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Characteristics of very late-onset schizophrenia-like psychosis classified with the biomarkers for Alzheimer's disease: a retrospective cross-sectional study

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ABSTRACT

Objectives: We aimed to investigate the association between very late-onset schizophrenia-like psychosis (VLOSLP), a schizophrenia spectrum disorder with an onset of ≥ 60 years, and Alzheimer's disease (AD) using biomarkers.

Design: Retrospective cross-sectional study.

Setting: Neuropsychology clinic of Osaka University Hospital in Japan.

Participants: Thirty-three participants were classified into three groups: eight AD biomarker-negative VLOSLP (VLOSLP−AD), nine AD biomarker-positive VLOSLP (VLOSLP+AD), and sixteen amnestic mild cognitive impairment due to AD without psychosis (aMCI−P+AD) participants.

Measurements: Phosphorylated tau levels in the cerebrospinal fluid and ^{18}F-Florbetapir positron emission tomography results were used as AD biomarkers. Several scales (e.g. the Mini-Mental State Examination (MMSE), Wechsler Memory Scale-Revised (WMS-R) Logical Memory (LM) I and II, and Neuropsychiatric Inventory (NPI)-plus) were conducted to assess clinical characteristics.

Results: Those in both VLOSLP−AD and +AD groups scored higher than those in aMCI−P+AD in WMS-R LM I. On the other hand, VLOSLP+AD participants scored in between the other two groups in the WMS-R LM II, with only VLOSLP−AD participants scoring significantly higher than aMCI−P+AD participants. There were no significant differences in sex distribution and MMSE scores among the three groups or in the subtype of psychotic symptoms between VLOSLP−AD and +AD participants. Four VLOSLP−AD and five VLOSLP+AD participants harbored partition delusions. Delusion of theft was shown in two VLOSLP−AD patients and five VLOSLP+AD patients.

Conclusion: Some VLOSLP patients had AD pathology. Clinical characteristics were different between AD biomarker-positive and AD biomarker-negative VLOSLP, which may be helpful for detecting AD pathology in VLOSLP patients.

Key words: very late-onset schizophrenia-like psychosis, late paraphrenia, late-onset schizophrenia, delusional disorder, Alzheimer's disease, cerebrospinal fluid, amyloid PET, neuropsychology

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Introduction

Very late-onset schizophrenia-like psychosis (VLOSLP) is a disease entity for psychotic disorders with an age of onset of over 60 years, proposed by the International Late-Onset Schizophrenia Research Group in 2000 (Howard *et al.*, 2000). It retains

concepts from older terms for late-onset psychotic disorders including "late paraphrenia," advocated by Kay and Roth circa 1960 (Kay and Roth, 1961; Roth, 1955). VLOSLP features characteristics such as a female preponderance, solitary living, persecutory (especially partition) delusions, and lack of negative symptoms (Howard *et al.*, 1992; Kay and Roth, 1961). Although current operational diagnostic criteria such as the Diagnostic and Statistical Manuals of psychiatric disease (DSM) (American Psychiatric Association, 2022) and International Criteria of Disease (ICD) (World Health Organization, 2019) do not differentiate psychotic disorders, including the schizophrenia spectrum, by age of onset, many researchers have studied late paraphrenia and/or VLOSLP because of their distinct characteristics, unknown etiology, and frequency in psychogeriatric clinical practice.

Although the criteria for VLOSLP states that the psychosis should not be attributed to affective disorders or to focal or structural brain abnormalities, whether psychotic symptoms in VLOSLP are related to neurodegenerative diseases remains uncertain. Several reports showed that many VLOSLP patients were diagnosed with dementia within several years of follow-ups (Brodaty *et al.*, 2003; Kørner *et al.*, 2009). Using nationwide population registry data, Stafford *et al.* showed that individuals with VLOSLP represented a high-risk group for subsequent dementia (Stafford *et al.*, 2021). Some pathological studies showed the predominance of argyrophilic grain disease, Lewy body disease in late-onset schizophrenia, delusional disorders (Nagao *et al.*, 2014), and primary age-related tauopathy in late-onset schizophrenia (Casanova *et al.*, 2002). In the context of AD, there were few reports about AD pathology in VLOSLP and late-onset psychosis has been rather studied as symptoms of mild behavioral disorder (MBI), pre-dementia late-onset neuropsychiatric symptoms (Creese and Ismail, 2022). Although differentiating late-onset psychotic disorders with concurrent AD pathology from late-onset psychosis attributable to AD with subtle cognitive impairments is considered difficult, clinical characteristics such as details of psychosis may differ (Fischer *et al.*, 2020).

For the present study, we included patients from our neuropsychology clinic's cohort who were diagnosed with VLOSLP and had been tested for AD biomarkers to confirm the presence of VLOSLP patients who were presumed to have a concurrent AD pathology. We then compared the demographic, neuropsychological, and psychiatric characteristics of those with positive and negative results for AD biomarkers. For comparison, we also enrolled patients with amnestic mild cognitive impairment (aMCI) due to AD without psychotic symptoms. Although we previously reported a case with VLOSLP and AD confirmed with biomarkers and a longitudinal follow-up (Satake *et al.*, 2021), it remains unclear to what extent VLOSLP patients may have Alzheimer's disease (AD) pathology and what characteristics are different between VLOSLP with and without AD pathology. We hypothesized that some VLOSLP patients will be positive for AD biomarkers and that they will have different characteristics from those who are negative for AD biomarkers and those with aMCI due to AD but without psychosis.

Methods

Study design

This was a retrospective observational study with no intervention. The information from all participants was anonymized prior to analysis as unlinked data to prevent the identification of personal information. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The Osaka University Clinical Research Review Committee (Suita, Japan) approved this study. The requirement of written informed consent was waived by the Review Committee and opt-out was implemented.

Participants

We selected participants from the database of consecutive Japanese patients visiting the neuropsychology clinic in the Department of Psychiatry at Osaka University Hospital for the first time from January 2018 to December 2021. Cases lacking data on Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Neuropsychiatric Inventory (NPI)-plus were excluded. We defined VLOSLP according to the criteria adopted by previous studies (Kanemoto *et al.*, 2022). The inclusion criteria were as follows: (1) onset of delusions and/or hallucinations at the age of 60 years or more, and (2) existence of delusions and/or hallucinations at the first visit. The existence of psychosis (delusions and/or hallucinations) was confirmed by the NPI-plus sub-items of delusions and hallucinations. The exclusion criteria were as follows: (1) an MMSE score <24; (2) a global CDR score $\geq$; (3) diagnosis of affective disorder; (4) abnormal localized findings on magnetic resonance imaging (MRI) scans, indicating cerebrovascular disease or brain tumor; and (5) a concurrent organic disease that could cause psychosis or physical symptoms suggestive of the

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disease. We identified the VLOSLP patients who also had data of AD biomarkers (cerebrospinal fluid [CSF] phosphorylated tau [p-tau] or amyloid positron emission tomography [PET]). We then divided VLOSLP patients into those with positive and negative results for AD biomarkers, which we described further in a latter section.

We also selected aMCI patients from the same database. The diagnosis of aMCI was also based on the Petersen's criteria adopted by previous studies (Kazui *et al.*, 2017) which were as follows: (1) a memory complaint documented by the patient or another source; (2) a score of 1.5 standard deviation (SD) below the education-adjusted normal value in the story A recall task in the logical memory (LM) II subtest of the Wechsler Memory Scale-Revised (WMS-R); (3) a score of MMSE ≥; 24; (4) a CDR global score = 0.5; and (5) normal basic and instrumental activities of daily living evaluated with Lawton's Physical Self-Maintenance Scale and Instrumental Activities of Daily Living Scale (Lawton and Brody, 1969). For the present analysis, we selected patients with aMCI due to AD without psychosis from all aMCI patients; the exclusion criteria were: (1) existence of psychosis at the first visit; (2) showing negative results for AD biomarkers; (3) onset <60 years; (4) diagnosis of affective disorder; (5) abnormal localized findings on MRI scans, indicating cerebrovascular disease or brain tumor; and (6) coexistence of organic diseases that could cause psychosis or physical symptoms suggestive of them.

