Original Paper

Morphological substrate of chronic schizophrenia in elderly patients: a clinicopathological study

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Submitted: 21 February 2025 · Accepted: 06 March 2025 · Copyedited by: Cinthya Aguero · Published: 13 March 2025

Abstract

Objective: Patients with schizophrenia are at a higher risk of developing dementia, but the basis of cognitive impairment is a matter of discussion. Conflicting results regarding the association of schizophrenia with Alzheimer disease (AD) may partly be attributable to the inclusion of non-AD lesions, which few clinicopathological studies have considered. Therefore, a re-evaluation of an autopsy cohort of elderly schizophrenics published previously [1] was performed.
Material & methods: Among 99 consecutive autopsy cases of patients who met the DSM-5 and ICD.10 criteria for schizophrenia (mean age 69.5 ± 8.25 years), 56 showed moderate to severe dementia. All brains were blindly examined using the current criteria for AD and looking for concomitant lesions. They were compared with the frequency of AD in an autopsy series of 1.750 aged demented individuals
Results: Four cases revealed the features of definite AD, five probable AD, and three aged 82–89 years were classified as primary age-related tauopathy (PART). Two cases were a cortical type of dementia with Lewy bodies (DLB), one Lewy body disease of brainstem type; six showed hippocampal sclerosis, 14 argyrophilic grain disease (AGD), and one progressive supranuclear palsy (PSP). Other co-pathologies were frequent lacunes in basal ganglia, moderate cerebral amyloid angiopathy, minor development anomalies in the entorhinal cortex, Fahr's disease, metastatic tumors, and acute or old cerebral infarctions (n = 4 each). Definite AD was seen in 48 % of the age-matched demented control group.
Conclusions: In this cohort of elderly schizophrenic patients, only 7.6 % fulfilled the neuropathological criteria of definite or probable AD and 3.6 % of PART compared to 6 % to 13.7 % typical and atypical AD in the literature, whereas a considerable number of cases showed non-AD co-pathologies. This is in line with other studies showing that the frequency of AD in elderly schizophrenics may be equal to or less than in age-matched controls. Further studies are needed to elucidate the mechanisms of cognitive decline in schizophrenia.

Keywords: Schizophrenia; Cognitive impairment; Neuropathology; Alzheimer disease; Concomitant pathologies

Abbreviations

AD - Alzheimer disease, **ADNC** - Alzheimer disease neuropathological changes, **AGD** - Argyrophilic grain disease, **CAA** - Cerebral amyloid angiopathy, **CI** - Cognitive impairment, **DLB** - Dementia with Lewy bodies, **NFT** - Neurofibrillary tangle, **PART** - Primary age-related tauopathy, **SCZ** - Schizophrenia.

Introduction

Current literature suggests that the pathology of schizophrenia (SCZ) has mainly developmental origins based on genetic factors, perinatal abnormalities, and other factors [2], but this cannot explain the evidence of accelerated cognitive decline and increased risk of dementia in elderly patients with SCZ [3–19]. The prevalence of dementia among US adults with SCZ at 66 years of age was 23.2–27.9 % compared with 1.3 % in the group without serious mental illness and at age 80 increased to 70.2 % in the group of schizophrenia and 11.3 % in the control group (6.2 times higher) [19]. Among New Zealanders with SCZ aged 65 years or older, 23 % had a dementia diagnosis [16], while in a population-based study in Taiwan, SCZ patients exhibited a 1.8-fold risk of dementia compared to controls, with a higher risk of developing Alzheimer disease (AD) [15]. Up to now, no clear relationship between cognitive decline/dementia and SCZ has been found, and the cause of this impairment is still unclear [6, 15, 18–23]. MRI studies revealed brain structural abnormalities with reduced gray matter volumes in the right orbitofrontal cortex and cingulate gyrus [4], prefrontal cortex, hippocampus, and subcortical structures [22], hippocampus [24, 25], hippocampus and amygdala [26, 27], and in the mediodorsal thalamus and pulvinar, which was confirmed by postmortem assessment [28]. SCZ patients showed a higher brain-predicted age difference compared to age- and sex-matched controls [11]. Recent studies identified disconnectivity in corticocortical and corticostriatal circuits, each with specific clinical symptoms [29, 30].

