Early-onset dementia in Chinese: Demographic and etiologic characteristics

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Abstract

Objective: Data on early-onset dementia in Chinese is limited. This study aimed to report the diagnostic profiles and characteristics of patients with early-onset dementia in a university-affiliated cognitive disorder clinic in Hong Kong.

Methods: We prospectively collected data of consecutive patients who were referred between January 2012 and December 2018. All patients were referred for diagnostic evaluation of cognitive symptoms. Patients with symptom-onset at age 65 or before were recruited. We excluded patients with (1) cognitive deficits referable to an isolated event or toxin and (2) significant mood disorders.

Results: Of the 93 patients included, four patients had temporal lobe epilepsy mimicking dementia. Three patients had cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), one patient had Niemann-Pick disease type C and two patients had undetermined aetiology. The remaining 83 patients had primary degenerative dementia. The most frequent diagnosis was Alzheimer’s disease (AD) (70%), followed by frontotemporal dementia (FTD) (22%) and parkinsonian disorders (8%). The mean age of symptom onset was 57.8 ± 5.8 years. Ten (17%) AD patients had non-amnestic presentation. Fifteen FTD patients consented for mutation screening in the GRN (progranulin), MAPT (microtubule-associated protein tau) and C9orf72 genes, none were positive.

Conclusions: Early-onset dementia had a broader differential diagnoses than late-onset dementia, and includes a number of rare hereditary diseases. Patients with suspected early-onset dementia should be thoroughly evaluated to identify any treatable causes.

Keywords: Early-onset dementia, Chinese, genetics

INTRODUCTION

Many people assume dementia only affects older population, but there are increasing awareness for patients who suffer from dementia at a younger age. The term early-onset dementia (EOD) refers to dementia with symptom onset at age 65 years or before. It has been reported that the prevalence of EOD is between 78 and 700 per 100,000 population. For patients who presented with cognitive decline after an obvious insult (e.g. stroke or toxin), the diagnosis may be straightforward. However, it poses a significant diagnostic challenge if patients do not report any causal antecedent event. Furthermore, some rare hereditary diseases caused by genetic mutations can present as cognitive decline in early adulthood. Etiological causes or genetic contribution of EOD may differ with ethnicity. China has the world’s largest population, but the literature on EOD in Chinese is limited. This study aimed to investigate the diagnostic profiles and characteristics of suspected EOD patients in a university-affiliated cognitive disorder clinic in Hong Kong.

METHODS

We prospectively collected data of consecutive patients who were referred to a university-affiliated movement and cognitive disorder clinic in Hong Kong from January 2012 to December 2018. This is an outpatient clinic based in...
neurology. Patients were referred from general practitioners and non-neurology specialists for diagnostic evaluation of cognitive symptoms. We included patients who were referred for (1) cognitive decline as the primary referral reason and (2) symptom onset at age 65 years or before. We excluded patients with (1) cognitive deficits referable to an isolated event or toxin (e.g. stroke, traumatic brain injury, encephalitis, and alcohol) and (2) significant mood disorders (e.g. depression, anxiety). Data collected include demographics, clinical presentation, neurological examination, neuroimaging, cognitive tests and ancillary genetic tests.

Etiological diagnosis of primary degenerative dementia was classified into Alzheimer’s disease (AD), frontotemporal dementia (FTD) and parkinsonian disorders according to published clinical diagnostic criteria. For a diagnosis of AD, criteria of the National Institute on Aging-Alzheimer’s Association (NIA-AA) were applied. For a diagnosis of behavioural variant FTD (bvFTD), criteria of the International Behavioural Variant FTD Criteria Consortium (FTDC) were applied. For diagnosis of language-variant FTD (also known as primary progressive aphasia, PPA), namely semantic dementia (SD) and progressive nonfluent aphasia (PNFA), criteria by Gorno-Tempini et al. were applied. For a diagnosis of Lewy body dementia (LBD), criteria of the Dementia with Lewy Bodies Consortium were applied. Diagnosis of multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) were made according to criteria by Gilman et al. and Höglinger GU et al. respectively. If one or more causes of dementia were suspected, the most clinical relevant cause will be chosen as the final diagnosis.

RESULTS

A total of 277 patients were referred for workup of cognitive symptoms from January 2012 to December 2018. Ninety-three patients met the inclusion and exclusion criteria. Four patients were found to have temporal lobe epilepsy mimicking dementia. All of them presented with recurrent complex partial seizures in the absence of generalized tonic clonic convulsions. Two of the four patients had intracranial space occupying lesion, one was a right medial sphenoidal cavernous meningioma (Figure 1) and the other was a macroprolactinoma. All of them were diagnosed by detailed history taking, supported by neuroimaging and electroencephalogram (EEG) findings. In addition to some form of memory disturbance, family members also complain that the patient often does not seem to be listening or appears to be daydreaming. With careful and tactful questioning, family members were able to describe repetitive movements involving the hands or the mouth in most instances. In two of the patients, their family members were asked to videotape these stereotypic episodes, which were later identified to be typical automatisms by neurologist. For the 2 patients with intracranial space occupying lesion, none of them had neither headache nor motor deficits.