Assessment of clinical features

We routinely assessed the physical condition, demographic data, and medical history at our neuropsychology clinic and performed standard neuropsychological examinations. In addition, the patients underwent routine laboratory tests and brain neuroimaging. General cognition was assessed using MMSE. Memory was evaluated with the LM I and LM II subtests. Attention was evaluated with weighted raw score sums for the Attention/Concentration (A/C) index composed of Mental Control, Digit Span, and Visual Memory Span subtests in WMS-R. In addition, psychomotor speed, visuospatial cognition, and language were evaluated using the Digit-Symbol-Coding, Block Design, and Information in Wechsler Adult Intelligence Scale-III (WAIS-III). These were conducted by clinical psychologists and neuropsychiatrists specializing in geriatric psychiatry. Neuropsychiatric symptoms were assessed using the NPI-plus, the original NPI-12 with an additional subitem for cognitive fluctuation (Cummings, 1997; Mori, *et al.*, 2012), by neuropsychiatrists specializing in geriatric psychiatry. This study allowed missing data on scales other than MMSE, CDR, and NPI-plus. Detailed information on psychiatric symptoms of VLOSLP participants was collected and summarized through chart review.

Amyloid PET and CSF analysis

We used ^{18}F-Florbetapir amyloid PET results and CSF p-tau levels as AD biomarkers. We collected the results of amyloid PET and CSF testing performed within three years from the first visit for the comparison of cross-sectional data with other clinical data. When the two biomarkers were not concordant, we followed the result of amyloid PET.

^{18}F-Florbetapir was injected intravenously as a slow bolus in an antecubital vein at a mean ± SD dose of 270 ± 51 MBq (range, 182–370 MBq). A 20 min list-mode PET scan was obtained after an uptake time of 40 min (range, 40–43 min), following the imaging acquisition guidelines for Amyvid (https://pi.lilly.com/us/amyvid-uspi.pdf). KMa and ES, who are both nuclear medicine specialists, evaluated each PET result as positive or negative for AD.

We obtained CSF samples from patients who were admitted to our university hospital for diagnosis and treatment. All samples were collected via a lumbar puncture between 10:00 and 12:00 while the patient was fasting; the first 1 mL of CSF from each lumbar tap was discarded. All CSF samples were sent to SRL, Inc. (Tokyo, Japan), where both p-tau and total tau (t-tau) levels were measured in duplicate using enzyme-linked immunosorbent assay (Finoscholar™ p-Tau and hTau [NIPRO Corporation, Osaka, Japan]); we adopted the cutoff ≥ 50 pg/mL of p-tau, which the SRL, Inc. set for the diagnosis of AD.

Amyloid concentrations in the CSF were also analyzed. The CSF samples were centrifuged at 430 × *g* for 5 min. The supernatants were aliquoted and stored at -80°C until assay. Aβ 1-40 and Aβ 1–42 concentrations were measured with enzyme-linked immunosorbent assay kits (Human β Amyloid [1–40] ELISA Kit Wako II (298-64601), Human β Amyloid 1–42 ELISA Kit, High-Sensitive (296-64401) [FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan]) according to the manufacturer's protocol. Genotyping of APOE polymorphisms was performed by performing the TaqMan SNP assay (Assay ID: C____904973_10, C___3084793_20) as previously described (Morihara *et al.*, 2014).

Statistical Analyses

All participants were classified into three groups: VLOSLP with negative results for AD biomarkers

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(VLOSLP−AD), VLOSLP with positive results (VLOSLP+AD), and aMCI due to AD without psychosis (aMCI−P+AD). We compared the three groups using the Kruskal–Wallis test for continuous variables (e.g. some demographic characteristics and neuropsychological test scores). We also performed the Dunn–Bonferroni post hoc test when we found statistically significant differences. The Fisher's exact test was used for the categorical variables (e.g. other demographic characteristics and for NPI-plus sub-items). For delusions and hallucinations on the NPI-plus, the Fisher's exact test was also used to compare responses of the VLOSLP−AD and VLOSLP+AD groups to each sub-question about psychosis. All statistical analyses used were two-tailed with $p < 0.05$ considered to indicate statistical significance. These analyses were performed using SPSS Statistics for Windows, Version 27.0. (IBM Corp., Armonk, NY, USA).

Results

Demographic characteristics, AD biomarkers, and APOE genotyping in the selected participants

A enrollment flowchart is shown in Figure 1. Of the 805 patients who visited our neuropsychological clinic from January 2018 to December 2021, 679 had NPI-plus and CDR data. Of these, 36 met the criteria for VLOSLP, and 100 met the criteria for aMCI without psychosis. Finally, 8 patients in VLOSLP−AD, 9 patients in VLOSLP+AD, and 16 patients in aMCI−P+AD were enrolled as participants in this study. The numbers of testing for amyloid PET and CSF p-tau were not significantly different between the groups (Table 1). Five participants had CSF p-tau levels <50 pg/mL in the VLOSLP−AD group; all in the aMCI−P+AD and VLOSLP+AD groups had >50 pg/mL. In one participant in the VLOSLP−AD, amyloid PET and CSF p-tau showed conflicting results (PET showed a negative result but p-tau was positive at 61 pg/mL); we adopted the result of amyloid PET in classifying this patient.

Table 1 summarizes other demographic characteristics, CSF tau, and Aβ concentrations, and the results of APOE genotyping in the three groups. No significant differences in education years, MMSE scores, CDR scores, CDR sum of boxes, sex distribution, percentage living alone, cholinesterase inhibitor use, and antipsychotic use were seen. Age and onset age showed significant differences ($p = 0.017$ and 0.024, respectively). The post hoc analysis showed participants in VLOSLP+AD were older than those in aMCI−P+AD at the first visit (median [interquartile range: IQR] = 84.0 [82.0–86.0] vs 77.5 [71.5–80.0]) and those in VLOSLP−AD at the onset age (median [IQR] = 82.0 [78.0–84.0] vs 67.0 [65.0–78.5]). CSF t-tau and p-tau scores were significantly different among the three groups ($p = 0.011$ and 0.003, respectively). Dunn's post hoc analysis showed both tau scores were lower among VLOSLP−AD patients than among VLOSLP+AD and aMCI−P+AD patients (t-tau, median [IQR] = 228.0 [209.0–275.0] vs 603.0 [399.5–783.0] and 590.5 [345.0–633.0]; p-tau, median [IQR] = 47.5 [41.0–49.0] vs 77.0 [65.5–92.0] and 79.5 [64.0–83.0], respectively). CSF Aβ1-40 and Aβ1-42 concentrations and Aβ1-42/Aβ1-40 ratio were not significantly different. The proportion of APOE ϵ4 carriers was also not significantly different.

Neuropsychological tests

Table 2 summarizes the results of the neuropsychological tests. LM I, II, and weighted raw score sums for A/C of WMS-R showed significant differences ($p = 0.001$, 0.001, and 0.017, respectively). Dunn's post hoc analysis revealed the following: in LM I, participants in VLOSLP−AD and VLOSLP+AD showed higher scores than those in aMCI−P+AD (median [IQR] = 12.5 [9.0–16.5] and 12.0 [9.0–18.0] vs 3.0 [2.0–6.0]); in LM II, VLOSLP−AD participants showed higher scores than aMCI−P+AD participants (median [IQR] = 10.5 [6.5–13.5] vs 0.0 [0.0–2.0]); and in weighted raw score sums for A/C, VLOSLP−AD participants showed lower scores than aMCI−P+AD participants (median [IQR] = 52.0 [41.0–55.0] vs 58.5 [58.0–61.0]). Results of the Digit-Symbol-Coding, Block Design, and Information subtests in WAIS-III were not significantly different in the three groups.

