The first case series of Chinese patients in Hong Kong with familial Alzheimer's disease compared with those with biomarker-confirmed sporadic late-onset Alzheimer's disease

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ABSTRACT

Introduction: Patients with familial Alzheimer's disease are being increasingly reported in Hong Kong. The objectives of this study were to report the clinical features of these patients, and to compare them with those with biomarker-confirmed sporadic late-onset Alzheimer's disease.

Methods: All symptomatic Chinese patients with familial Alzheimer's disease who attended Queen Mary Hospital, Memory Clinic between January 1998 and December 2016 were included. Information about clinical features, baseline Mini-Mental State Examination score, and presenting cognitive symptoms or atypical clinical features were collected. Their clinical features were compared with those of 12 patients with sporadic late-onset Alzheimer's disease with cerebrospinal fluid biomarker evidence of Alzheimer's disease and 14 patients with late-onset Alzheimer's disease and positive amyloid loading on Pittsburgh compound B imaging.

Results: There were three families with familial Alzheimer's disease among whom eight family members were affected. The mean (± standard deviation) age of onset and the Mini-Mental State Examination score were 48.4 ± 7.7 years and 7.9 ± 9.2, respectively. Compared with the sporadic late-onset Alzheimer's disease patients, those with familial Alzheimer's disease had an earlier age of onset and presentation (both P<0.001) and received the correct diagnosis later (median [interquartile range], 7.5 [5.3-14.5] vs 2 [1.0-3.3] years; P<0.001). Patients with familial disease had a lower Mini-Mental State Examination score at presentation than those having late-onset Alzheimer's disease (mean, 7.9 ± 9.2 vs 17.6 ± 7.2; P=0.01). They also had fewer delusions, and less dysphoria and irritability (0% vs 41.7%, 0% vs 50% and 0% vs 54.2%; P=0.04, 0.01 and 0.01, respectively). There was a trend of less frequent amnesia among patients with familial Alzheimer's disease compared with those having late-onset Alzheimer's disease (75% vs 100%; P=0.05).

Conclusion: Clinical features differ for patients with familial Alzheimer's disease compared with those with late-onset Alzheimer's disease. There is a delay in diagnosis. Promotion of public awareness of familial Alzheimer's disease is much needed.

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New knowledge added by this study

- There is a significant delay in the diagnosis of familial Alzheimer's disease (FAD) in Hong Kong.
- Patients with FAD had fewer delusions and less dysphoria and irritability compared with patients with sporadic late-onset Alzheimer's disease.

Implications for clinical practice or policy

- Promotion of public awareness of FAD is much needed.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia. It is frequently classified as early-onset AD (EOAD) if onset is before the age of 65 years and thereafter as late-onset AD (LOAD). Familial AD (FAD) is a special form of EOAD with an autosomal dominant inheritance, and can be caused by mutations in presenilin (*PSEN*) 1 or 2 and amyloid precursor protein (*APP*) genes. Not all patients with EOAD have autosomal dominant FAD, which accounts for less than 1% of all AD.[1] The first patient diagnosed with AD by Alois Alzheimer was called Auguste Deter; she was admitted to a psychiatric unit because of amnesia and hallucinations at the age of 51 years.[2] Deoxyribonucleic acid was extracted from a histological section of Auguste Deter's

香港首個研究比較家族性阿爾茨海默病患者與經生物標誌物證實的晚發性阿爾茨海默病患者

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引言：香港的家族性阿爾茨海默病患者越來越多。本研究旨在報告這些患者的臨床特徵，並與經生物標誌物證實的晚發性阿爾茨海默病的患者進行比較。

方法：1998年1月至2016年12月期間，所有到瑪麗醫院記憶診所就診的具症狀的家族性阿爾茨海默病患者均參與這研究。我們收集患者的臨床特徵、基線迷你精神狀態檢查（MMSE）評分，以及呈現認知症狀或非典型臨床特徵的資料。將他們的臨床特徵與以下兩組患者進行比較：12例經腦脊髓液生物標誌物證實的晚發性阿爾茨海默病患者，以及14例正常澱粉樣蛋白載體匹茲堡複合物B成像的晚發性阿爾茨海默病患者。

