

Alzheimer's disease: insights for risk evaluation and prevention in the Chinese population and the need for a comprehensive programme in Hong Kong/China

Anita Yee, Nancy BY Tsui, YN Chang, Clarea SM Au, Manson Fok, LT Lau, Teresa Chung, Gregory Cheng, Rick YC Kwan, Angela YM Leung, Johnson YN Lau, David LK Dai *

ABSTRACT

With the ageing of the global population, China is projected to be impacted significantly by the rising number of patients with Alzheimer's disease (AD). A cure for AD is not yet available, so society should be prepared for an increasing AD-related burden. In this review, we examine this impending problem and provide overviews on (a) the magnitude of the problem of AD in Hong Kong/China in the near future; (b) the genetic and lifestyle risk factors that contribute to AD; (c) current diagnostic approaches and the potential of newly discovered genetic biomarkers for early detection; (d) medications, non-pharmacological interventions, and possible preventive measures; and (e) the need for social and psychological care from the community. In Hong Kong, primary care and AD-related support for at-risk individuals, patients, and caregivers are inadequate. A joint effort from the medical community, government, universities, non-governmental organisations/charities, and industry should initiate the development of a long-term programme for AD. Finally, we outline recommendations for the relevant parties to consider.

Hong Kong Med J 2018;24:492–500

DOI: 10.12809/hkmj187244

¹ A Yee, PhD

^{1,2} NBY Tsui, PhD

¹ YN Chang

³ CSM Au

^{1,2,4} M Fok, MB, BS, FRCS

² LT Lau, PhD

² T Chung, MPhil

⁴ G Cheng, MD, PhD

⁵ RYC Kwan, PhD

⁵ AYM Leung, PhD, FHKAM

^{1,2} JYN Lau, MD, FRCP

⁶ DLK Dai *, FRCP, FHKAM (Medicine)

¹ Avalon Genomics (HK) Limited, Shatin, Hong Kong

² Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hungghom, Hong Kong

³ Yan Oi Tong Clarea Au Eldergarten, Kwun Tong, Hong Kong

⁴ Faculty of Health Sciences, Macau University of Science and Technology, Macau

⁵ Centre for Gerontological Nursing, School of Nursing, The Hong Kong Polytechnic University, Hungghom, Hong Kong

⁶ Hong Kong Alzheimer's Disease Association, Hong Kong

* Corresponding author: davidlkai@gmail.com

This article was published on 20 Sep 2018 at www.hkmj.org.

Introduction

Alzheimer's disease (AD) is the most common form of dementia among older adults. It is an age-related chronic condition characterised by gradual decline in memory, cognitive function, and physical status. Patients with AD lose their self-management abilities and require long-term care as the disease progresses. The average survival of patients after diagnosis is approximately 8 to 10 years. Currently, no treatment effectively reverses or halts the disease's progression.

There are two main types of AD. Early-onset familial AD occurs before age 60 years. It accounts for around 1% of AD cases and typically has strong familial aggregation. Causative variants have been identified in genes encoding amyloid precursor protein (APP), presenilin-1, and presenilin-2. Late-onset AD (the focus of this review) is often called sporadic AD. It is the more common type of AD, and it usually occurs after age 60 years.

Both genetic and environmental factors contribute to the disease's development. Before the disease manifests, a continuum of biological and molecular changes has accumulated. Clinical stages that precede AD, including preclinical AD and mild cognitive impairment (MCI), have been proposed.¹ By establishing biomarkers associated with the pre-symptomatic changes, at-risk individuals can be identified for preventive interventions to delay further cognitive decline.

Given the ageing population and the potential impact of AD, the Hong Kong Alzheimer's Disease Association has assembled a number of experts to identify information critical to Hong Kong/China and to prepare appropriate recommendations. This review aimed to provide key information about AD, from prevention, diagnostics, and treatment to continuous care. The review also recommended an implementable plan for the medical community,

government, universities, non-government organisations (NGOs), charities, and industry to consider.