Psychiatric symptoms

Table 3 summarizes the NPI-plus results. The VLOSLP−AD and VLOSLP+AD groups did not differ significantly in delusions and hallucinations. However, there were significant differences in disinhibition (38% in VLOSLP−AD, 22% in VLOSLP+AD, and 0% in aMCI−P+AD), irritability (50% in VLOSLP−AD, 0% in VLOSLP+AD, and 6% in aMCI−P+AD), and nighttime behaviors (75% in VLOSLP−AD, 22% in VLOSLP+AD, and 25% in aMCI−P+AD). There were no significant differences among the three groups in the other psychiatric symptoms. Table 4 describes the psychotic content elicited from VLOSLP patients on their initial visit. Four in eight and five in nine VLOSLP−AD and VLOSLP+AD patients, respectively, harbored partition delusions. Delusion of

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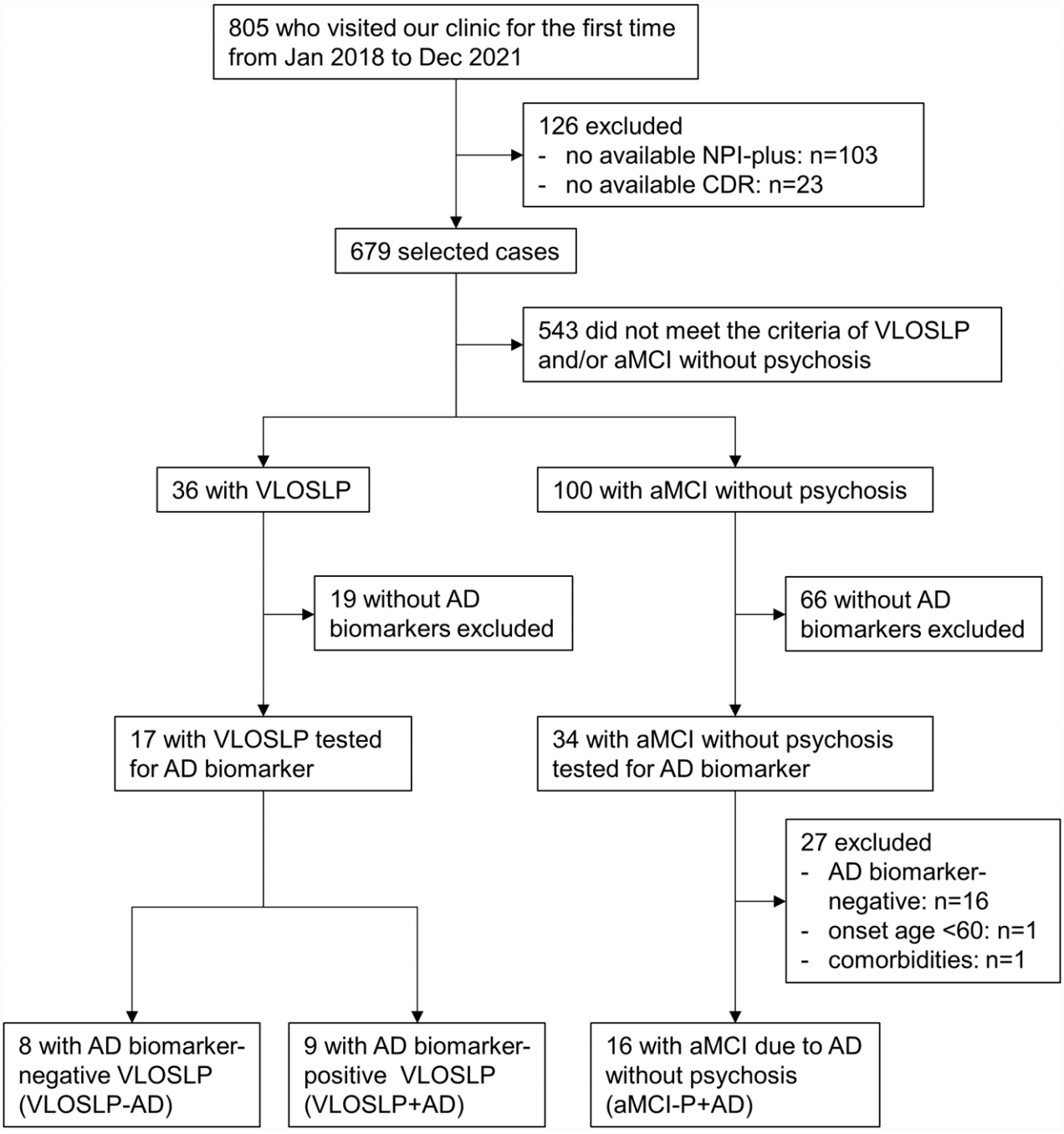

Figure 1. Enrollment flowchart. Abbreviation: NPI-plus, Neuropsychiatric inventory-plus; CDR, Clinical Dementia Rating; aMCI, amnestic mild cognitive impairment; VLOSLP, very late-onset schizophrenia-like psychosis; AD, Alzheimer's disease.

theft was shown in two in eight VLOSLP−AD patients and five in nine VLOSLP+AD patients. That someone intruded into their house and stole something was the most frequent delusion.

Discussion

We classified patients as AD biomarker-positive or AD biomarker-negative VLOSLP groups using amyloid PET results and CSF p-tau levels. We further characterized both groups by comparing them with patients with aMCI due to AD without psychosis. The results revealed that despite similar general cognitive abilities and sex distribution among the three groups, they had significant demographic, neuropsychological, and phenomenological differences along several characteristics.

In our cohort, several VLOSLP patients were positive for AD biomarkers. Previous pathological studies on late-onset schizophrenia and delusional disorders did not suggest the presence of an AD

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Table 1. Demographic characteristics, CSF tau and Aβ concentration, and results of APOE genotyping

	VLOSLP−AD ($N = 8$)	VLOSLP+AD ($N = 9$)	aMCI−P+AD ($N = 16$)	H	*P*	POST HOC DIFFERENCES
Age, years	80.5 [72.5–81.5]	84.0 [82.0–86.0]	77.5 [71.5–80.0]	8.109	**0.017**	VLOSLP+AD > aMCI−P+AD
Female	7 (88%)	7 (78%)	12 (75%)	–	0.868	
Onset age, years	67.0 [65.0–78.5]	82.0 [78.0–84.0]	75.5 [70.5–79.0]	7.443	**0.024**	VLOSLP−AD < VLOSLP+AD
Education, years	12.0 [12.0–14.0]	12.0 [12.0–16.0]	12.0 [10.5–16.0]	0.290	0.986	
MMSE	27.0 [25.0–28.5]	27.0 [26.0–28.0]	26.0 [24.0–27.0]	5.419	0.067	
CDR	0.5 [0.5–0.5]	0.5 [0.5–0.5]	0.5 [0.5–0.5]	1.957	0.376	
CDR-SOB	2.0 [1.0–2.5]	2.0 [1.0–3.0]	2.5 [1.8–3.5]	2.400	0.301	
Living alone	8 (25%)	9 (56%)	16 (31%)	–	0.412	
Use of psychotropic drugs						
ChE-I	0 (0%)	1 (11%)	0 (0%)	–	0.515	
Antipsychotics	0 (0%)	1 (11%)	0 (0%)	–	0.515	
Benzodiazepine	1 (13%)	1 (11%)	0 (0%)	–	0.258	
Anticholinergic drugs	0 (0%)	0 (0%)	0 (0%)	–	–	
Other psychotropic drugs	1 (13%)	0 (0%)	1 (6%)	–	0.727	
Tested for Amyloid PET	5 (63%)	5 (56%)	10 (63%)	–	–	
Tested for CSF tau	6 (75%)	8 (89%)	10 (63%)	–	–	
Tested for CSF Aβ	5 (63%)	7 (78%)	6 (38%)	–	–	
t-tau, pg/ml	228.0 [209.0–275.0]	603.0 [399.5–783.0]	590.5 [345.0–633.0]	9.018	**0.011**	VLOSLP−AD < VLOSLP+AD, aMCI−P+AD
p-tau, pg/ml	47.5 [41.0–49.0]	77.0 [65.5–92.0]	79.5 [64.0–83.0]	11.655	**0.003**	VLOSLP−AD < VLOSLP+AD, aMCI−P+AD
Aβ 1-40, pmol/L	1805.2 [1667.3–2611.1]	2644.8 [2446.8–2912.6]	2354.6 [1738.6–2725.1]	1.998	0.368	
Aβ 1-42, pmol/L	152.0 [130.0–302.3]	128.3 [118.6–207.9]	96.5 [71.0–144.0]	3.432	0.180	
Aβ 1-42/1-40	0.0842 [0.0780–0.1037]	0.0546 [0.0462–0.0712]	0.0471 [0.0263–0.0630]	3.357	0.187	
APOE ϵ4 carrier	1/6 (17%)	3/7 (43%)	5/10 (50%)	–	0.480	