結果：3個家庭共8名患者患有家族性阿爾茨海默病，他們的平均（標準差）發病年齡為48.4（7.7）歲，MMSE評分7.9（9.2）。與晚發性阿爾茨海默病患者相比，具有家族性阿爾茨海默病患者的發病年齡和出現症狀均較早（兩者P<0.001），亦較遲接受正確診斷（中位數7.5年，四分位數5.3-14.5年，比中位數2年，四分位數1.0-3.3年；P<0.001）。患有家族性疾病的患者比晚發性阿爾茨海默病的患者的MMSE評分較低（平均值±標準差，7.9±9.2比17.6±7.2；P=0.01）。他們出現妄想的情況較少、較少煩躁和較少易激惹（0%比41.7%、0%比50%和0%比52.4%；P=0.04、0.01和0.01）；另外也較少出現健忘症（75%比100%；P=0.05）。

結論：家族性阿爾茨海默病患者與晚發性阿爾茨海默病患者的臨床特徵不同，診斷有延遲。有必要提高公眾對家族性阿爾茨海默病的認識。

brain and 100 years later a heterozygous mutation p.Phe176Leu was discovered in the *PSEN1* gene.[2] Unlike reports of FAD in the western population, little has been written about this condition in the Chinese population.[1]

Apart from the difference in age of onset (AOO), EOAD shows a number of differences in clinical features when compared with LOAD. Patients with EOAD often have a non-amnestic presentation with visuospatial dysfunction and apraxias; neuropsychologically they exhibit dysexecutive function, and poor visuospatial and motor skills.[3] Structural imaging also reveals that patients with EOAD exhibit more frontal or temporoparietal atrophy rather than the hippocampal atrophy seen in patients with LOAD.[3] Patients with EOAD exhibit more hypometabolism in the temporoparietal cortex while those with LOAD exhibit more hypometabolism over the medial temporal lobe.[3] Our previous systematic review revealed that FAD patients can present with atypical clinical features including myoclonus, seizures, cerebellar dysfunction, spastic paraparesis, and neuropsychiatric manifestations.[1] These factors may contribute to under-recognition of EOAD or FAD among local Chinese population.

Diagnosis of FAD is clinically important for the affected family. Genetic counselling may be offered to potential asymptomatic carriers if desired, as they may benefit from prenatal diagnosis and planning of personal affairs.[4] Identification of asymptomatic carriers can also identify potential candidates for future drug trials of disease-modifying agents. With respect to preventive therapies, two clinical trials—the DIAN-TU (Dominantly Inherited Alzheimer Network Trial Unit) and API (Alzheimer's Prevention Initiative)—are ongoing to test the efficacy of passive immunotherapy among normal or mildly symptomatic FAD mutation carriers.[5,6] Thus, it is important to enhance local doctors' knowledge of FAD.

The objectives of this study were to report the clinical features of the first case series of Chinese FAD patients in Hong Kong, and to compare their clinical features with those of biomarker-confirmed sporadic LOAD patients. We hypothesised that patients with FAD had more atypical clinical features, and that this could contribute to a delay in correct diagnosis.

Methods

Patients with familial Alzheimer's disease

This was a retrospective case series of FAD patients diagnosed between January 1998 and December 2016 in the memory clinic of Queen Mary Hospital, Hong Kong. The FAD patients were identified by reviewing the case records of all patients diagnosed with EOAD during the study period. The study was performed in accordance with the principles outlined in the Declaration of Helsinki. All symptomatic FAD patients with confirmed mutations in *PSEN1* or *APP* genes were included. To date, no FAD family with *PSEN2* has been identified in Hong Kong. All these patients are pure Chinese. Detailed histories were obtained from primary caregivers. All patients underwent a physical examination, laboratory blood tests (including vitamin B_{12}, folic acid, and thyroid function), computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, and completed the Cantonese version of Mini-Mental State Examination (MMSE).[7] These patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria of AD.[8] In this study, AOO was defined as the age at first appearance of symptoms that interfered with social or occupational functioning. Age of correct diagnosis (AOCD) was defined as the age at which diagnosis of FAD was confirmed with genetic mutation. Duration of symptoms was defined as the difference between AOO and AOCD in years. Initial presenting cognitive symptoms and behavioural and psychological symptoms of

dementia (BPSD) according to the Neuropsychiatric Inventory (NPI) were specifically collected from primary caregivers and were immediately recorded in the medical records.[9] Of note, BPSD—including delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour—were recorded as binary variables (ie present or absent) as not all NPI scores could be retrieved.[9] Authors (SYF and LSC), who were blinded to the hypothesis, retrieved the information related to initial presenting cognitive symptoms and BPSD.

Selection of patients

In summary, three families among whom eight patients were affected were included in this case series. Two families have been reported previously.[10,11] For reference purposes, there were 18 patients with EOAD and no positive family history during the study period.