Prevalence and incidence

The global prevalence of dementia among people aged ≥ 60 years is 5% to 7%.² In 2010, approximately 35.6 million people lived with dementia, and this number is expected to double every 20 years. Approximately two-thirds of dementia cases are attributed to AD. There are regional differences in the disease's prevalence, with estimates of 6.9% in Western Europe, 6.5% in North America,² and 4.6% among the Chinese population, including Hong Kong.³ The prevalence of dementia increases exponentially with age. For the age-group of 60 to 64 years, the prevalence is 2% and 0.6% for Caucasian and Chinese people, respectively; while for the age-group of 80 to 84 years, it increases to 13% and 9.4%, respectively. The annual incidence rate (per 1000 individuals) of dementia worldwide was estimated to be 7.5, with regional rates of 8.0 in China, 8.8 in Western Europe, and 10.5 in North America.⁴

China has one of the largest elderly populations. Between 2015 and 2030, the proportion of the population aged ≥ 60 years is estimated to increase from 15% to 25% in China and Macau and from 22% to 34% in Hong Kong.⁵ With this population ageing, the number of patients with AD is expected to increase substantially in the near future.

Progression from asymptomatic to disease manifestation

Pathophysiology

A notable pathological feature of AD is the aggregation of amyloid- β ($A\beta$) peptides in the brain. Amyloid- β peptides are derived from proteolytic cleavage of APP by β - and γ -secretases. This process produces diverse types of $A\beta$ peptides, among which the $A\beta_{42}$ peptide is strongly self-aggregating. When the clearance mechanism is impaired, the level of $A\beta$ peptides in the brain rises, and the peptides assemble into insoluble extracellular amyloid plaques, which are neurotoxic.⁶ Other pathological features include the formation of intracellular neurofibrillary tangles from abnormally hyperphosphorylated and cleaved tau proteins, neuroinflammatory responses triggered by the presence of aggregated $A\beta$, and oxidative stress induced by reactive oxygen species generated in $A\beta$ -altered cells.^{6,7} Although the specific sequences of pathological events remain uncertain, the consequences of synaptic/neuronal dysfunction, neuronal degeneration, reduced neural network connectivity, and brain atrophy are well established and commonly found in the hippocampus, which is the key functional location of memory.

華籍人口認知障礙症的風險與預防，以及應對香港／中國社區的綜合方案的需要

伊芳盈、徐寶賢、張元寧、歐雪明、霍文遜、劉樂庭、鍾之樺、鄭彥銘、關耀祖、梁綺雯、劉耀南、戴樂群

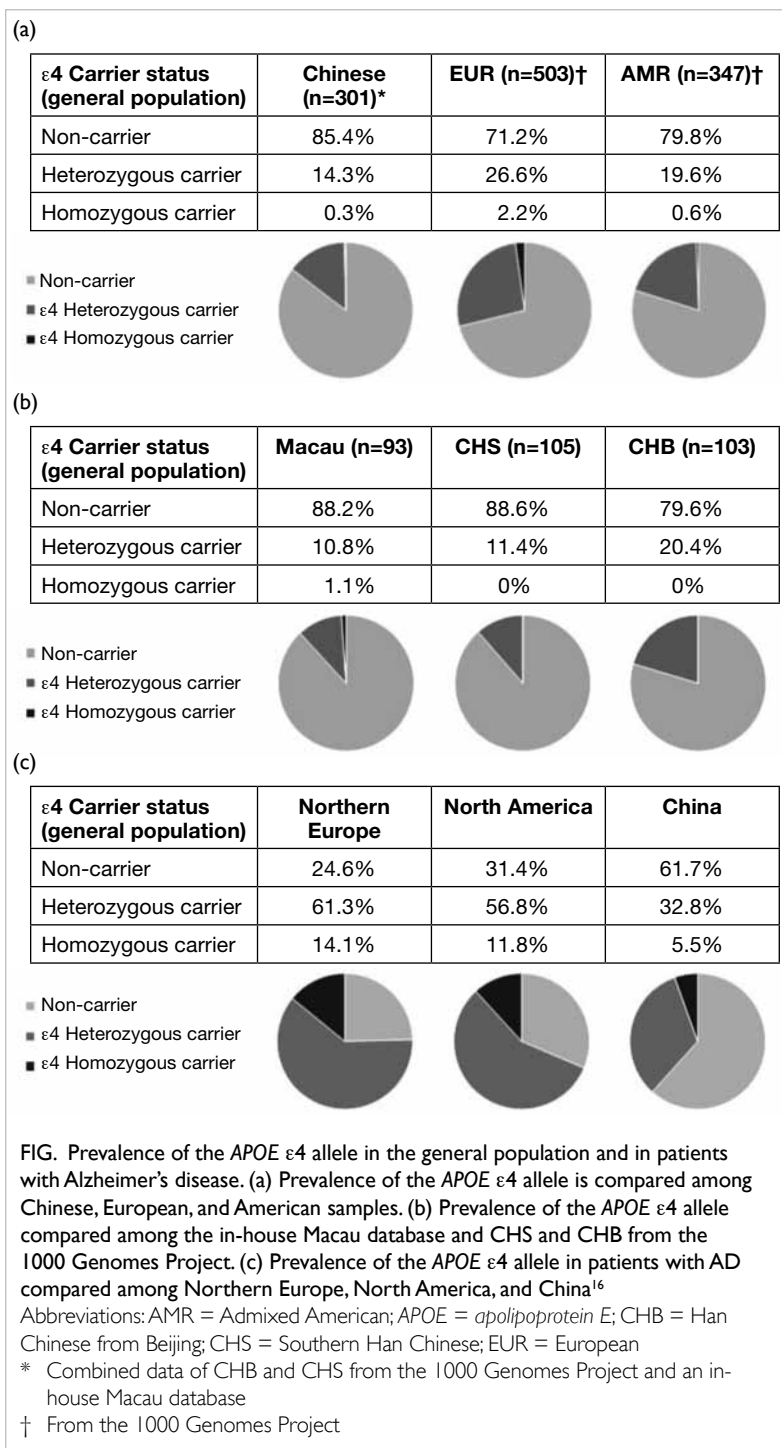
隨着全球人口老化，認知障礙症的患者數量相應增加，中國預計亦是受到重大影響的國家之一。目前認知障礙症尚無法治癒，故此社會應為不斷增加的疾病負擔作好準備。本文探討認知障礙症的現況，包括於香港／中國的嚴重性、遺傳和後天風險因素、目前的診斷方法及利用新型遺傳標誌物作早期篩查的可行性、藥物／非藥物治療和預防方法，以及社會支持和心理輔助。目前香港對認知障礙症的高危人群、病人和照顧者的基層醫療和支援尚未足夠。醫學界、政府、大學、非政府機構／慈善機構和商界應聯手合作，制定一個應對認知障礙症的長遠方案。我們最後提出一些建議供有關方面考慮。

