

Etiology of Dementia in Thai Patients

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Keywords

Etiology · Dementia · Thai · Asian

Abstract

Introduction: Molecular imaging has been developed and validated in Thai patients, comprising a portion of patients in the dementia registry. This should provide a more accurate diagnosis of the etiology of dementia, which was the focus of this study. **Methods:** This was a multicenter dementia study. The baseline characteristics, main presenting symptoms, and results of investigations and cognitive tests of the patients were electronically collected in the registry. Functional imaging and/or molecular imaging were performed in patients with an equivocal diagnosis of the causes of dementia, especially in atypical dementia or young onset

dementia (YOD). **Results:** There were 454 patients in the study. The mean age of the patients was 78 years, with 60% female. Functional imaging and/or molecular imaging were performed in 57 patients (57/454 patients, 13%). The most common cause of dementia was Alzheimer's disease (AD; 50%), followed by vascular dementia (VAD; 24%), dementia with Lewy bodies (6%), Parkinson's disease dementia (6%), frontotemporal dementia (FTD; 2.6%), progressive supranuclear palsy (2%), multiple system atrophy (0.8%), and corticobasal syndrome (0.4%). YOD accounted for 17% (77/454 patients), with a mean age of 58 years. The causes of YOD were early onset amnesic AD (44%), VAD (16%), behavioral variant FTD (8%), posterior cortical atrophy (6.5%), and logopenic variant primary progressive aphasia (5.2%). **Conclusion:** AD was the most common cause of dementia in Thai patients and the distribution of other types of dementia and

main presenting symptoms were similar to previous reports in Western patients; however, the proportion of YOD was higher.

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Introduction

The increased aging population is leading to a rising number of dementia patients. The Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2016 assessed the global prevalence, mortality, and overall burden of dementia in 195 countries from 1990 to 2016, revealing an increase in individuals who lived with dementia from 20.2 million in 1990 to 43.8 million in 2016. Dementia is the fifth leading cause of death, and also negatively affects families and healthcare systems globally [1]. Thailand has been classed as an aging society since 2002, when the proportion of elderly reached more than 10% of the population [2]. The prevalence of dementia was 2.35–3.1% [2, 3].

The most common cause of dementia is Alzheimer's disease (AD; 50–75%), followed by vascular dementia (VAD; 20%), dementia with Lewy bodies (DLB; 5%), and frontotemporal lobar dementia (FTLD; 5%); however, most data were from the Western countries [4, 5]. Following advances in biomarker and genetic marker development, diagnosis of the etiology of dementia can be made with more confidence. Moreover, in order to discover interventions that prevent, delay, or modify the course of the disease, a preclinical diagnosis is needed. Thus, biomarker criteria are included in the diagnosis criteria of dementia, especially in the research framework. Whether adding biomarker information would change the proportion of causes of dementia is still in doubt.

A study in Thailand reported the following causes of dementia in 207 patients: AD 55%, VAD 20%, mixed dementia 14%, Parkinson's disease dementia (PDD) 10%, and frontotemporal dementia (FTD) 1% [6]. However, it was conducted in a single center without any neuroimaging biomarkers. The Collaborative Aging and Dementia Research Society Thailand (CART) is a dementia research working group comprised of experts in dementia from 4 university hospitals and 2 large tertiary care hospitals. Molecular imaging has been developed and validated in Thai patients and was performed in a portion of patients in the CART registry. This should provide a more accurate diagnosis of the etiology of dementia. The purpose of this study was to study the causes of dementia in Thai patients.

Materials and Methods

This was a cross-sectional, multicenter CART study carried out in 2018–2019. The baseline characteristics, main presenting symptoms, and results of investigations and cognitive function tests of the patients were electronically collected in the CART dementia registry using a standard consensus case report form.