Two patients with familial Alzheimer's disease

This family has not been reported in detail previously. The family was referred to our memory clinic more than 10 years ago (Fig). The first case (II3; patient No. 5) was a 52-year-old woman who complained of progressive short-term memory impairment with impaired daily function, occupational performance, and management of personal finances. Her father (I1) and eldest brother (II1) had been diagnosed with dementia at around 50 years of age by doctors in China. As a result of these symptoms, her husband had divorced her, and she received care from her friend. Single-photon emission CT of the brain showed bilateral hypoperfusion over the frontal and temporoparietal lobes. She consented to genetic testing and gene sequencing for known FAD mutations, which was subsequently performed by The Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto. A heterozygous missense mutation p.His163Arg in the *PSEN1* gene was detected. She received rivastigmine treatment. Five years later, because of her poor drug compliance and impaired ability to carry out cooking and housework, arrangements were made for her to live in an elderly care home. Another patient (II4; patient No. 4) was her 46-year-old brother who was diagnosed with dementia by another hospital. He also consented to have genetic testing. The same heterozygous missense mutation was found.

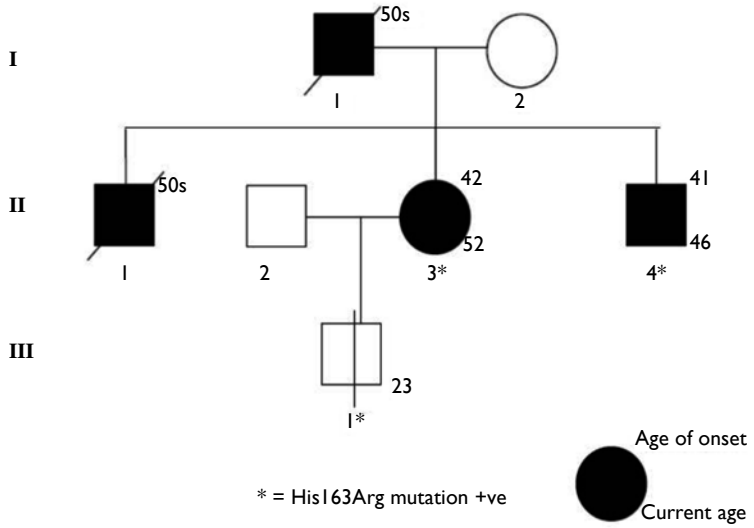

FIG. Pedigree of the FAD family of patient No. 4 and 5
Abbreviation: FAD = familial Alzheimer's disease
Squares and circles represent men and women, respectively. Affected individuals are indicated by filled symbols, and unaffected individuals by open symbols. Current age and age at onset are shown

Late-onset Alzheimer's disease with biomarker confirmation

Late-onset AD is defined as AD with AOO that occurs at or after the age of 65 years. During the study period, 12 patients with LOAD underwent cerebrospinal fluid (CSF) examination that revealed an AD pattern of CSF biomarkers (ie low amyloid-beta [Aβ42], and elevated total tau and phosphorylated tau [pTau]) within 1 month of clinical assessment.[12] In addition, 14 patients with LOAD underwent ^{11}C-Pittsburgh compound B (PIB) and ^{18}F-2-fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET) within 3 months of clinical assessment. Bilateral temporoparietal hypometabolism was evident on ^{18}FDG PET and positive amyloid loading on ^{11}C-PIB (ie binding occurred in more than one cortical brain region: frontal, parietal, temporal, or occipital).[13] Clinically, these patients also fulfilled the NINCDS-ADRDA criteria for AD. These patients had no history of stroke and their CT or MRI brain showed no evidence of infarcts or extensive white matter changes. For these 26 patients with LOAD, similar clinical information including basic demographics, AOO, AOCD (based on the availability of biomarkers' results), disease duration, Cantonese version of MMSE, initial presenting cortical symptoms, and BPSD was collected. For reference purposes, there were 2480 patients with LOAD without CSF biomarkers or FDG and PIB-PET examination during the same period of time.

Statistical analysis

Parametric variables are expressed as mean ± standard deviation (SD). Non-parametric variables are expressed as median with interquartile range (IQR). Chi squared test or Fisher's exact test were

used to compare categorical variables. Independent sample *t* test or Mann-Whitney *U* test was used to compare continuous variables when appropriate. Statistical significance was inferred by a two-tailed P value of <0.05. All statistical analyses were performed using the SPSS (Windows version 18.0; SPSS Inc, Chicago [IL], US).