Diagnostic criteria

The criteria for diagnosing AD include significant decline in at least two cognitive domains, one of which is learning and memory, and the deficits' interference with daily abilities and independence.⁸ The characteristics of MCI include concern about change in cognition and evidence of lower performance in one or more cognitive domains, while the abilities of independent living are preserved.⁹ Validated assessment tools, such as the Mini-Mental State Examination, Montreal Cognitive Assessment, Clinical Dementia Rating, and Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), are commonly used. In the preclinical AD stage, elderly people are asymptomatic with normal cognitive performance, but adverse molecular changes in the brain may have accumulated significantly, which may lead to subsequent disease development.¹

Conversion from mild cognitive impairment to Alzheimer's disease

Not all subjects with MCI convert to AD. A meta-analysis revealed that the cumulative proportion of subjects with MCI who progressed to AD was 33.6% in studies conducted in specialist clinical settings and 28.9% in population studies.¹⁰ The adjusted annual conversion rates from MCI to AD were 8.1% and 6.8% in specialist settings and population studies, respectively. In Hong Kong, 15.9% of subjects with MCI had developed dementia at the end of a 2-year follow-up, according to a prospective study.¹¹ Subjects with MCI were more prone to AD progression if they had the risk factors of *apolipoprotein E* (*APOE*) $\epsilon 4$ allele, abnormal cerebrospinal fluid (CSF) tau level, hippocampal and medial temporal lobe atrophy, entorhinal atrophy, depression, diabetes, hypertension, older age, female



sex, lower Mini-Mental State Examination score, or higher ADAS-Cog score.¹² Some of these factors will be further elaborated in the next section.

Risk and protective factors in Alzheimer's disease

Late-onset AD has contributions from both genetic and environmental factors. Genetics predisposes

individuals to susceptibility to AD before birth. Environmental exposure modifies the risk of disease development. In addition, co-morbidity of AD with other diseases appears to occur frequently, probably due to interactions between disease pathways.