Data other than of APOE ϵ4 carrier are presented as median [interquartile range] or number (%); The percentage of APOE ϵ4 carriers is the rate (%) of ϵ4 carriers divided by the number of participants who underwent APOE genotyping. The Kruskal–Wallis test was used for continuous variables, and the post hoc Dunn's test was performed when statistically significant results were found. Fisher's exact test was used for categorical data. All statistical analyses used a two-tailed test with statistical significance set at $p < 0.05$; statistically significant *p*-values are in bold. Onset age means the age at cognitive deterioration or psychosis was noted. Abbreviations: APOE, apolipoprotein E; AD, Alzheimer's disease; VLOSLP, very late-onset schizophrenia-like psychosis; VLOSLP−AD, VLOSLP showing negative results for AD biomarkers; VLOSLP+AD, VLOSLP showing positive results for AD biomarkers; aMCI−P+AD, amnestic mild cognitive impairment due to AD without psychosis; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; CDR-SOB, CDR sum of boxes; ChE-I, cholinesterase inhibitor; PET, positron emission tomography; CSF, cerebrospinal fluid; Aβ, amyloid beta; t-tau, total tau; p-tau, phosphorylated tau.

Table 2. Neuropsychological profiles

	VLOSLP−AD ($N = 8$)		VLOSLP+AD ($N = 9$)		aMCI−P+AD ($N = 16$)				
	N	Median [IQR]	N	Median [IQR]	N	Median [IQR]	H	p	post hoc differences
WMS-R									
Logical Memory I	8	12.5 [9.0–16.5]	9	12.0 [9.0–18.0]	16	3.0 [2.0–6.0]	14.267	**0.001**	VLOSLP−AD, VLOSLP+AD > aMCI−P+AD
Logical Memory II	8	10.5 [6.5–13.5]	9	4.0 [3.0–6.0]	16	0.0 [0.0–2.0]	14.898	**0.001**	VLOSLP−AD > aMCI−P+AD
weighted raw score sums for A/C	7	52.0 [41.0–55.0]	8	51.0 [47.5–61.0]	8	58.5 [58.0–61.0]	8.124	**0.017**	VLOSLP−AD < aMCI−P+AD
WAIS-III									
Digit-Symbol-Coding	5	44.0 [29.0–45.0]	6	37.0 [35.0–41.0]	9	39.0 [33.0–42.0]	0.095	0.954	
Block Design	5	24.0 [21.0–39.0]	6	27.0 [20.0–30.0]	9	24.0 [20.0–25.0]	0.884	0.643	
Information	5	15.0 [12.0–15.0]	6	13.0 [7.0–15.0]	9	13.0 [9.0–15.0]	0.488	0.783	

The two-tailed Kruskal–Wallis test was used, and the post hoc Dunn's test was performed when statistically significant differences ($p < 0.05$) were found; statistically significant p-values are in bold. Abbreviations: AD, Alzheimer's disease; VLOSLP, very late-onset schizophrenia-like psychosis; VLOSLP−AD, VLOSLP showing negative results for AD biomarkers; VLOSLP+AD, VLOSLP showing positive results for AD biomarkers; aMCI−P+AD, amnestic mild cognitive impairment due to AD without psychosis; IQR, interquartile range; WMS-R, Wechsler Memory Scale-Revised; A/C, Attention/Concentration; WAIS-III, Wechsler Adult Intelligence Test Third Edition.

pathology (Casanova *et al.*, 2002; Nagao *et al.*, 2014). This difference may be due to heterogeneity in inclusion criteria [e.g. Nagao *et al.* excluded patients with delusions of theft (Nagao *et al.*, 2014), while 7 of 17 participants with VLOSLP showed delusions of theft in our study]. Moreover, the participants also differed in age: the median age of participants in VLOSLP+AD group was 84.0 years, while the average age at death was reported as 63.3 years by Nagao *et al.* (Nagao *et al.*, 2014) and 77.3 years by Casanova *et al.* (Casanova *et al.*, 2002). Such differences may have led to the absence of AD pathology in their reports. Other longitudinal reports have suggested that some VLOSLP patients may transition to AD dementia after a few years (Brodaty *et al.*, 2003; Stafford *et al.*, 2021). To our knowledge, this study is the first to show that a considerable number of VLOSLP patients may have AD pathology using AD biomarkers.

As many as nine of 17 (52.9%) VLOSLP patients in this study had AD biomarkers, perhaps because of advanced age. In the Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably cohort, 24.2% of participants had subjective cognitive decline (SCD) at a mean age of 69.7 years. In the Alzheimer's Disease Neuroimaging Initiative cohort, 25.5% of MCI cases at the mean age of 72.1 years were amyloid PET-positive (Hansson *et al.*, 2018). Additionally, in European memory clinic cohorts, 46.3% and 40.4% of SCD cases with a mean age of 66.5 years were positive for Aβ 42 and p-tau, respectively, in the CSF (Wolfsgruber *et al.*, 2019). Furthermore, the number of people with AD pathology increases with age up to mid-90s (Nelson *et al.*, 2011). The median age of VLOSLP patients in our cohort was over 80 years; thus, it is plausible that more than 50% of them had AD pathology. However, despite the lack of significant differences in age at examination, the participants in the VLOSLP+AD group had a higher age of onset than those in the VLOSLP−AD group. This difference is difficult to attribute solely to age-dependent positivity for AD biomarkers. We have also previously reported a case in which a VLOSLP patient was positive for AD biomarkers and progressed to AD dementia over a two-year follow-up (Satake *et al.*, 2021). To conclude that AD pathology in VLOSLP is incidental and unrelated to psychotic symptoms would be hasty.