Several reports have provided conflicting results regarding the association between SCZ and Alzheimer disease (AD). However, both disorders partially overlap in terms of psychiatric symptoms and some aspects of cognitive impairment (CI) and interference with each other through amyloid evolvability [23]. In both, the left hippocampus and amygdala volume are significantly smaller. Still, the hippocampus / amygdala ratio was significantly lower in SCZ compared to AD and age-matched controls, which correlated with the age at disease onset [26]. On the other hand, behavioral and social dysfunction in both disorders has been linked to hyperactivity within the fronto-parieto-limbic brain systems [31].

Earlier studies suggesting that the frequency of AD pathology (Alzheimer disease neuropathologic changes - ADNC) is increased in elderly schizophrenics [32–34] are questionable. In the largest postmortem series of 544 people with schizophrenia (mean age 77 years), with an overall frequency of AD of 28 %, it increased from 6 % among those under age 65 to 45 % in those over age 85 years [35]. Although no control group was included and the diagnostic criteria of AD were not clearly defined, its frequency was more common than in age-related populations [36]. Among 100 autopsy cases of SCZ (mean age 76.5 years), 72 % showed cognitive impairment, but only 9 % were diagnosed with AD and 4 % with other dementing disorders [8]. Several postmortem studies showed that the frequency of AD in SCZ is not different from that in age-matched controls [37, 38] or in the general population [1, 7, 39–41] or showed even less incidence than expected [39, 42]. No differences in β-amyloid (Aβ) deposition between SCZ and comparison groups indicated that the mechanisms of dementia development in SCZ may not share the neuropathology of AD [43] and that the Aβ levels in SCZ patients are not different from elderly controls [3]. Neurofibrillary tangle (NFT) densities in the hippocampus, entorhinal, and inferior temporal cortex in elderly patients with late-onset SCZ were not significantly different from controls [44]. A recent meta-analysis reported lower severity for both plaques and NFTs in the SCZ group versus AD and that no higher rates of ADNC were found in cognitively impaired SCZ patients compared with age-matched controls [10]. On the other hand, ADNC and argyrophilic grain pathology have been observed in elderly SCZ patients with cognitive

decline [45, 46]. A recent study distinguished two types of SCZ patients with incident dementia: those with coexisting neurodegenerative diseases (AD, argyrophilic grain disease /AGD/, etc.) and those without such co-pathologies [47].

Given the current controversy about the morphological basis of CI in elderly schizophrenics, the postmortem findings in a cohort of elderly patients with chronic SCZ (published by [1]) were re-examined and compared with a large autopsy series of demented elderly subjects.

Material and methods

The study included 99 patients (mean age at death 69.5 ± 8.25, range 60–89 years; 68 older than 65 years) who met the DSM-5 and ICD-10 criteria of schizophrenia and had a complete neuropathological examination. They died between 1980 and 1999. The clinical data were retrospectively derived from hospital records evaluated by an experienced psychiatrist. For each case, information was obtained on the age at onset of psychiatric disease, age at first hospitalization, family, medical, and neurological history, alcohol and drug abuse, drug and, in particular, antipsychotic medication, clinical signs and symptoms including extrapyramidal side effects of neuroleptic treatment, other motor, sensory and cognitive impairment, and the clinical status immediately before death. Based on these data, each case was psychiatrically classified [48]. Most had residual SCZ, some paranoid or undifferentiated forms. The mean duration of illness was 35.15 ± 10.17, with a range of 14–60 years. Exclusion criteria were severe neurological disease (e.g., Huntington or Parkinson disease), acute stroke, and brain tumors.