We did not include patients with history of stroke in this study, as the vast majority of patients with post-stroke dementia were referred and managed in general medical clinic in our hospital. There were 5 patients who had imaging features of significant vascular burden on brain imaging, but did not meet the diagnostic criteria for probable vascular dementia according to National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN). Out of these 5 patients, 2 had high amyloid load on positive emission topography (PET) using \(^{11}\text{C}-\text{Pittsburgh Compound B (PIB)}\) and were classified as having Alzheimer’s disease. The other 3 patients had genetically-proven CADASIL. Two of them had history of transient ischaemic attack, but cognitive symptoms began prior to the vascular event. None of them had classical migraine history. None...
of them reported a family history of dementia. All patients had no known vascular risk factors, but extensive subcortical white matter changes on brain magnetic resonance imaging (MRI) (Figure 2). Only one patient had anterior temporal involvement. Exons 2-6 and 11 of the NOTCH3 gene were sequenced by the Sanger method. Pathogenic heterozygous NOTCH3 variant c.1630C>T p.(Arg544C) was detected in all 3 patients.

One patient had genetically-proven Niemann-Pick disease type C. He presented with insidious onset of cognitive decline and gait instability since age 30 years. Examination revealed vertical supranuclear gaze palsy especially on downward gaze, which is a characteristic finding of this disease. All coding exons and flanking introns (40 nucleotides) of the NPC1 gene were sequenced in both directions by Sanger sequencing. Two pathogenic heterozygous variants, c.2903A>G p.(Asn968Ser) and c.3634G>T p.(Val1212Leu) were detected.

Two patients had cognitive impairment of undetermined aetiology despite extensive investigations. One of them had extensive leucodystrophy of frontal predominance on MRI, normal cerebrospinal fluid (CSF), normal very long chain fatty acid (VLCA) and normal enzymatic screening for metachromatic leucodystrophy (MLD). Further workup with whole exome sequencing was planned.

The remaining 83 patients had primary degenerative dementia, with the most frequent diagnosis being AD (n = 58, 70%). Ten (17%) had non-amnestic presentations. Five had visuospatial/ apraxic presentation, four had language presentation and one had dysexecutive/ parkinsonian presentation. Six patients with atypical presentations had abnormal amyloid accumulation on 11C-PIB PET brain. For example, one patient (W) complained of inability to write since the age of 52 years. She had particular difficulties in dressing, brushing and tying her shoelaces. At this stage, her memory was reported as slightly impaired by relatives. She was extremely impaired on visuospatial tasks and grossly apraxic. 11C-PIB PET brain revealed uptake patterns typical for AD (Figure 3). The youngest AD patient (C) presented with cognitive and motor slowing since the age of 40 years. Examination showed parkinsonian features including mask face, bradykinesia and rigidity. Family history was negative for early-onset dementia. MRI brain showed biparietal atrophy and normal hippocampal volume (Figure 4). 11C-PIB PET brain revealed high amyloid load. Genetic testing revealed a likely pathogenic variant c.781G>A p.(Val261Ile) in the PSEN1 gene.

In total, 24 patients underwent 11C-PIB PET brain. The reason for 11C-PIB PET brain was ‘diagnostic uncertainty’ in 19 patients and ‘research purpose’ (AD biomarker study) in 5 patients. Three patients had negative 11C-PIB

![Figure 2. MRI axial FLAIR images of patient C showing high-signal intensity lesions in bilateral periventricular and deep white matter, but no lesions in the anterior temporal lobe.](image-url)
Figure 3. $^{11}$C-PIB PET brain images of patient W showing localized retention of $^{11}$C-PIB over bilateral frontal, parietal, temporal, occipital lobes, cingulate gyrus and precuneus. This signifies the presence of high amyloid deposition and serves as the neuropathologic hallmarks of Alzheimer’s disease.

Figure 4. MRI T1-weighted coronal (left) and axial (right) images of patient C with PSEN1 mutation and early-onset Alzheimer’s disease, showing biparietal atrophy with relatively preserved hippocampus volume.
PET brain, two of them presented with language decline in which family members described as ‘forgetful’/memory loss’ and ‘cannot recall names of friends/colleagues’. Both were diagnosed probable Alzheimer’s disease on first presentation, but as the disease progressed they exhibited typical fluent dysphasia of semantic dementia, developed disinhibited behaviours and computed tomography (CT) brain revealed progressive ‘knife-blade’ atrophy of temporal lobes (Figure 5).