Results

Case series of familial Alzheimer's disease

There were three affected families with eight affected patients. Their clinical features are summarised in Table 1. The mean (± SD) AOO and MMSE score were 48.4 ± 7.7 years and 7.9 ± 9.2, respectively. The mean duration of symptoms before genetic diagnosis was 10.1 ± 7.1 years. Patients 1 and 3 were initially misdiagnosed with depression and Parkinson's disease with dementia, respectively. The three most common presenting cognitive symptoms were amnesia (75%), disorientation (63%), and anomia (38%).

Comparison with late-onset Alzheimer's disease

The comparison of demographics between FAD and LOAD patients is summarised in Table 2. The AOO and AOCD were much earlier for FAD than LOAD patients (48.4 ± 7.7 vs 77.9 ± 6.7 years and 57.9 ± 8.2 vs 80.7 ± 6.2 years; both P<0.001). The duration of symptoms was much longer for FAD patients than LOAD patients (median [IQR]: 7.5 [5.3-14.5] vs 2.0 [1.0-3.3] years; P<0.001). Patients with FAD had a lower presenting MMSE score than those with LOAD (7.9 ± 9.2 vs 17.6 ± 7.2; P=0.01). More patients with FAD had been educated to secondary level or above than LOAD patients (P=0.001).

The comparison of cognitive symptoms and BPSD between FAD and LOAD patients is summarised in Tables 3 and 4, respectively. There

TABLE 1. A summary of all FAD patients attending the memory clinic of Queen Mary Hospital from January 1998 and December 2016

Patient No.	AOO (years)	Age of diagnosis of FAD (years)	Sex	Education level	Presenting MMSE score	Mutation	Initial cognitive symptoms	Atypical clinical features	Neuroimaging findings
1	40	48	Female	Tertiary	18	*APP* p.Val717Ile	Amnesia, depression, impairment of judgement, anomia, acalculia, impairment in handling banking	Initially misdiagnosed as depression	MRI brain: bilateral hippocampal atrophy; SPECT brain: hypoperfusion over the left temporoparietal lobes and right parietal lobes
2	50	66	Female	Illiterate	14	*APP* p.Val717Ile	Anomia, apathy, spatial disorientation	Seizure	CT brain with medial temporal lobe atrophy; SPECT: bilateral hypoperfusion over bilateral frontal and temporoparietal lobes
3	58	62	Male	Secondary	5	*APP* p.Val717Ile	Amnesia with spatial disorientation, auditory hallucination and parkinsonism	Initially diagnosed as Parkinson's disease with dementia	CT brain: left thalamic infarct
4	41	46	Male	Secondary	23	*PSEN1* p.His163Arg	Amnesia	NA	NA
5	42	52	Female	Secondary	0	*PSEN1* p.His163Arg	Amnesia	NA	SPECT brain: bilateral hypoperfusion over the frontal and temporoparietal lobes
6	51	58	Male	Secondary	3	*PSEN1* p.Phe386Ile	Amnesia, disorientation, apathy, dysexecutive syndrome	NA	MRI brain: bilateral hippocampal atrophy
7	60	66	Male	Secondary	0	*PSEN1* p.Phe386Ile	Amnesia, disorientation, apraxia	NA	MRI brain: bilateral hippocampal atrophy
8	45	65	Female	Secondary	0	*PSEN1* p.Phe386Ile	Amnesia, disorientation, anomia, prosopagnosia, dysexecutive syndrome, anxiety	Seizure	CT brain: severe medial temporal lobe atrophy

Abbreviations: AOO = age of onset; *APP* = amyloid precursor protein gene; CT = computed tomography; FAD = familial Alzheimer's disease; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NA = not available; *PSEN1* = presenilin 1 gene; SPECT = single-photon emission computed tomography

TABLE 2. Comparison of clinical features between FAD and sporadic LOAD

Characteristic/clinical feature	Data*		P value
	FAD (n=8)	Sporadic LOAD (n=26)	
Age of onset (years)	48.4 ± 7.7	77.9 ± 6.7	<0.001†
Age of correct diagnosis (years)	57.9 ± 8.2	80.7 ± 6.2	<0.001†
Duration of symptoms (years)	7.5 (5.3-14.5)	2.0 (1.0-3.3)	<0.001‡
Presenting MMSE score	7.9 ± 9.2	17.6 ± 7.2	0.01†
Education level			
Illiterate	1 (12.5)	19 (73.1)	0.001§
Primary	0 (0)	3 (11.5)	
Secondary	6 (75)	2 (7.7)	
Tertiary	1 (12.5)	2 (7.7)	