The MMSE and CDR scores of VLOSLP participants were similar to those of aMCI−P+AD participants. Previous studies also showed that late paraphrenia patients had poorer general cognitive function than control individuals (Naguib and Levy, 1987; Almeida *et al.*, 1995). However, to assess differences between VLOSLP with and without a specific neuropathology, the domain-specific

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Table 3. Proportion of neuropsychiatric inventory-plus sub-items present

	VLOSLP−AD ($N = 8$)	VLOSLP+AD ($N = 9$)	aMCI−P+AD ($N = 16$)	P
Delusions	7 (88%)	8 (89%)	–	1.000
1. Danger	4 (50%)	4 (44%)	–	1.000
2. Theft	2 (25%)	5 (56%)	–	0.335
3. Affair	0 (0%)	0 (0%)	–	–
4. Phantom Border	1 (13%)	3 (33%)	–	0.576
5. Capgras	0 (0%)	0 (0%)	–	–
6. House not home	0 (0%)	0 (0%)	–	–
7. Abandonment	2 (25%)	0 (0%)	–	0.206
8. Talks to TV	0 (0%)	0 (0%)	–	–
9. Other	3 (38%)	3 (33%)	–	1.000
Hallucinations	3 (38%)	4 (44%)	–	1.000
1. Auditory	1 (13%)	3 (33%)	–	0.576
3. Visual	2 (25%)	1 (11%)	–	0.576
Agitation	2 (25%)	1 (11%)	5 (31%)	0.513
Dysphoria	3 (38%)	1 (11%)	3 (19%)	0.476
Anxiety	5 (63%)	3 (33%)	3 (19%)	0.101
Euphoria	0 (0%)	0 (0%)	0 (0%)	–
Apathy	4 (50%)	6 (67%)	7 (44%)	0.600
Disinhibition	3 (38%)	2 (22%)	0 (0%)	**0.029**
Irritability	4 (50%)	0 (0%)	1 (6%)	**0.012**
Aberrant Motor Behavior	0 (0%)	0 (0%)	1 (6%)	1.000
Nighttime Behaviors	6 (75%)	2 (22%)	4 (25%)	**0.047**
Appetite and eating disorders	3 (38%)	2 (22%)	2 (13%)	0.344
Cognitive Fluctuation	3 (38%)	1 (11%)	3 (19%)	0.476

Data are presented as numbers (%). The two-tailed Fisher's exact test was used. Statistically significant p-values ($p < 0.05$) are in bold. The numbers prefixed to delusions and hallucinations contents correspond to the numbers of the NPI sub-question. Abbreviations: AD, Alzheimer's disease; VLOSLP, very late-onset schizophrenia-like psychosis; VLOSLP−AD, VLOSLP showing negative results for AD biomarkers; VLOSLP+AD, VLOSLP showing positive results for AD biomarkers; aMCI−P+AD, amnestic mild cognitive impairment due to AD without psychosis.

neuropsychological profiles must be compared. WMS-R subtests showed that patterns in memory and attention differed between patients in the VLOSLP and aMCI−P+AD groups. WMS-R LM showed that episodic memory was better in participants in the VLOSLP groups than those in the aMCI−P+AD group, and WMS-R weighted score sums for A/C showed that attention was worse in the VLOSLP participants than in the aMCI−P+AD participants. Late-onset delusional disorders patients with a mean age of 83.5 years scored better on delayed recall and recognition, including WMS-R LM II, and worse on several tests such as the digit span test than those with AD dementia without psychosis with a mean age of 79.6 years (Harris *et al.*, 2014), which is compatible with our report. On the other hand, Van Assche *et al.* (2019) investigated the differences among VLOSLP patients with a mean age of 79.3 years, AD dementia patients with psychosis with a mean age of 78.8 years, and dementia with Lewy bodies (DLB) patients with a mean age of 76.2 years; they found that VLOSLP patients were superior to AD dementia patients with psychosis in episodic memory and comparable in attention (Van Assche *et al.*, 2019). Although this difference in attention may be explained by the presence or absence of psychosis in the AD groups, other reports showed no significant differences in attention between psychotic and non-psychotic AD (Jeste *et al.*, 1992; D'Antonio *et al.*, 2019). In the study by Harris *et al.* and our study, VLOSLP patients were older than AD patients, unlike in the report by van Assche *et al.* Such age differences could have also led to the differences in attention scores.

The comparison of episodic memory among the three groups clarified the neuropsychological differences between the VLOSLP−AD and VLOSLP+AD groups. On the WMS-R LM I, VLOSLP+AD participants scored close to VLOSLP−AD participants and significantly higher than aMCI−P+AD participants. However, on the WMS-R LM II, VLOSLP+AD participants scored worse, and their scores were not significantly different from those of aMCI−P+AD participants. Mean scores (SD) on the Japanese versions of the WMS-R LM I and LM II were reported to be 15.5 (6.4) and 9.9 (6.6) in normative Japanese individuals aged 75 years or older with a mean age of 79.3 years (Kawano *et al.*, 2013). Therefore, it is possible that VLOSLP−AD participants showed little memory impairment, while VLOSLP+AD participants

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Table 4. Details of psychosis in every participant

	No.	Age	Gender	Living alone	MMSE	WMS-R LM I	WMS-R LM II	Main psychotic symptoms	Partition delusions	Delusions of theft	NPI-Delusions	NPI-Hallucinations
VLOSLP–AD	1	67	F		30	14	13	PD, AH: a strange monk living upstairs threatened her; VH: something white sometimes appeared in front of her	✓		1,4	1,3,4
	2	68	F		24	11	8	VH: a cockroach was in a spaghetti; a spider was in a cup of coffee				3
	3	77	F		27	6	6	PD: neighbors spied on her and intruded into her house	✓	✓	2	
	4	80	M		25	9	7	PD: his family members tried to abandon him			7	
	5*	81	F	✓	28	9	0	PD: her husband's visiting nurse intruded into her house and stole her precious things	✓	✓	1,2	
	6	81	F	✓	29	16	14	PD: a neighbor living upstairs spied on her	✓		9	
	7	82	F		25	17	13	PD: neighbors bad-mouthed her			1,9	
	8	82	F		27	19	14	PD: neighbors bad-mouthed her, GD: she was able to negotiate with the city capitol to create a new airport in her town			1,7,9	7
VLOSLP+AD	1**	68	F		28	11	1	PD: unspecified neighbors intruded into her house, moved her belongings, followed her out of her house, and cast lights on her	✓		1,9	
	2	79	F		27	16	4	PD: her past cleaning service staff intruded into her house and stole her things		✓	2	
	3	82	F	✓	27	18	13	VH: spectral unknown person and things appeared				3
	4	84	F	✓	26	19	6	PD, AH: unknown male and female staying beyond her house's wall threatened her	✓		1	1,2,7
	5	84	M	✓	28	9	4	PD: her mother's death was due to someone's bullying			9	
	6	85	F	✓	28	22	8	PD, AH: her sister-in-law living in neighborhood intruded into her house and steals things; the intruders made noises	✓	✓	2,4	1
	7	86	M	✓	26	9	5	PD, AH: Incorporeal and unknown male and female living upstairs observed and threatened him	✓	✓	1,2,4,9	1,2

Table 4. Continued

No.	Age	Gender	Living alone	MMSE	WMS-R LM I	WMS-R LM II	Main psychotic symptoms	Partition delusions	Delusions of theft	NPI-Delusions	NPI-Hallucinations
8	90	F		25	1	0	PD: money was stolen by welfare facility staff		✓	2	
9	91	F		27	12	3	PD: daughter-in-law withdrew her cash and had an affair; unknown person intruded into her house and used things	✓	✓	1,2,4	

*Presents case 2 and ** presents case 1 in the previous report (Satake *et al.*, 2021). Checkmark (✓) indicates the presence of symptoms. The numbers in the "NPI-Delusions" and "NPI-Hallucinations" rows correspond to the delusions and hallucinations sub-questions in the NPI. Abbreviations: VLOSLP, very late-onset schizophrenia-like psychosis; VLOSLP+AD, VLOSLP showing positive results for AD biomarkers; VLOSLP−AD, VLOSLP showing negative results for AD biomarkers; F, Female; M, Male; MMSE, Mini-Mental State Examination; WMS-R, Wechsler Memory Scale-Revised; LM, Logical Memory; PD, Persecutory Delusions; VH, Visual Hallucinations; AH, Auditory Hallucinations; GD, Grandiose Delusions.

showed mild episodic memory impairment. De Simone *et al.* reported that greater attenuation from immediate recall to delayed recall in a story recall test predicted the progression from aMCI to AD dementia (De Simone *et al.*, 2017). The pattern of WMS-R LM in VLOSLP+AD participants agrees with the findings in aMCI destined to convert to AD dementia. It has also been reported that even in people with normal cognitive function, episodic memory is worse in those with AD-related pathology than in those without (Malek-Ahmadi *et al.*, 2016). Considering these previous reports, the WMS-R results in this study indicated that VLOSLP+AD participants had episodic memory impairment attributed to AD pathology.