Genetic factors

The estimated heritability of AD ranges from 60% to 80%.¹³ Among the reported AD-associated genetic variants, the APOE $\epsilon 4$ allele is most prominent. In Caucasians, the odds ratios (ORs) of developing AD for individuals carrying one and two copies of $\epsilon 4$ allele have been reported as 2.8 and 11.8, respectively.¹⁴ Comparable results have also been obtained in Chinese people, with ORs of 3.1 and 11.7, respectively.¹⁵

The population frequency of the $\epsilon 4$ allele is relatively low in Chinese people (Fig a), particularly Southern Chinese people (Fig b). Among patients with AD, the allele frequencies of $\epsilon 4$ vary geographically, with the lowest frequency observed in Chinese patients (heterozygous: 32.8%; homozygous: 5.5%) [Fig c].¹⁶ This observation indicates potential variation in the genetic makeup of patients with AD in different ethnic groups. The relatively low $\epsilon 4$ allele frequency in Chinese patients with AD also suggests the existence of genetic factors in addition to $\epsilon 4$ allele in the Chinese population.

Genome-wide association studies (GWASs) allow the identification of disease-associated variants without *a priori* hypotheses about potential candidates. More than 10 novel genetic markers for AD have been identified by GWASs thus far. They have modest effect sizes (ORs around 1.2, or 0.83 for alleles with protective effects). Meta-analyses of validation studies have confirmed the contributions of *CR1* (rs6656401)¹⁷ and *CD33* (rs3865444)¹⁸ to AD susceptibility in Chinese people. We have also retrieved relevant articles from PubMed about each of the GWAS-identified single nucleotide polymorphisms (SNPs) (using the keywords "Alzheimer's disease", "Chinese", and the gene name or SNP identifier) and conducted a meta-analysis (methodology is shown in the online supplementary Appendix). We found a significant association of rs610932 in the *MS4A* gene cluster in Chinese patients with AD (Fig S1a). Negative results were obtained for other reported SNPs (Fig S1b-f).

Recent advances in next-generation sequencing have allowed investigation of rare variants on a genome-wide scale with single-base resolution. Using this technology, a rare missense mutation in *TREM2* (rs75932628), which has an allelic frequency of 0.64%, was found to confer a significant risk of AD in Caucasians (OR: 2.9).¹⁹

In the future, large-scale GWASs focusing on Chinese patients would be worthwhile, to facilitate comprehensive identification of novel Chinese-

specific SNP markers. This represents an important medical research area for Hong Kong/China.

Environmental factors

Diet

The traditional Mediterranean diet is widely accepted as optimal for health. Higher adherence to this diet is associated with reduced total mortality and incidence of cardiovascular, neoplastic, and neurodegenerative diseases. The Mediterranean diet is characterised by high intake of vegetables, legumes, fruits, nuts, and cereals; moderate consumption of fish; low to moderate intake of dairy products; olive oil as the major source of fat; low consumption of meat; and regular but moderate intake of wine during meals. With regard to cognitive health, greater adherence to the Mediterranean diet has been related to better cognitive function and lower risk of AD.²⁰ Among older Chinese women, the “vegetables-fruits” dietary pattern has been associated with reduced risk of cognitive impairment. It includes frequent intake of vegetables, fruits, soy, and soy products and low consumption of fats and oils.²¹ This shares some food items with the Mediterranean diet and may suggest the potential importance of foods with anti-oxidant and anti-inflammatory properties for improvement of cognitive health.

Sleep

Sleep disturbances are common in patients with AD—difficulty falling asleep, more disrupted nocturnal sleep, and increased wakefulness after sleep onset. These lead to reduction of total sleep time and excessive daytime sleepiness.²² Sleep disturbances can result from neurodegenerative changes and emergent AD, and conversely, they can increase the risk of AD. Increased sleep fragmentation has been related to lower baseline cognitive performance and a more rapid rate of cognitive decline.²³ Animal studies have revealed a potential mechanism of the influence of sleep on AD. During sleep, there is more convective exchange of CSF and interstitial fluid in the brain due to increased interstitial space surrounding brain cells.²⁴ This convective flux increases clearance of A β peptides and other toxic compounds compared with that during wakefulness. Poor-quality or insufficient sleep may slow down the removal of neurotoxic substances from the brain, leading to increased susceptibility to AD. This reciprocal relationship between sleep and AD forms a vicious cycle that may cause further pathological changes in patients.