A neuropathological examination was performed according to standard protocols and a macroscopic examination of the brain. Histological examination of multiple paraffin blocks was performed using routine stains (H&E, cresyl violet, Klüver-Barrera or Heidenhain stain, Bodian silver impregnation, Holzer stain for fibrillary gliosis), immunohistochemistry for glial fibrillary protein (GFAP), β-amyloid (clone 4G8), tau (antibody AT-8) and α-synuclein. TDP-43 pathology was not examined since no antibodies were available at that time. Braak NFT stages, Thal Aβ phases, and the CERAD criteria [49] were evaluated, and the diagnosis of AD was made according to the NIA-AA criteria [50]. The diagnosis of other neurodegenerative disorders (dementia with Lewy bodies /DLB, AGD, progressive supranuclear palsy, etc.) was performed according to current criteria. Furthermore, large and small cerebral infarcts [51], cerebral amyloid angiopathy (CAA), and other co-pathologies (e.g., hippocampal sclerosis, Fahr's disease, cerebral metastases, or minimal developmental anomalies) were described.

Results

Of the 99 patients who met DSM-5 and ICD-10 criteria for SCZ, 56 showed moderate to severe dementia (mean MMSE 15.4 ± 8,3; range 6–22), often more involving sensory than motor behavior and/or various domains of cognitive functions, in particular executive and attentional dysfunctions, short term memory and behavioral disorders. Patients with CI were significantly older (mean age 73.36 ± 6.85 years) than non-demented ones (mean 64.02 ± 6.54 years) ($p < 0.001$) and had a longer duration of illness (mean 41.1 vs 28.9 years) ($p < 0.001$). The brain weight of the demented was significantly lower than that of the non-demented (1119.5 ± 106.1 g vs 1216.3 ± 136.2 g) ($p < 0.001$).

Only two patients (aged 60 and 67 years, respectively) met the neuropathological criteria of definite AD or typical ADNC (Braak stage V–VI, ABC 3/3/3), i.e., 2.1 % of the total, and 1.4 % (1/68) of those over age 65 years). Probable AD (Braak stages IV–V, CERAD B, ABC 2/2/2) was diagnosed in five (aged 71–89, mean 79 years) or intermediate ADNC, i.e., 7.6 % of the total and 7.3 % of those older than 65. Two females aged 63 and 65 years fulfilled the diagnosis of diffuse DLB, and another one showed nigral degeneration with subcortical Lewy bodies without cortical involvement, thus meeting the criteria of Lewy body (LB) disease of the brainstem type. Three females, aged between 82 and 89 years, met the criteria of primary age-related tauopathy (PART) (Braak stage IV, NIA, and CERAD negative with only minimal Aβ deposits and CAA) [52], all three had APOE ε2/3 genotype. In summary, definite / probable AD accounted for 7.6 % of the total cohort and 10.3 % of those over age 65. Further, 3 %

were PART, compared to 48 % AD in an autopsy cohort of 1,750 age-matched demented patients [53]. The other brains of SCZ patients with mild to moderate CI showed Braak states II–IV (mean 2.47), Thal Aβ stages 1–2, occasional Lewy bodies and AGD (14 each), and many with mild to moderate CAA, and more than a half, lacunes in basal ganglia and cerebral white matter.

Other neuropathological changes were sequelae of frontal lobotomies (n = 8), minor developmental anomalies (less neuronal clustering in layer II of the entorhinal cortex, n = 7), hippocampal sclerosis (n = 6), Fahr's disease, cerebral metastases (four each), recent and old cerebral infarcts (four), and one with the diagnosis of progressive supranuclear palsy.

The essential clinical and neuropathological data are given in **Table 1**.

Discussion

In the present sample of 99 subjects older than 60 years with chronic SCZ, 56 % showed moderate to severe CI/dementia, only seven met the neuropathological criteria of probable or definite AD, and three that of PART, a rare form of AD-like changes but Braak stages up to IV and minimal Aβ pathology [52]. Thus, only 10.9 % of the present sample were classified as having the likelihood of ADNC or AD-related pathology, whereas the majority of the cases