The second most frequent diagnosis was FTD \((n = 18, 22\%)\), followed by parkinsonian disorders \((n = 7, 8\%)\). Among the 18 patients with FTD, 5 had behavioural-variant frontal temporal dementia \((bvFTD)\), 9 had semantic dementia \((SD)\) and 4 had progressive nonfluent aphasia \((PNFA)\). All the language-variant FTD diagnoses were imaging-supported. Fifty percent of patients reported a family history of dementia in first-degree relatives. Six \((33\%)\) patients had a concomitant motor syndrome (3 had parkinsonian features, two had amyotrophic lateral sclerosis and one had spastic paraesthesia). Fifteen patients consented for mutation screening in the \(GRN\) (progranulin), \(MAPT\) (microtubule-associated protein tau) and \(C9orf72\) genes, none were positive. Among the 7 patients with parkinsonian disorders, 3 had Lewy body dementia \((LBD)\), 3 had multiple system atrophy \((MSA)\) and one had progressive supranuclear palsy \((PSP)\). For patients diagnosed with MSA and PSP, although the primary referral symptom was cognitive impairment, all patients also reported unsteady gait with falls on detailed history taking.

Excluding the 4 patients with temporal lobe epilepsy, the mean age of symptom onset was 57.8 ± 5.8 years (ranged 37 to 65 years) and 49 patients \((55\%)\) were females. The mean educational attainment was 8.6 ± 3.9 years (ranged 0 to 18 years). The mean MMSE on presentation was 20.1 ± 5.8 (ranged 4 to 30, data not available in 7 patients). Forty one patients \((46\%)\) were holding a job when the disease strikes them. In terms of laboratory evaluations, all patients had normal levels of vitamin B12, folate and thyroid-stimulating hormone. Serum venereal disease research laboratory \((VDRL)\) were non-reactive in all patients. In terms of structural neuroimaging, 80 patients \((90\%)\) had MRI brain performed. CT brain was performed in patients who were contraindicated or not cooperative for MRI brain.

DISCUSSION

To our knowledge, this is the first study to investigate the causes of EOD in Chinese population. Compared with older dementia patient, the differential diagnosis of EOD is much broader, clinical presentation is often atypical and requires a more extensive evaluation. Most importantly, some potentially treatable conditions may mimics dementia, which makes the need of a specific and timely diagnosis crucial.

In our study, we found 4 patients \((4.3\%)\) who presented with cognitive symptoms to have undiagnosed temporal lobe epilepsy (2 of which had space-occupying lesions in the brain). In a prospective study of 1,000 consecutive memory
A number of rare genetic conditions can also present as cognitive decline. These include CADASIL, disorders of amino acid and organic acid metabolism, lysosomal storage diseases, leucodystrophies and mitochondrial diseases. Genetic counselling and testing as well as specialized biochemical screening are often required.

For the 3 CADASIL patients in our study, all of them had pathogenic variant p.Arg544Cys in exon 11 of NOTCH3 gene. This variant has been reported in multiple literatures and is a prevalent cause of CADASIL in Taiwan and southern Korea. In a study involving Taiwan Han Chinese with CADASIL, the R544C mutation was found to associate with lower frequency of anterior temporal involvement, later age at onset and higher frequency of cognitive dysfunction. Consistent with finding of the Taiwan group, only one of 4 CADASIL patient had anterior temporal involvement on MRI brain.

We diagnosed one patient with adult-onset Niemann-Pick disease type C (NP-C) in this study. The same NPC1 mutation had been reported before in Chinese patients with NP-C. NP-C is a rare lysosomal storage disorder of autosomal recessive inheritance. It is caused by mutations of either the NPC1 (95% of families) or the NPC2 gene. Patients show a very heterogeneous spectrum of symptoms, such as cognitive impairment, cerebellar symptoms, dystonia, psychiatric disorders and vertical supranuclear gaze palsy (VSGP). Among the various symptoms, VSCP is a highly important sign for NP-C diagnosis.

Compared with late-onset AD, people who develop early-onset AD often experience atypical symptoms rather than memory problems. Koedam et al. described that a third of patients with early-onset AD present with non-memory symptoms compared with only 6% of patients with late-onset AD. Atypical presentations of AD include disorders of language, visuospatial skills and praxis. These `focal` presentations of AD are particularly challenging for clinicians because memory impairment is traditionally seen as the hallmark of AD. For example, the language disorder of AD might potentially be confused with the language-variant FTD. In a pathological series, Forman et al. reported that 17% of the patients with clinically diagnosed FTD had AD pathology. In our study, we diagnosed atypical variants of AD in 10 patients, 6 of which were confirmed by 11C-PiB PET brain. Although the clinical utility of amyloid PET is still under investigation, the diagnostic value of amyloid PET is reported to result in changes in the diagnostic process work-up of EOD and increase the diagnostic confidence of managing physicians. From the author’s experience, amyloid PET not only aids an accurate diagnosis at an early stage, it also brings `relief` to many caregivers as they were able to have a better understanding of their loved one’s condition and they felt more confident as to the next steps ahead.