Physical activity

Physical activity attenuates the risk of cerebrovascular diseases and improves attention, processing speed, executive function, and memory. Moreover, aerobic

exercise reversed age-related volume loss of the hippocampus in older adults without dementia.²⁵ Any frequency of moderate exercise performed in midlife and late life has been shown to reduce the risk of MCI (ORs: 0.61 and 0.68, respectively).²⁶ In a randomised controlled trial on older adults with memory problems, subjects assigned to an intervention group that performed moderate-intensity physical activity over a 6-month period showed improvement in ADAS-Cog scores, and such effect was sustained even after 18 months.²⁷ Taken together, studies have indicated a positive impact of physical activity on cognitive function, probably via improving cerebral metabolism, circulation, and endurance towards oxidative stress. All of these are important in brain plasticity and thus potentially prevent AD.

Cognitive reserve

This hypothesis proposes that individuals with greater cognitive reserve can tolerate more pathological changes, thus delaying the onset of AD. However, at the time of onset, these individuals may show more rapid cognitive decline because more pathological changes have been accumulated.²⁸ With greater cognitive reserve, the brain may be more resilient to cognitive damage or use compensatory networks more effectively when coping with pathology. Education is a major contributor to cognitive reserve. Higher education has been shown to reduce the risk of dementia and protect against further cognitive decline for an additional 7 years after the first signs appear, as compared with less-educated counterparts.²⁹ Occupational attainment and engaging in leisure activities also reduce the risk of developing dementia.²⁸

Co-morbidity with other diseases

Diabetes mellitus

The incidence of AD is 50% to 100% higher in people with type 2 diabetes mellitus (T2DM) than that in those without.³⁰ Higher blood glucose level has been associated with increased risk of dementia, even among people without T2DM.³¹ The pathological features of T2DM and AD are similar in many ways. While T2DM is characterised by aggregation of islet amyloid polypeptide in the pancreas and loss of β -cells, A β plaques and neuronal loss occur in the brains of patients with AD. Impairment of insulin signalling may be an underlying pathological process common to both diseases. Chronic hyperglycaemia, activation of inflammatory pathways, oxidative stress, and accumulation of advanced glycation end products could alter insulin receptor sensitivity and lead to peripheral insulin resistance in T2DM.³² A similar disturbance in the brain could account for the abnormalities in AD.

Depression

A meta-analysis revealed that late-life depression was associated with an increased risk of AD (OR: 1.65).³³ People with MCI were also depressed more often than normal controls. Reciprocally, patients with depression had higher deficiencies of executive function, memory, and attention.³⁴ Molecular mechanisms proposed to link depression with AD include activation of the hypothalamic-pituitary-adrenal axis and elevation of glucocorticoid production levels in depression. Prolonged dysregulation of these pathways can cause damage to the hippocampus.

Biomarkers for early detection of Alzheimer's disease

Imaging

Brain imaging enables characterisation of pathological progression. Hippocampal atrophy is a relevant marker of memory loss and can be assessed by structural magnetic resonance imaging (MRI). Reduction in hippocampal volume by 10% to 15% and 15% to 30% were found in people with amnesic MCI and AD, respectively, relative to healthy controls.³⁵ Longitudinal analysis has also shown a higher rate of atrophy in patients with AD and MCI-to-AD converters.³⁶ Amyloid imaging can be conducted using positron emission tomography (PET) with Pittsburgh compound B (PIB) tracer. Retention of ¹¹C-PIB correlates with brain amyloid level and can differentiate patients with AD from normal individuals. Among patients with MCI, those who exhibited higher ¹¹C-PIB retention were more likely to convert to AD than those with lower retention.³⁷ Brain glucose metabolism can be assessed using ¹⁸F-fluorodeoxyglucose (FDG) PET scanning. Reduction in glucose metabolism is associated with decline in cognitive ability. Glucose metabolic reduction has been shown to be particularly prominent in the medial temporal lobe of patients with MCI, while such reduction has been observed in the parietotemporal, frontal, and posterior cingulate cortices in patients with AD.³⁸ Imaging techniques to detect tau deposition, inflammation, and neurotransmitter alterations have also been developed and may serve as biomarkers after careful evaluation.