Dementia was defined as progressive cognitive decline leading to interference with the activities of daily living. Young onset dementia (YOD) was classified if the onset of symptoms began at a younger than 65 years. The Thai Mental State Examination (TMSE) and Montreal Cognitive Assessment – Thai version (MOCA) were used to evaluate global cognitive function, with the cutoff point of 24/23 of TMSE and 25/24 of MOCA to define normal cognition/cognitive impairment. Blood chemistry and at least 1 modality of neuroimaging (CT or MRI dementia protocol of the brain) were performed in all patients to exclude medical and surgical treatable causes. Whole brain ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG PET), ¹¹C-Pittsburgh compound B positron emission (PiB PET), ¹⁸F-THK-5351 positron emission (Tau PET) and/or technetium-99m TRODAT-1 single-photon emission CT (TRODAT SPECT) were performed in patients with an equivocal diagnosis of the causes of dementia or to confirm the diagnosis, especially in atypical dementia or YOD. The causes of dementia were diagnosed by trained neurologists, psychiatrists, and geriatrists using standard criteria [7–15].

Descriptive analysis was conducted using the mean ± SD for continuous variables and frequencies/percentages for categorical variables. Baseline characteristics, TMSE, MOCA scores, and the main presenting symptoms were compared between patients with amnesic AD dementia and VAD, DLB, PDD, or FTD (including the behavioral variant of FTD, nonfluent agrammatic variant primary progressive aphasia [PPA], and semantic variant PPA). Differences between groups were assessed by the χ^2 test for categorical variables and the independent-samples *t* test for continuous variables. The study was approved by the Human Research Ethics Committee of Thammasat University No. 1 (Faculty of Medicine), project No. MTU-EC-IM-0-213/60. Consent was informed and signed by the rightful relatives, and the Ethics Committee approved this consent procedure.

Results

The study comprised a total of 454 patients. The baseline characteristics of the patients are presented in Tables 1 and 2. The mean age of the patients was 78 years, and 60% were female. The mean duration of education was 8.5 years. The mean TMSE and MOCA scores were 17 and 14. Vascular risk factors were common in the patients. The most common cause of dementia was AD (50%), followed by VAD (24%), DLB (6%), PDD (6%), FTD (2.6%), progressive supranuclear palsy (PSP; 2%), multiple system atrophy (0.8%), and corticobasal syndrome (CBS; 0.4%).

Table 1. Baseline characteristics of the study patients ($n = 454$)

Age at diagnosis, years	77.6±8.6
Sex	
Male	181 (40)
Female	273 (60)
Education, years	8.5±5.4
TMSE score	17.4±6.2
MOCA score	13.8±5.5
Hypertension	326 (72)
Diabetes mellitus	131 (29)
Hyperlipidemia	372 (82)
Old ischemic stroke	87 (19)
Coronary artery disease	27 (6)
Smoking	5 (1)
Atrial fibrillation	17 (4)
Family history of dementia	140 (31)
<i>Diagnosis</i>	
AD and variant	
Late onset amnesic AD	176 (39)
Early onset amnesic AD	35 (8)
LV PPA	9 (2)
PCA	5 (1)
VAD	111 (24)
Movement disorder-related dementia	
DLB	29 (6)
PDD	28 (6)
PSP	10 (2)
MSA	4 (0.8)
CBS	2 (0.4)
Frontotemporal dementia and variant	
Behavioral variant FTD	11 (2)
Nonfluent agrammatic variant PPA	2 (0.4)
Semantic variant PPA	1 (0.2)
Other causes of dementia	
Mixed dementia	16 (4)
Suspected non-AD pathology	2 (0.4)
Unidentified causes	13 (3)

Data are presented as the mean ± SD or n (%). AD, Alzheimer's disease; VAD, vascular dementia; LV, logopenic variant; PPA, primary progressive aphasia; PCA, posterior cortical atrophy; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; CBS, corticobasal syndrome; FTD, frontotemporal dementia.

YOD accounted for 17% (77/454 patients), and the mean age of onset was 58 years. Forty-nine percent of patients were female. The mean MOCA score was 14.6. The main chief complaints were memory impairment (51%), behavioral problems (15%), motor problems (13%), language problems (7%), executive impairment (5%), neuropsychiatric symptoms (4%), and visuospatial impairment (4%). The causes in this subgroup of patients were early onset amnesic AD (34/77 patients, 44%), VAD (12 pa-

tients, 16%), behavioral variant FTD (6 patients, 8%), posterior cortical atrophy (PCA; 5 patients, 6.5%), logopenic variant (LV) PPA; 4 patients, 5.2%), PSP (3 patients, 3.9%), multiple system atrophy (2 patients, 2.6%), PDD (2 patients, 2.6%), DLB (2 patients, 2.6%), semantic variant PPA (1 patient, 1.3%), familial prion disease (1 patient, 1.3%), and unknown causes (5 patient, 6.5%).