Table 1: Demographic and essential neuropathological data

	Demented	Non-demented	Total
Number of patients	56	43	99
Age at death (years)	73.3 ± 6.85	64.25 ± 6.45	69.5 ± 8.25
Age at onset (years)	31.7 ± 4.3	32.4 ± 5.6	32.0 ± 5.0
Duration of illness (years, mean)	41.1	28.9	35 ± 0
MMSE score	15.4 ± 8.3	27.3 ± 9.8	21.5 ± 8.9
Brain weight (g)	1119.5 ± 106.15	1216.3 ± 136.25	
Typical ADNC (Braak V–VI)	2 (3.6 %)	0	2 (2.02 %)
Intermediate ADNC (Braak III–IV)	5 (8.9 %)	0	5 (5.05 %)
PART (Braak IV)	3 (5.4 %)	0	3 (3.03 %)
DLB	2 (3.6 %)	0	2 (2.02 %)
LBD (brainstem)	0	1 (2.3 %)	1 (1.01 %)
Lewy bodies	9 (16.1 %)	5 (11.6 %)	14 (14.14 %)
AGD	7 (12.5 %)	7 (16.3 %)	14 (14.14 %)
PSP	0	1 (2.3 %)	1 (1.01 %)
Fahr's disease	2 (3.6 %)	2 (4.7 %)	4 (4.04 %)
Hippocampal sclerosis	4 (7.1 %)	2 (4.7 %)	6 (6.06 %)
Microcerebrovascular lesions (lacunes)	35 (62.5 %)	16 (37.2 %)	51 (51.52 %)
Old infarcts	2 (3.6 %)	2 (4.7 %)	4 (4.04 %)
Developmental anomalies	4 (7.1 %)	3 (7.0 %)	7 (7.07 %)
CAA severity range	1–3 (2.5 ± 0.3)	0–2 (0.5 ± 0.1)	0–3 (1.5)
Thal Aβ plaques	2–4 (2.3 ± 0.5)	0–2 (1.0 ± 0.5)	0–4 (1.6)

MMSE: mini-mental state examination; ADNC: Alzheimer disease neuropathologic changes; PART: primary age-related tauopathy; LBD: Lewy body disease; DLB: dementia with Lewy bodies; AGD: argyrophilic grain disease; PSP: progressive supranuclear palsy; CAA: cerebral amyloid angiopathy

presented non-AD changes. These data are in accordance with other studies, like 9 % in a slightly older US cohort [38] 6.3 % or 13.7 % when including mild or atypical AD lesions [42]. Neuritic Braak stages III–IV were seen in 36.7 % of early-onset, 58.8 % of late-onset SCZ, and 11.1 % of controls. The restricted limbic tauopathy in both early- and late-onset schizophrenic patients was associated with sparse Aβ deposits [54], which would suggest the diagnosis of PART in this SCZ cohort. While of the subjects with SCZ, 68 % had definite CI, only 8 % fulfilled the criteria for AD [12]; according to others, all patients with early or late onset SCZ showed neuritic Braak stages of III or less, which may correspond to normal aging [44]. In a recent study, 12.5 % had an intermediate and none had high likelihood of ADNC [47]. All these values are at the lower end of the range of AD prevalence in the general population reported in various epidemiological studies [55, 56] or among cognitively intact age-related subjects, where the incidence of definite AD was 11.6 % [57]. Among 100 non-demented subjects aged over 65 years, 18 % fulfilled the criteria of probable but none that of definite AD [58]. In an older study, elderly patients with late-onset SCZ showed NFT densities in the hippocampal CA1 field, entorhinal, and inferior temporal cortex corresponding to Braak stage III or less that were not significantly different from controls [44]. These and other results support the notion that there is no increased frequency of ADNC in elderly patients with chronic SCZ, which were derived from retrospective [8, 36, 42, 59, 60] and prospective studies [61]. They are at variance with previous studies showing an increased incidence of AD in elderly schizophrenics [32, 35], which are difficult to interpret due to methodological shortcomings. Al-though neuritic plaques and hippocampal NFTs were related to dementia severity in schizophrenic patients, none of them were pathologically diagnosed as AD due to the lack of significant Aβ deposition [62], suggesting that these findings correspond to PART [52].

Biomarker studies in patients with SCZ also showed heterogeneous results. While one study reported significantly lower levels of serum total tau and phosphorylated tau than in healthy controls [63], an 83-year-old female with late-onset SCZ had slightly elevated cerebrospinal fluid total tau and slightly decreased Aβ-42 indicating AD [64]. A recent study showed both positive and negative cerebrospinal fluid AD biomarkers in a patient with very late-onset SCZ, but no significant differences in MMSE scores and psychotic symptoms between the groups [65].