Abbreviations: FAD = familial Alzheimer's disease; LOAD = late-onset Alzheimer's disease; MMSE = Mini-Mental State Examination
* Data are shown as mean ± standard deviation, median (interquartile range), or No. (%)
† *t* Test
‡ Mann-Whitney *U* test
§ Chi squared test

TABLE 3. Comparison of cognitive symptoms between FAD and sporadic LOAD

Cognitive symptom	No. (%) of patients		P value*
	FAD (n=8)	Sporadic LOAD (n=26)	
Amnesia	6 (75.0)	26 (100)	0.05
Agnosia	1 (12.5)	5 (19.2)	1.0
Apraxia	1 (12.5)	6 (23.1)	1.0
Anomia	3 (37.5)	6 (23.1)	0.65
Dyslexia	0 (0)	0 (0)	-
Dysgraphia	0 (0)	1 (3.8)	1.0
Dysexecutive syndrome	2 (25.0)	9 (34.6)	1.0
Depression	1 (12.5)	2 (7.7)	1.0
Parkinsonism	1 (12.5)	0 (0)	0.24

Abbreviations: FAD = familial Alzheimer's disease; LOAD = late-onset Alzheimer's disease
* Fisher's exact test

TABLE 4. Comparison of BPSD between FAD and sporadic LOAD

BPSD	No. (%) of patients		P value†
	FAD (n=8)	Sporadic LOAD (n=24)*	
Delusion	0 (0)	10 (41.7)	0.04
Hallucination	1 (12.5)	3 (12.5)	1.0
Agitation	0 (0)	9 (37.5)	0.07
Dysphoria	0 (0)	12 (50.0)	0.01
Anxiety	1 (12.5)	5 (20.8)	1.0
Euphoria	0 (0)	2 (8.3)	1.0
Apathy	2 (25.0)	10 (41.7)	0.68
Disinhibition	0 (0)	1 (4.2)	1.0
Irritability	0 (0)	13 (54.2)	0.01
Aberrant motor behaviour	0 (0)	2 (8.3)	1.0

Abbreviations: BPSD = behavioural and psychological symptoms of dementia; FAD = familial Alzheimer's disease; LOAD = late-onset Alzheimer's disease
* BPSD could not be traced for two patients
† Fisher's exact test

was a trend wherein patients with FAD were less likely to present with amnesia (75% vs 100%; P=0.05) than those with LOAD although it was still their main presenting cognitive symptom. Patients with LOAD more commonly presented with delusion, dysphoria, and irritability than FAD patients (0% vs 41.7%, 0% vs 50%, and 0% vs 54.2% respectively; P=0.04, 0.01, and 0.01, respectively).

Discussion

In this case series, there was significant delay in making a correct diagnosis of FAD among patients who presented at a late stage of dementia compared with patients with LOAD. Patients with LOAD more often presented with BPSD such as delusion, dysphoria, and irritability.

There are several factors that contribute to the delay in diagnosis and thus the late presentation of FAD patients to the memory clinic. First, the availability of genetic tests is not well known to local doctors. Currently doctors in public hospitals can consult with a clinical biochemist if they encounter a family with at least two generations having EOAD. Genetic tests can be arranged for *PSEN1*, *APP*, and *PSEN2* sequentially. Second, patients with FAD may have atypical clinical features. In our case series, two patients were initially misdiagnosed as depression and Parkinson's disease with dementia. Our previous systematic review indicated that patients with FAD and *PSEN1* mutations can present with parkinsonism, seizures, spastic paraparesis, myoclonus, and cerebellar dysfunction.[1] Chinese FAD patients with an *APP* mutation can present with atypical phenotypes with a prominent psychiatric manifestation, behavioural and language variants.[1] Patients with FAD with a *PSEN2* mutation can present with a later AOO even within the same family.[1] It is important for local doctors to be aware of the possibility of these atypical clinical features in their EOAD patients, especially if there is a positive family history of EOAD. Third, since FAD is not treatable, genetic testing may not be considered. Nonetheless, genetic counselling is important for patients with FAD. Asymptomatic carriers are also potentially valuable for future clinical trials.[4-6]

In terms of cognitive symptoms, patients with FAD tended to present slightly less frequently with amnesia than those with LOAD, although amnesia remained their main presenting cognitive symptom. This is in agreement with previous studies that reported EOAD patients to have more prominent frontoparietal dysfunction than medial temporal dysfunction.[3,14,15] Our study also identified that LOAD patients have more positive symptoms of BPSD including delusions and irritability. Table 5 summarises the differences in BPSD between FAD and LOAD patients in our study and in other reported studies between EOAD and LOAD patients.[16-18]