Functional imaging and/or molecular imaging were performed in 57 patients (57/454 patients, 13%), which consisted of FDG PET in 52 patients, PiB PET in 46 patients, Tau PET in 31 patients, and TRODAT SPECT in 12 patients. The diagnoses of these patients were late onset AD (11 patients), early onset AD (9 patients), behavioral variant FTD (7 patients), PSP (6 patients), DLB (5 patients), PCA (5 patients), LV PPA (3 patients), VAD (3 patients), multiple system atrophy (2 patients), suspected non-AD pathology (2 patients), nonfluent agrammatic variant PPA (1 patient), PDD (1 patient), CBS (1 patient), and familial prion disease (1 patient).

Patients with VAD, as compared to those with AD, were older (75 vs. 72 years, $p = 0.012$), a lower proportion were female (54 vs. 67%, p value = 0.023), and a higher proportion had hyperlipidemia (96 vs. 77%, $p < 0.001$; Table 3). Patients with DLB had higher mean TMSE scores as compared to AD (21 vs. 17, $p = 0.009$). Patients with PDD were older (76 vs. 72 years, $p = 0.027$), and had higher TMSE scores (20 vs. 17, $p = 0.039$). Patients with FTD were younger (mean age 64 vs. 72 years, $p = 0.017$) as compared to AD subjects.

The first main presentation symptoms were different among types of dementia (Table 2, 3). Most AD patients presented with memory problems (82%). Sixty-four (58%) VAD patients presented with memory problems and 22% with motor symptoms. DLB patients presented with memory complaints (48%), neuropsychiatric (17%), and motor symptoms (17%), while more than half of PDD patients presented with motor symptoms (57%) followed by memory problems (18%). FTD patients presented with behavioral change (31%) and neuropsychiatric (23%) and language problems (23%).

Discussion

The prevalence of dementia increases with age. Dementia UK 2014 showed that the prevalence of dementia in the age groups of 75–79, 80–84, 85–89, and 90–94 years were 6, 11, 18, and 30%, respectively. The majority of dementia (> 97%) cases presented as late onset dementia [5]. Our study showed that the mean age of patients at the

Table 2. Baseline characteristics of dementia classified by etiology

Diagnosis (<i>n</i>)	Age at onset, years	Female, %	Education, years	TMSE score	Main chief complaint (%)
Late onset AD (176)	75 (66–97)	67	8±5	18±6	Memory impairment (80) Neuropsychiatric problems (10)
Early onset AD (35)	58 (45–65)	66	10±5	13±6	Memory impairment (91)
LV PPA (9)	66 (56–78)	50	10±5	10±7	Language problems (40) Memory impairment (25)
PCA (5)	58 (56–61)	60	8±5	17±5	Visuospatial problems (60) Memory impairment (40)
VAD (111)	75 (43–92)	55	7±5	16±5	Memory impairment (58) Motor problems (22)
DLB (29)	75 (55–91)	52	10±6	20±4	Memory impairment (48) Neuropsychiatric problems (17) Motor problems (17)
PDD (28)	76 (59–85)	57	8±6	20±5	Motor problems (57) Memory impairment (18) Behavioral problems (11)
PSP (10)	69 (58–79)	46	9±5	19±6	Motor problems (50) Executive problems (20) Behavioral problems (20)
MSA (4)	64 (48–75)	25	8±6	19±3	Motor problems (50) Executive problems (25) Language problems (25)
CBS (2)	77 (74–79)	50	11±8	15±2	Motor problems (100)
Behavioral variant FTD (11)	63 (40–79)	42	10±6	22±5	Behavioral problems (34) Neuropsychiatric problems (24)
PPA (3)	69 (61–80)	67	10±6	14±8	Language problems (67)

Data are presented as the mean (range), mean ± SD, or as indicated. AD, Alzheimer's disease; VAD, vascular dementia; LV, logopenic variant; PPA, primary progressive aphasia; PCA, posterior cortical atrophy; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; CBS, corticobasal syndrome; FTD, frontotemporal dementia.

onset of dementia was 78 years, with 60% female, and most presenting with moderate dementia (mean TMSE of 17 and MOCA score of 14). The findings were consistent with a previous study in Thai dementia patients [6].