The claim that antipsychotic drug treatment resulted in increased frequency of neurofibrillary ADNC, while schizophrenic patients who did not receive neuroleptics, showed similar changes in age-matched controls [66], was not confirmed by others [36, 37, 67]. In the present cohort, all patients had a long history of neuroleptic drug use, and a large proportion showed extrapyramidal side effects. The low frequency of AD in the present and other studies [42] does not support the assumption that long-term antipsychotic/neuroleptic medication promotes the development of neuritic ADNC, which is in line with Japanese studies [37, 59].

A possible explanation of CI in chronic SCZ without considerable ADNC could be the sequelae of frontal lobotomy, which was performed in 8 patients of the present cohort. Sparse neuropathological studies of lobotomized schizophrenics revealed loss of neurons in the dorsomedial thalamus as a probable consequence of disconnection of the prefrontal cortex to central regions of the brain since the dorsomedial thalamus represents a major efferent projection to the prefrontal cortex [68]. A 69-year-old patient with SCZ who died 32 years after prefrontal lobotomy showed severe demyelination of the frontal lobe and marked retrograde degeneration and gliosis in the thalamic nuclei [69]. These data suggest an explanation of cognitive impairment in lobotomized patients with SCZ, not only by neuronal loss in specific brain areas but also by disconnectivity of cortico-cortical and cortico-thalamic circuits. Unfortunately, in the present cohort, no such studies were performed in order to find an alternative explanation for cognitive changes in chronic SCZ in the absence of neurodegenerative proteinopathies.

There is little data regarding non-ADNC in patients with SCZ. In our cohort, three patients at autopsy presented LB disorders and six AGD, which is much less than in other studies. In an earlier study, 7.3 % of patients with SCZ showed αSyn-positive structures, which were consistent with DLB and

incidental LB disease, which did not differ from controls [70]. Another study reported an incidence rate of LB pathology and AGD of 26.1 % and 21.7 %, respectively [45], while among 196 older patients with SCZ, 12.7 % presented DLB disease at autopsy (21 DLB and 4 Parkinson disease) [62]. Other neurodegenerative changes, such as TDP-43 pathology, were reported in 29 % of patients with SCZ [71] or even in 56.3 % [47].

Limitations of the present study are due to the fact that this is a re-evaluation of the neuropathology of archival material that does not allow any correlation between the neuropathological diagnoses and clinical correlates, as well as the specific implications of neuroleptic therapy on neuropathological changes. Moreover, TDP-43 pathology could not be assessed since respective antibodies were unavailable at the time of the study. However, the goal was to emphasize the relatively minor importance of AD and PART compared to other co-pathologies in patients with chronic SCZ and CI.

Furthermore, no studies of the sequelae of prefrontal lobotomy were performed that could have demonstrated secondary degenerative changes in relevant brain areas.

Conclusion and further aspects

Older patients with chronic and CI / dementia show a heterogeneous neuropathological substrate: a comparatively small group with AD and related pathologies (PART and LATE) and those with other coexisting pathologies. In older schizophrenic patients with AD-related pathologies, there are no or only little differences between those with and without incident dementia or with age-related controls. Unfortunately, there are currently only very few clinicopathological studies considering non-AD pathologies in chronic SCZ with and without cognitive and behavioral impairment and their impact on the clinical aspects and course of the disease, as well as the impact of antipsychotic treatment. In particular, the effects of antipsychotics and other therapies on brain circuitry should be examined using serial brain sections. To understand the neurobiological and pathogenic aspects of incident CI/dementia in older patients with early and late-onset SCZ, further clinico-pathological studies in well-documented cohorts are needed.

Acknowledgments

The author thanks Mr. E. Mitter-Ferstl for his secretarial and editorial work.

Funding statement

The study was funded by the Society for the Promotion of Research in Experimental Neurology, Vienna, Austria.

Conflict of interest statement

The author declares no conflict of interest.

Ethics approval

This study adheres to all relevant international, national and/or institutional guidelines for ethical standards.

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