FTD represents the second most common form of EOD after AD. FTD encompasses 3 distinct clinical syndromes including behavioural variant FTD (bvFTD) characterized by prominent behavioural abnormalities, and 2 language variants (semantic variant and nonfluent variant) collectively known as primary progressive aphasia (PPA). In our study, 50% patients reported a family history of dementia in first-degree relatives, which is higher than that reported in other Asian countries. This is probably due to the limitation of obtaining a reliable family history of cognitive disorders in relatives based on clinical history alone, with a risk of overestimating the frequency of a positive family history. For the genetics of FTD, it has been reported in Western populations mutations in three genes (MAPT, GRN and C9orf72) account for the majority cases. In Asian populations, these mutations appeared to be far less common. Similarly, we did not find abnormal C9orf72 expansion nor pathogenic MAPT or GRN mutation in our cohort. Our finding is consistent with the results reported by the group in Korea and in Mainland China.

It is now accepted that FTD and amyotrophic lateral sclerosis (ALS) are part of the same clinicopathological spectrum. It has been reported that in about 5 to 10% of FTD patients develop ALS signs, even though other reports claim that in around 50% of FTD cases subclinical motor neuron degeneration can be found. This
discrepancy is likely due to different methods of assessment and disease definition. Two of our FTD patient developed specific features of ALS including progressive muscle wasting with fasciculations and hyperreflexia, whereas one of our FTD patients had progressive spastic paraparesis. Although hereditary spastic paraparesis (HSP) can be complicated with subcortical dementia in certain genetic subtypes, our patient had typical clinical presentation and regional atrophy on brain imaging consistent with FTD.

Apart from ALS, FTD is also commonly associated with atypical parkinsonism. The clinical phenotypes include the ‘classical’ presentation of progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), progressive akinesia, freezing of gait, and a number of additional clinical variants. In a prospective cohort of 191 patients with FTD conducted in Korea, the prevalence of parkinsonism was 38.7%. We only identified 3 FTD patients (16.6%) with parkinsonism in our study, but this can be related to the small sample size.

We identified 3 patients with multiple system atrophy (MSA) and one patient with PSP in the current study. Increasing evidence had shown that significant cognitive impairment, even early in the disease, could be associated with PSP and MSA. A group in United Kingdom reported cognitive problems as the initial presenting complaint in 15% of a sample of 187 cases of PSP. Evidence for early cognitive impairment associated with MSA is sparse, because significant cognitive decline is an exclusion feature by current consensus. However, dementia was identified in 10 cases (17.2%) of a group of 58 Japanese patients when deliberately ignored the dementia exclusion criterion in making the clinical diagnosis. As a result of these findings, Brown and colleagues had suggested cognitive impairment should not be an exclusion criterion for diagnosis of MSA. In 2014, the Neuropsychology Task Force of the Movement Disorder Society Multiple System Atrophy (MODIMSA) study group had set short-term goals that include the further quantification of cognitive impairment in MSA for the purpose of revising current consensus diagnostic criteria.

In view of the complexity of EOD, careful clinical evaluation and longitudinal follow-up of patients with this disease is crucial to obtain an accurate diagnosis. Due to cultural and language differences, Chinese patients and their caregivers often presented their cognitive changes as ‘memory impairment’. Detailed questioning is required to identify the specific underlying deficit, which may be ‘naming impairment’ of PPA, ‘slow thinking’ of parkinsonian disorders, or even ‘altered consciousness’ of focal epilepsy. As suggested in the algorithm proposed by Rossor et al., many of the diseases that cause dementia in young adults also cause additional neurological or systemic features, and identification of these features can guide the choice of investigations. Although extremely rare, clinicians should be aware of the possibility of inherited metabolic diseases with adult-onset forms. Furthermore, majority of patients with EOD required extensive investigations including dedicated neuroimaging and genetic evaluation, hence close working relationships with experienced neuroradiologists and geneticists is essential.

In conclusion, comprehensive assessments of patients presenting with early-onset cognitive impairment is important, especially to identify potential treatable conditions. A correct etiological diagnosis of early onset dementia allows proper genetic counselling, prognostic guidance to the family and planning for the future.

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REFERENCES