There are many causes of dementia. AD is the most common cause, although the reported prevalence varies [4–6]. Cunningham et al. [5] reviewed the pathophysiological processes of dementia and found that AD was the most common cause (50–75%), followed by VAD (20%), DLB (5%), and FTLD (5%). A systemic review and meta-

analysis showed that the incidence of DLB was 3.8% of new dementia diagnoses, with a prevalence of 4.2% of dementia cases in community settings and 7.5% in secondary care settings [16]. Our registry showed that AD was the most common cause of dementia (50%), VAD was the second most common cause (24%), followed by DLB (6%), PDD (6%), FTD (3%), and PSP (2%), which was similar to previous studies in Western patients. Some studies combined tau-associated neurodegenerative diseases, CBS, and PSP with FTD because they shared clini-

Table 3. Baseline characteristics and symptoms at presentation in common dementia

	AD (n = 211)	VAD (n = 111)	p value	DLB (n = 29)	p value	PDD (n = 28)	p value	FTD (n = 14)	p value
Age at diagnosis, years	72±8	75±8	0.012	75±8	0.102	76±6	0.027	64±10	0.017
Sex									
Male	69 (33)	51 (46)		14 (48)		12 (43)		7 (54)	
Female	142 (67)	60 (54)	0.023	15 (52)	0.106	16 (57)	0.302	6 (46)	0.125
Education, years	8.5±5.5	7.4±5.1	0.055	9.7±5.7	0.358	8.1±5.6	0.680	10±6	0.408
TMSE score	17.2±6.2	16.3±5.8	0.319	20.9±4	0.009	20.3±5.1	0.039	20.2±7.1	0.272
MOCA score	13.5±5.3	12.8±5.7	0.424	15.1±4.3	0.185	17.2±6.2	0.043	14.8±6	0.508
Hypertension	147 (70)	90 (81)	0.050	21 (72)	0.661	19 (68)	0.731	9 (69)	0.891
Diabetes mellitus	65 (31)	32 (29)	0.674	4 (14)	0.066	6 (21)	0.294	4 (31)	0.980
Hyperlipidemia	163 (77)	106 (96)	<0.001	26 (93)	0.066	16 (57)	0.016	10 (77)	0.928
Coronary artery disease	13 (6)	7 (6)	0.984	2 (7)	0.856	4 (14)	0.123	–	0.353
Smoking	2 (1)	1 (0.9)	0.957	–	0.602	1 (4)	0.247	–	0.722
Atrial fibrillation	11 (5)	5 (5)	0.760	1 (3)	0.698	–	0.213	–	0.395
First main presenting symptom									
Memory impairment	174 (82)	64 (58)		14 (48)		5 (18)		1 (8)	
Language problems	–	–		–		–		3 (23)	
Visuospatial impairment	3 (1)	3 (3)		–		1 (4)		–	
Executive impairment	3 (1)	4 (4)		3 (10)		–		1 (8)	
Behavioral symptoms	11 (5)	6 (5)		2 (6)		3 (11)		4 (31)	
Neuropsychiatric symptoms	17 (8)	10 (9)		5 (17)		3 (11)		3 (23)	
Motor symptoms	3 (1)	24 (22)	<0.001	5 (17)	<0.001	16 (57)	<0.001	1 (8)	<0.001

Data are presented as the mean ± SD or n (%). AD, Alzheimer's disease; VAD, vascular dementia; DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, frontotemporal dementia.

cal frontal lobe dysfunction and pathologic tauopathy. If combining FTD, PSP, and CBS, the prevalence of tauopathy-related dementia in our registry would reach 5%. The main presenting symptoms in patients with different causes of dementia were rather similar to previous reports.