There are several potential reasons for the different clinical features between FAD and LOAD patients. First, patients with FAD have a genetic mutation that increases the production of Aβ42 from early on in life. This explains the much earlier AOO.[19] Second, pathological studies of the brain of FAD patients seldom noted non-AD pathological changes. On the contrary, 42% of LOAD patients exhibited at least one other concurrent clinicopathological diagnosis such as vascular dementia, dementia with Lewy bodies, hippocampal sclerosis, or Pick's disease.[20] Third, amyloid plaques in LOAD patients are mostly compact or diffuse while those in FAD

TABLE 5. A comparison between our study findings on BPSD with other studies comparing EOAD and LOAD patients[16-18]

Study	Sample size	Key findings (all statistically significant)
Toyota et al[18]	EOAD (n=46); LOAD (n=261) Diagnosis based on clinical criteria and SPECT	LOAD patients more commonly manifested delusion (50.6% vs 13.0%), hallucination (22.6% vs 4.3%), agitation (44.8% vs 28.3%), disinhibition (16.5% vs 4.3%), and aberrant motor behaviour (43.7% vs 26.1%) than EOAD patients
Park et al[17]	EOAD (n=435); LOAD (n=435) Diagnosis based on clinical criteria; matching was performed by propensity score	LOAD patients more commonly manifested delusions (26.2% vs 19.1%) and hallucinations (14.6% vs 10.1%) than EOAD patients. EOAD patients manifested more apathy (59.4% vs 46.2%) than LOAD patients
Mushtaq et al[16]	EOAD (n=40); LOAD (n=40) Diagnosis based on clinical criteria; two groups were matched for education, gender, MMSE score, disease duration and severity	LOAD patients had higher symptom severity scores (NPI) for delusions (1.37 ± 0.49 vs 0.94 ± 0.42), agitation (2 ± 0 vs 1.2 ± 0.4), anxiety (3.03 ± 0.91 vs 2.57 ± 0.5), disinhibition (1 ± 0 vs 0.12 ± 0.33), and night-time behavioural disturbances (2.47 ± 0.71 vs 1.35 ± 0.48) than EOAD patients
Present study	FAD (n=8); LOAD (n=26) Diagnosis based on genetic mutation confirmation, CSF biomarkers, and PIB-PET scan	LOAD patients more commonly presented with delusion (41.7% vs 0%), dysphoria (50% vs 0%), and irritability (54.2% vs 0%)

Abbreviations: BPSD = behavioural and psychological symptoms of dementia; CSF = cerebrospinal fluid; EOAD = early-onset Alzheimer's disease; FAD = familial Alzheimer's disease; LOAD = late-onset Alzheimer's disease; MMSE = Mini-Mental State Examination; NPI = neuropsychiatric inventory score; PIB-PET = Pittsburgh compound B positron emission tomography; SPECT = single-photon emission computed tomography

patients exhibit various morphologies associated with the specific *PSEN* mutation.[20] Fourth, *PSEN* 1 and 2 form the catalytic subunit of γ-secretase and apart from amyloid beta precursor protein, there are over 90 other substrates upon which γ-secretase can act; this may explain the wide range of phenotypes for FAD patients with *PSEN* mutations.[20]

The strength of the study is that the diagnoses of FAD and LOAD were supported by genetic analyses and imaging/CSF biomarkers, respectively. There are a number of limitations in our study. First, FAD accounted for only a minority of EOAD cases and thus our results may not be generalised to sporadic EOAD patients. Second, the severity of BPSD could not be compared. In future, NPI scores should be compared. In addition, detailed neuropsychological tests were not performed because of the busy clinical setting in our memory clinic. Third, the sample size is small and our results must be treated as preliminary. Fourth, the presence or absence of symptoms depends on the recall of primary caregivers and is subject to recall bias. Fifth, apolipoprotein E status is an important genetic contributor to LOAD but it was not checked in all LOAD patients in this study.[4] Despite these limitations, this is the first local study in Hong Kong to compare Chinese FAD and LOAD patients.

In summary, there are differences in clinical features between patients with FAD, who receive a correct diagnosis much later, and patients with LOAD. Promotion of public awareness of FAD in Hong Kong is much needed to help those families that are affected but not yet identified.

Declaration

All authors have disclosed no conflicts of interest.

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