 61 demented patients institutionalized in a state psychiatric hospital. Moderate to marked improvement was noted in approximately one third of patients who received loxapine or haloperidol (32% and 35%, respectively) and in only 9% of placebo-treated patients. Adverse effects, including sedation and extrapyramidal symptoms, were common in both active treatment groups. Reisberg et al.[84] identified improvement in behavioral symptoms, including psychotic phenomena, in 56% of AD patients treated with thioridazine. Side effects, most frequently sedating, anticholinergic or extrapyramidal in nature, were reported by approximately half of all patients treated. Gottlieb et al.[85] evaluated the effects of low-dose depot fluphenazine and found significant benefits with fewer side effects in eight of 10 AD patients studied. The therapeutic efficacy of antipsychotics in AD is modest compared with that seen in schizophrenia and is frequently complicated by the development of side effects.

Treatment of AD patients with cholinergic agents has recently been shown to reduce psychotic symptoms. In a double-blind crossover study, Cummings et al.[79] compared the antidelusional efficacy of physostigmine, an acetylcholinesterase inhibitor, with that of haloperidol in two patients with AD. Physostigmine was found to ameliorate delusions with fewer side effects than haloperidol in both patients. A follow-up study using a similar design and a larger sample of AD patients confirmed these results.[81] Thus, preliminary findings suggest that cholinergic deficiency has an important role in the pathogenesis of psychosis, and that readjustment of acetylcholine levels can improve psychotic symptoms in AD.

The use of cholinergic agents has also been associated with improvement of psychotic symptoms in schizophrenia. Pfeiffer and Jenney[86] administered subcutaneous injections of arecoline, a cholinomimetic agent, to 23 chronic schizophrenics. Prophylaxis to adverse peripheral effects was achieved by prior administration of probantheline. Clinical improvement in the form of a "lucid interval" lasting about 30 minutes was seen in 83% of patients studied. Another study[87] investigated the effects of physostigmine in five chronic schizophrenics refractory to phenothiazines. The addition of oral physostigmine to their phenothiazine regimen resulted in marked but transient improvement in all patients. These studies suggest that enhanced central cholinergic activity may temporarily offset dopaminergic excess in schizophrenia, resulting in clinical improvement.

Thus, dopaminergic/cholinergic balance may be central to the treatment of both AD and schizophrenia. Dopamine hyperactivity is strongly correlated with the positive symptoms of schizophrenia, and antipsychotic medications, acting via dopamine receptor blockade, are efficacious in their treatment. In AD, where diminished cholinergic activity results in relative dopaminergic excess, these medications also show utility. Preliminary observations suggest that cholinergic agents may also benefit AD patients with psychotic symptoms.

SUMMARY

Schizophrenia and AD share many clinical and pathophysiologic features. Delusions, hallucinations, apathy, avolition, and altered affect are characteristic of schizophrenia, and are frequent neuropsychiatric concomitants of the cognitive dysfunction observed in AD. These psychiatric symptoms evident in both disorders point to a shared cerebral pathology. Radiologic and pathologic findings indicate a predilection for limbic involvement, with atrophy and structural changes of medial limbic regions prominent in both disorders. Increasing evidence points to the role of limbic system dysfunction in the pathophysiology of psychotic symptoms,[65,88,89] and the limbic alterations of schizophrenia and AD likely contribute to psychotic symptoms in both disorders. Disturbances in the dopamine/acetylcholine axis are characteristic of both schizophrenia and AD. Increased attention to the clinical and pathophysiologic analogies of AD and schizophrenia may provide additional insight into the mechanisms of both disorders.

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