The difference in age of onset between the VLOSLP+AD and −AD groups is that the +AD group had a shorter time between onset and the initial visit. VLOSLP patients generally have few negative symptoms and maintain cognitive function, which delays their consultation at the clinics (Roth and Kay, 1998). The pathophysiology of AD may hasten their consultation at a memory clinic through subtle functional changes related to neurodegeneration. Our findings are consistent with the results of a previous study that revealed the dementia hazard ratio associated with VLOSLP was the highest in the first year after VLOSLP diagnosis, although rates of dementia remained higher in the VLOSLP group than in the control group for up to 20 years of follow-up (Stafford *et al.*, 2021).

In the psychiatric symptoms assessed by NPI-plus, the presence of disinhibition, irritability, and nighttime behaviors was the most frequent in VLOSLP−AD among the three groups. Although there is insufficient literature about psychiatric symptoms other than psychosis and negative symptoms in VLOSLP, emotional dysregulation, impulsivity, and sleep disturbances have often been emphasized in the schizophrenia spectrum disorders (Cohrs, 2008; Freeman *et al.*, 2009; Hoptman, 2015; Joseph and Siddiqui, 2022). Irritability, disinhibition, and sleep disturbances are also frequent in MCI and neurodegenerative diseases (Apostolova *et al.*, 2014; Guarnieri *et al.*, 2012). Among those diseases, irritability was reported to be a frequent initial symptom in argyrophilic grain disease (Togo *et al.*, 2005), and sleep disturbances were more common in MCI with Lewy bodies than in MCI due to AD (Donaghy *et al.*, 2020). The higher prevalence of these symptoms in VLOSLP−AD may be explained as psychiatric symptoms of psychotic disorders and potential comorbidities of neurodegenerative diseases other than AD.

The VLOSLP+AD and −AD groups did not differ significantly on the sub-questions of delusions and hallucinations in the NPI-plus; persecutory

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delusions were frequent in both VLOSLP groups, consistent with previous reports (Kay and Roth, 1961). Delusions of theft were more frequent in VLOSLP+AD than in VLOSLP−AD, although the difference was not significant. On the other hand, as shown in Table 4, all seven patients in both groups with delusion of theft scored lower than 10 on the WMS-R LM II, and all five patients in both groups with scores higher than 10 in the task did not show delusions related to theft. Although AD frequently accompanies delusions of theft (Ropacki and Jeste, 2005), patients with probable AD dementia and delusions of theft show more severe episodic memory impairment than those without similar delusions (Na *et al.*, 2018). Therefore, our results indicate that delusions of theft in VLOSLP may be associated with episodic memory impairment with or without AD pathology. They also suggest that delusions of theft may tend to be more prevalent in VLOSLP patients with AD pathology because of worse memory impairment than in those without AD pathology.

Regarding misidentification delusions, one patient with VLOSLP−AD and three patients with VLOSLP+AD were evaluated as having phantom border symptom in the NPI-plus. Fisher *et al.* reported those delusions to be more dementia-related delusions than persecutory delusions (Fischer *et al.*, 2020). However, all of the phantom border delusions scored in NPI in the present study were associated with partition delusion that "someone intruded into the house," and these delusions were considered to be mainly persecutory delusions rather than misidentification delusions, and were not necessarily of a quality that would lead to suspicion of dementia. The proportions of the participants harboring persecutory delusions and partition delusions were 87.5% and 50% in VLOSLP−AD, and 88.9% and 55.6% in VLOSLP+AD, respectively. The overall similarity in the content of psychotic symptoms between VLOSLP−AD and +AD made it difficult to predict the AD biomarker results on their own. However, given the small sample size and the lack of uniformity in the assessment of psychosis, it is not possible to determine from these results alone whether AD biomarker-positive and AD biomarker-negative VLOSLP psychosis are truly similar. Future evaluation of semi-structured psychosis with a larger sample may reveal features that may be useful in differentiating between the two.

The present study proposes that AD pathology may be directly involved in the emergence of psychosis in VLOSLP with AD pathology. However, we think it is challenging to attribute the psychosis solely to AD pathology. Recent pathological studies have shown that in people older than 80 years, individuals with AD pathology often have other neurodegenerative changes and vascular diseases (Beach and Malek-Ahmadi, 2021; Yu *et al.*, 2020); even in older VLOSLP patients with AD pathology, the influence of these age-related co-pathologies may not be ignored. We previously reported that there is a certain number of VLOSLP patients with positive results for indicative biomarkers of DLB (Kanemoto *et al.*, 2022). Therefore, VLOSLP+AD patients in this study also might have Lewy body disease pathology. However, the involvement of a concurrent AD pathology in the pathogenesis of VLOSLP should be considered. With regard to pharmacotherapy, the usefulness of antipsychotic drugs for VLOSLP was already demonstrated (Howard *et al.*, 2018; Scott *et al.*, 2011). However, such uses of antipsychotics could be tailored to the specific neuropathology the patient has. In the future, new drugs, especially disease-modifying ones, may be candidates for the treatment of VLOSLP with specific neuropathologies. Further clarification of the link between neuropathology and VLOSLP would be helpful for the treatment of VLOSLP.

Limitation

Apart from the small number of participants, there are several limitations. First, selection bias in this study cannot be overlooked. Although we attempted to generalize the results of this study to general VLOSLP, two substantial biases existed: the implementation of testing for AD biomarkers and the fact that participants visited our neuropsychology clinic. AD biomarker testing was performed for research and clinical necessity. AD biomarkers are of greater value for assessing neuropathology in younger patients (Ossenkoppele *et al.*, 2015). Therefore, we may have tended to perform AD biomarker testing in relatively young MCI patients without psychosis, with a view to drug trials and future clinical use of disease-modifying drugs. In contrast, our use of AD biomarker testing for VLOSLP patients was not subject to age of onset bias. The differences in the selection criteria for testing might have led having older participants in the VLOSLP groups than in the aMCI−P+AD group. With regard to patient visit bias, patients who visited our neuropsychology clinic likely presented with more cognitive decline than the general VLOSLP population, as VLOSLP patients often do not voluntarily visit memory or psychiatric clinics owing to preserved function and lack of insight (Lam *et al.*, 2016). However, many VLOSLP patients in this study were referred from community psychiatric clinics and outreach teams organized by psychiatrists for the differential diagnosis of mild dementia

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with psychosis and VLOSLP. Second, the AD biomarkers we used may not reflect pathology perfectly. However, ^{18}F-Florbetapir PET is a reliable tracer for AD and is predictive even of early-stage disease (Clark *et al.*, 2011; Palmqvist *et al.*, 2015); CSF p-tau is also reliable in detecting early-stage AD (Mattsson *et al.*, 2017). Furthermore, the CSF t-tau, Aβ1-42 and Aβ1-42/1-40 scores of participants in VLOSLP and aMCI groups were compatible with the presumed pathologies (Blennow and Zetterberg, 2018; Hansson *et al.*, 2019; Mattsson *et al.*, 2009). Third, we had several statistical limitations. Although many statistical comparisons were conducted, we did not conduct statistical correction for multiple comparisons. We focused on avoiding the risk of a β-error rather than α-error in this small sample size exploratory study. Note that when the Benjamini-Hochberg procedure was performed to evaluate the false discovery rate in each table, only WMS-R LM1, 2 and the weighted raw score sums of A/C were considered significant, and these differences were considered relatively robust. In addition, due to the small sample size, it was not possible to perform a multivariate analysis. Fourth, as mentioned previously in the discussion, we did not control confounders for psychosis (e.g. physical disorders, financial backgrounds, recent impactful events, sensory impairments, and medications). They were difficult to regulate due to lack of data. Finally, some VLOSLP patients had cognitive impairment that could be considered MCI. Our classification for VLOSLP could have included a group with MCI and psychosis. However, VLOSLP patients performed better on the episodic memory test than aMCI−P+AD patients, while they performed worse on the attention test. This suggests that while a small percentage of the VLOSLP patients in this study met the criteria for MCI, they remained distinct from the MCI patients. Future longitudinal studies with a larger sample size and more detailed assessment of psychotic symptoms that address many of the limitations of this study are needed.