Most AD patients presented with late onset amnesic AD (176/225, 78%). However, 16% of the patients (35/225) presented with early onset amnesic AD, 9 patients with LV PPA, and 5 patients with PCA. A previous review showed that early onset AD comprised approximately 5–6% of AD, which had a larger genetic predisposition, more aggressive course, and presented with less memory impairment and greater involvement of other cognitive domains [17]. However, our registry showed a higher proportion of early onset AD. This may be due to most of the registry data coming from university hospitals, where patients with atypical dementia were referred. Early onset AD in our registry was classified into amnesic (35 patients) and AD variants: LV PPA (4 patients), and PCA (5 patients). Early onset amnesic AD (mean age 58 years) presented with memory impairment (91%) and the chief complaint of patients with PCA (mean age 58 years) was

visuospatial problems (60%). PCA is a neurodegenerative syndrome that primarily affects the parietal and occipital lobes, and AD was the most common underlying pathology [18]. The majority of PCA patients have an early age at disease onset, typically presenting between the age of 50 and 65 years. The proportion of AD patients presenting with PCA was about 5% in a specialist cognitive clinic, and up to 13% in cases of early onset AD [19, 20]. All patients with PCA in our registry, for which the diagnosis was confirmed by functional and molecular imaging, had presented with a young onset of dementia, and accounted for 11% (5/44 patients) of early onset AD cases.

YOD made up 17% of our samples. Unlike late onset dementia, YOD is slightly more prevalent in men than women. The most common cause of YOD in our registry was AD, followed by VAD and FTD. Devineni and Onyike [21] showed that the prevalence of YOD ranges from 42.8 to 68.2 per 100,000, and the frequency of YOD in specialist clinics ranges from 7.3 to 44%, depending on regions, centers in the clinical focus, local practices, referral base, and sampling methods. AD was also the most common cause of YOD, while the second most common cause was FTD in some studies and VAD in others.

Functional and/or molecular imaging were performed in 57 patients (13%) in our study. The indication in most patients was atypical dementia. Functional and molecular imaging have been increasingly applied to diagnose dementia with more confidence and for early detection in mild or presymptomatic patients, especially in AD patients, where early treatment has been studied with the aim to intervene in the course of disease. Although the diagnostic criteria in other causes of dementia mainly uses clinical criteria, functional and/or molecular imaging were added as the supportive and/or indicative biomarkers. Previous studies showed that 10–30% of individuals clinically diagnosed with AD dementia by experts did not have an AD pathology at autopsy, and a similar portion had normal amyloid PET or amyloid beta 42 in their cerebrospinal fluid [22, 23]. Thus, adding the results of molecular imaging, AD pathology could be diagnosed before the autopsy. However, there were some limitations. Despite the high cost of the investigation, patients are not reimbursed for these procedures in routine clinical practice in many countries, including Thailand. Moreover, adding the functional and/or molecular imaging might not help the diagnosis in some cases of dementia, such as familial prion disease or suspected non-AD pathology.

This was a large dementia registry in Thailand, using recent criteria in diagnosis and integrating the results of functional and/or molecular imaging with the clinical criteria. However, the data mainly came from the 4 participating university hospitals and 2 tertiary care hospitals, and the prevalence of each type of dementia might be different in ordinary community hospitals. This was a cross-

sectional study, and some data were lacking or incomplete. Some patients did not have both TMSE and MOCA at diagnosis, but most had another test later on.

In conclusion, AD was the most common cause of dementia in Thai patients and the etiology of dementia and main presenting symptoms were similar to previous reports in Western patients. However, the proportion of dementia in the young was higher.

Statement of Ethics

The study was approved by the Human Research Ethics Committee of Thammasat University No. 1 (Faculty of Medicine), project No. MTU-EC-IM-0-213/60. Consent was informed and signed by the rightful relatives.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

P.A.D. and J.A.: conceptualization, methodology. P.A.D.: formal analysis, funding acquisition, writing. P.A.D., J.A., S.Po., K.J., P.Lo., M.P., L.C., C.C., and S.Pi.: investigation. All authors: review and editing.

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