Conclusions

Our findings suggest that VLOSLP is a prodromal feature of dementia or that VLOSLP independently confers risk for later dementia via other mechanisms (Stafford *et al.*, 2021). A number of VLOSLP patients had AD pathology in our retrospective cohort. The VLOSLP patients who tested positive for AD biomarkers were older at onset than those who tested negative. Episodic memory impairment in AD biomarker-positive VLOSLP was intermediate between aMCI due to AD without psychosis and AD biomarker-negative VLOSLP. The prevalence of psychiatric symptoms such as disinhibition, irritability, and nighttime behaviors differed between VLOSLP with positive and negative AD biomarkers and aMCI due to AD without psychosis. These clinical differences may be helpful for estimating the pathology of VLOSLP.

Conflict of interest

None.

Description of authors' roles

YS and HK designed the study. YS wrote the initial draft of the manuscript. HK, KMa, ES, KMo, TM, KY, and MI contributed to the interpretation of data and assisted in the preparation of the manuscript. DT, TS, FK, SS, SG, and TW contributed to data collection and interpretation and reviewed the article. All authors approved the article and agreed to be accountable for all aspects of the work.

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References

Almeida, O. P., Howard, R. J., Levy, R., David, A. S., Morris, R. G., Sahakian, B. J. (1995). Clinical and cognitive diversity of psychotic states arising in late life (late paraphrenia). *Psychological Medicine*, 25, 699–714. https://doi.org/10.1017/S0033291700034954.

American Psychiatric Association (2022). *Diagnostic and statistical manual of mental disorders*. 5th ed., text rev edition. *Available at* https://doi.org/10.1176/appi.books.9780890425787.

Apostolova, L. G. *et al.* (2014). Risk factors for behavioral abnormalities in mild cognitive impairment and mild Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, 37, 315–326. https://doi.org/10.1159/000351009.

https://doi.org/10.1017/S1041610222001132 Published online by Cambridge University Press

Beach, T. G. and Malek-Ahmadi, M. (2021). Alzheimer's disease neuropathological comorbidities are common in the younger-old. *Journal of Alzheimer's Disease*, 79, 389–400. https://doi.org/10.3233/JAD-201213.

Blennow, K. and Zetterberg, H. (2018). Biomarkers for Alzheimer's disease: current status and prospects for the future. *Journal of Internal Medicine*, 284, 643–663. https://doi.org/10.1111/joim.12816.

Brodaty, H., Sachdev, P., Koschera, A., Monk, D., Cullen, B. (2003). Long-term outcome of late-onset schizophrenia: 5-year follow-up study. *British Journal of Psychiatry*, 183, 213–219, https://doi.org/10.1192/bjp.183.3.213.

Casanova, M., Stevens, J., Brown, R., Royston, C., Bruton, C. (2002). Disentangling the pathology of schizophrenia and paraphrenia. *Acta Neuropathologica*, 103, 313–320. https://doi.org/10.1007/s00401-001-0468-6.

Clark, C. M. *et al.* (2011). Use of florbetapir-PET for imaging β-amyloid pathology. *JAMA*, 305, 275–283. https://doi.org/10.1001/jama.2010.2008.

Cohrs, S. (2008). Sleep disturbances in patients with schizophrenia: impact and effect of antipsychotics. *CNS Drugs*, 22, 939–962. https://doi.org/10.2165/00023210-200822110-00004.

Creese, B. and Ismail, Z. (2022). Mild behavioral impairment: measurement and clinical correlates of a novel marker of preclinical Alzheimer's disease. *Alzheimer's Research and Therapy*, 14, 1–5. https://doi.org/10.1186/s13195-021-00949-7.

Cummings, J. L. (1997). The neuropsychiatric inventory: assessing psychopathology in dementia patients. *Neurology*, 48, 10S–16S. https://doi.org/10.1212/wnl.48.5_suppl_6.10s.

D'Antonio, F. *et al.* (2019). Psychosis of Alzheimer's disease: neuropsychological and neuroimaging longitudinal study. *International Journal of Geriatric Psychiatry*, 34, 1689–1697. https://doi.org/10.1002/gps.5183.

De Simone, M. S. *et al.* (2017). Different deficit patterns on word lists and short stories predict conversion to Alzheimer's disease in patients with amnestic mild cognitive impairment. *Journal of Neurology*, 264, 2258–2267. https://doi.org/10.1007/s00415-017-8623-8.

Donaghy, P. C. *et al.* (2020). Mild cognitive impairment with Lewy bodies: neuropsychiatric supportive symptoms and cognitive profile. *Psychological Medicine*, 52, 1147–1155. https://doi.org/10.1017/S0033291720002901.

Fischer, C. E. *et al.* (2020). Revisiting criteria for psychosis in alzheimer's disease and related dementias: toward better phenotypic classification and biomarker research. *Journal of Alzheimer's Disease*, 73, 1143–1156. https://doi.org/10.3233/JAD-190828.

Freeman, D., Pugh, K., Vorontsova, N., Southgate, L. (2009). Insomnia and paranoia. *Schizophrenia Research*, 108, 280–284. https://doi.org/10.1016/j.schres.2008.12.001.

Guarnieri, B. *et al.* (2012). Prevalence of sleep disturbances in mild cognitive impairment and dementing disorders: a multicenter Italian clinical cross-sectional study on 431 patients. *Dementia and Geriatric Cognitive Disorders*, 33, 50–58. https://doi.org/10.1159/000335363.

Hansson, O. *et al.* (2018). CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimer's and Dementia*, 14, 1470–1481. https://doi.org/10.1016/j.jalz.2018.01.010.

Hansson, O., Lehmann, S., Otto, M., Zetterberg, H. and Lewczuk, P. (2019). Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's disease. *Alzheimer's Research & Therapy*, 11, 1–15. https://doi.org/10.1186/s13195-019-0485-0.

Harris, B. S., Kotsopoulos, E. J. and Yamin, S. (2014). Phenotypic cognitive impairment in late-onset delusional disorder. *International Psychogeriatrics*, 26, 965–975. https://doi.org/10.1017/S1041610214000106.

Hoptman, M. J. (2015). Impulsivity and aggression in schizophrenia: a neural circuitry perspective with implications for treatment. *CNS Spectrums*, 20, 280–286. https://doi.org/10.1017/S1092852915000206.

Howard, R., Castle, D., O'Brien, J., Almeida, O., Levy, R. (1992). Permeable walls, floors, ceilings, and doors. Partition delusions in late paraphrenia. *International Journal of Geriatric Psychiatry*, 7, 719–724. https://doi.org/10.1002/gps.930071006.

Howard, R. *et al.* (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. *The American Journal of Psychiatry*, 157, 172–178. https://doi.org/10.1176/appi.ajp.157.2.172.

Howard, R. *et al.* (2018). Antipsychotic treatment of very late-onset schizophrenia-like psychosis (ATLAS): a randomised, controlled, double-blind trial. *The Lancet Psychiatry*, 5, 553–563. https://doi.org/10.1016/S2215-0366(18)30141-X.

Jeste, D. V. *et al.* (1992). Cognitive deficits of patients with Alzheimer's disease with and without delusions. *The American Journal of Psychiatry*, 149, 184–189. https://doi.org/10.1176/ajp.149.2.184.

Joseph, S. M. and Siddiqui, W. (2022). Delusional disorder. [Updated 2022 Mar 30], StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK539855/.

Kanemoto, H. *et al.* (2022). Characteristics of very late-onset schizophrenia-like psychosis as prodromal dementia with Lewy bodies: a cross-sectional study. *Alzheimer's Research & Therapy*, 14, 137. https://doi.org/10.1186/s13195-022-01080-x.

Kawano, N., Awata, S., Ijuin, M., Iwamoto, K., Ozaki, N. (2013). Necessity of normative data on the japanese version of the Wechsler Memory Scale-Revised Logical Memory subtest for old-old people. *Geriatrics and Gerontology International*, 13, 726–730. https://doi.org/10.1111/ggi.12007.

Kay, D. W. K. and Roth, M. (1961). Environmental and hereditary factors in the schizophrenias of old age ("Late Paraphrenia") and their bearing on the general problem of causation in schizophrenia. *Journal of Mental Science*, 107, 649–686. https://doi.org/10.1192/bjp.107.449.649.

Kazui, H. *et al.* (2017). Neural basis of apathy in patients with amnestic mild cognitive impairment. *Journal of Alzheimer's Disease*, 55, 1403–1416. https://doi.org/10.3233/JAD-160223.

https://doi.org/10.1017/S1041610222001132 Published online by Cambridge University Press

Kørner, A., Lopez, A. G., Lauritzen, L., Andersen, P. K., Kessing, L. V. (2009). Late and very-late first-contact schizophrenia and the risk of dementia - a nationwide register-based study. *International Journal of Geriatric Psychiatry*, 24, 61–67. https://doi.org/10.1002/gps.2075.

Lam, C. C. S. F., Reeves, S. J., Stewart, R., Howard, R. (2016). Service and treatment engagement of people with very late-onset schizophrenia-like psychosis. *BJPsych Bulletin*, 40, 185–186. https://doi.org/10.1192/pb.bp.115.051599.

Lawton, M. P. and Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*, 9, 179–186. https://doi.org/10.1093/geront/9.3_Part_1.179.

Malek-Ahmadi, M., Perez, S. E., Chen, K., Mufson, E. J. (2016). Neuritic and diffuse plaque associations with memory in non-cognitively impaired elderly. *Journal of Alzheimer's Disease*, 53, 1641–1652. https://doi.org/10.3233/JAD-160365.

Mattsson, N. *et al.* (2009). CSF biomarkers and incipient alzheimer disease. *JAMA*, 302, 385–393. https://doi.org/10.1001/jama.2009.1064.

Mattsson, N. *et al.* (2017). 18 F-AV-1451 and CSF T-tau and P-tau as biomarkers in Alzheimer's disease. *EMBO Molecular Medicine*, 9, 1212–1223. https://doi.org/10.15252/emmm.201707809.

Mori, E., Ikeda, M. and Kosaka, K. (2012). Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. *Annals of Neurology*, 72, 41–52. https://doi.org/10.1002/ana.23557.

Morihara, T. *et al.* (2014). Transcriptome analysis of distinct mouse strains reveals kinesin light chain-1 splicing as an amyloid-β accumulation modifier. *Proceedings of the National Academy of Sciences of the United States of America*, 111, 2638–2643. https://doi.org/10.1073/pnas.1307345111.

Na, H-R., Kang, D. W., Woo, Y-S., Bahk, W-M., Lee, C-U., Lim, H. K. (2018). Relationship between delusion of theft and cognitive functions in patients with mild Alzheimer's disease. *Psychiatry Investigation*, 15, 413–416. https://doi.org/10.30773/pi.2017.09.20.

Nagao, S. *et al.* (2014). Argyrophilic grain disease as a neurodegenerative substrate in late-onset schizophrenia and delusional disorders. *European Archives of Psychiatry and Clinical Neuroscience*, 264, 317–331. https://doi.org/10.1007/s00406-013-0472-6.

Naguib, M. and Levy, R. (1987). Late paraphrenia: neuropsychological impairment and structural brain abnormalities on computed tomography. *International Journal of Geriatric Psychiatry*, 2, 83–90. https://doi.org/10.1002/gps.930020205.

Nelson, P. T. *et al.* (2011). Hippocampal sclerosis in advanced age: clinical and pathological features. *Brain*, 134, 1506–1518. https://doi.org/10.1093/brain/awr053.

Ossenkoppele, R. *et al.* (2015). Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA*, 313, 1939–1949. https://doi.org/10.1001/jama.2015.4669.

Palmqvist, S. *et al.* (2015). Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer's disease. *Neurology*, 85, 1240–1249. https://doi.org/10.1212/WNL.0000000000001991.

Ropacki, S. A. and Jeste, D. V. (2005). Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *American Journal of Psychiatry*, 162, 2022–2030. https://doi.org/10.1176/appi.ajp.162.11.2022.

Roth, M. (1955). The natural history of mental disorder in old age. *Journal of Mental Science*, 101, 281–301. https://doi.org/10.1192/bjp.101.423.281.

Roth, M. and Kay, D. W. K. (1998). Late paraphrenia: a variant of schizophrenia manifest in late life or an organic clinical syndrome? A review of recent evidence. *International Journal of Geriatric Psychiatry*, 13, 775–784. https://doi.org/10.1002/(SICI)1099-1166(1998110)13:.

Satake, Y. *et al.* (2021). Case report: usefulness of biomarkers for Alzheimer's disease in two cases with very-late-onset schizophrenia-like psychosis. *Frontiers in Psychiatry*, 12. https://doi.org/10.3389/fpsyt.2021.742659.

Scott, J., Greenwald, B. S., Kramer, E., Shuwall, M. (2011). Atypical (second generation) antipsychotic treatment response in very late-onset schizophrenia-like psychosis. *International Psychogeriatrics*, 23, 742–748. https://doi.org/10.1017/S1041610210002188.

Stafford, J., Dykxhoorn, J., Sommerlad, A., Dalman, C., Kirkbride, J. B., Howard, R. (2021). Association between risk of dementia and very late-onset schizophrenia-like psychosis: a Swedish population-based cohort study. *Psychological Medicine*, 1–9. https://doi.org/10.1017/S0033291721002099.

Togo, T. *et al.* (2005). Clinical features of argyrophilic grain disease: a retrospective survey of cases with neuropsychiatric symptoms. *American Journal of Geriatric Psychiatry*, 13, 1083–1091. https://doi.org/10.1097/00019442-200512000-00008.

Van Assche, L. *et al.* (2019). The neuropsychological profile and phenomenology of late-onset psychosis: a cross-sectional study on the differential diagnosis of very-late-onset schizophrenia-like psychosis, dementia with Lewy bodies, and Alzheimer's type dementia with psychosis. *Archives of Clinical Neuropsychology*, 34, 183–199. https://doi.org/10.1093/arclin/acy034.

Wolfsgruber, S. *et al.* (2019). Prevalence of abnormal Alzheimer's disease biomarkers in patients with subjective cognitive decline: cross-sectional comparison of three European memory clinic samples. *Alzheimer's Research & Therapy. Alzheimer's Research & Therapy*, 11, 1–11. https://doi.org/10.1186/s13195-018-0463-y.

World Health Organization. (2019). International statistical classification of diseases and, 11th revision, Available at: https://icd.who.int/.

Yu, L., Boyle, P. A., Dawe, R. J., Bennett, D. A., Arfanakis, K., Schneider, J. A. (2020). Contribution of TDP and hippocampal sclerosis to hippocampal volume loss in older-old persons. *Neurology*, 94, e142–e152. https://doi.org/10.1212/WNL.0000000000008679.

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