Cerebrospinal fluid characterisation

Cerebrospinal fluid is considered as a highly relevant sampling source for AD biomarkers because it directly interacts with the brain. Reduced levels of A β_{42} peptide in CSF have been detected in patients with AD, probably due to deposition into amyloid plaques in the brain.³⁹ Elevated levels of phosphorylated tau in CSF may reflect neurofibrillary

tangles in the brain, while total tau level is linked to cognitive decline. Integrating various biomarkers may further enhance the identification of elderly people who are at risk of developing AD. For example, a study in Hong Kong has shown that the AD-CSF Indices, an approach that combines A β_{42} , total tau, and phosphorylated tau, were able to differentiate patients with AD from controls without dementia with high sensitivity and specificity.⁴⁰ Another example utilised data extracted from whole-brain structural MRI and ¹⁸F-FDG PET scans, CSF biomarkers, and clinical variables including age, education, *APOE* genotype, and ADAS-Cog score; these were combined into a model that greatly reduced the misclassification rate of MCI-to-AD converters than that using clinical variables alone.⁴¹

Despite advances in brain imaging and CSF biomarkers for early detection, variability in measurement methods, the availability and cost of imaging, and the invasiveness of the lumbar puncture procedure impose limitations on their widespread use. Increasing efforts are being made to search for surrogate markers that serve similar functions.

Circulating biomarkers in blood

Blood samples can be obtained easily with standardised and minimally invasive methods. One of the earliest proposed blood biomarkers was homocysteine, the level of which is increased in AD.⁴² Recent studies have taken advantage of “omics” approaches to derive a signature of biomarkers. DNA methylation profiling of blood samples has revealed several AD-associated differential methylation sites⁴³ that may represent blood-specific epigenetic changes due to AD. The blood transcriptome approach revealed a blood RNA signature of 170 oligonucleotide probe sets that can differentiate patients with AD from controls with high sensitivity and specificity.⁴⁴ In another study, an RNA signature involving 48 genes was derived and applied to subjects with MCI to predict their cognitive changes.⁴⁵ Biomarkers may also be developed from the blood proteome, such as a panel of 18 out of 120 signalling proteins that serves as a classifier of AD.⁴⁶ Although further evaluations on the utility of proposed signatures are needed, these studies have demonstrated the feasibility of using blood as a sampling source for identification of surrogate AD biomarkers for early detection.

Current treatment

Medications

Drugs approved for AD treatment include acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and an N-methyl-D-aspartate receptor antagonist (memantine). They slow down cognitive decline by targeting cholinergic

transmission and glutamate release in the brain, respectively. Antidepressant, antipsychotic, and anti-anxiety drugs can be prescribed for behavioural symptoms.

Non-pharmacological intervention

Cognitive stimulation improves both general cognition and specific cognitive domains, such as attention and memory. Cognitive interventions are also beneficial to elderly people with MCI, with improvements to memory and delay of cognitive decline. Among the cognitive approaches of cognitive stimulation, cognitive training, and cognitive rehabilitation, clinical guidelines have recommended cognitive stimulation for all people with mild dementia⁴⁷ because of its efficacy (standardised mean difference of 0.41 for cognition), which is similar to that of cholinesterase inhibitor medication.⁴⁸ Cultural appropriateness should be considered when applying evidence-based non-pharmacological interventions, particularly to older adults. Multimodal activities can be mapped against domains within the Chinese culture. For instance, Six Arts, a core set of Confucian philosophical teachings comprising six disciplines (rites, music, archery, charioteering, literacy, and numeracy), corresponds to the major mind-body functional domains of social functioning, music and rhythm, visuospatial skills, and fine motor skills.⁴⁹

Social and psychological management

Patients with AD require continuous, integrated health care after diagnosis. Families are the major care providers outside clinical or institutional settings. Caring for a patient with AD is associated with significant risks to the caregiver's health and well-being.⁵⁰ Stress and anxiety may arise when caregivers perceive that caregiving demands exceed available resources. Promoting help-seeking through increasing awareness, scaling up the supply of diagnostic and care services, and reducing barriers to access resources can enhance both social and psychological support to the patients and their caregivers. In addition, public education about dementia can reduce stigmatising attitudes and alleviate any hindrances to early help-seeking and intervention.⁵¹

In view of public expectation and demand, the Dementia Community Support Scheme, a pilot scheme funded by the Community Care Fund of Hong Kong, was launched in February 2017 to provide dementia-related community support services in District Elderly Community Centres.⁵² The scheme provides elderly people with health care, training, and support services based on their individual care plans to enhance their cognitive

function, knowledge of home safety, self-care ability, physical functioning, social skills, and adherence to medication instructions. It also provides caregivers with training and support services, such as stress management, knowledge about taking care of elderly people with dementia, counselling services, and formation of carer support groups to alleviate their burden.

Our recommendations

The ageing society of Hong Kong and the upcoming ageing of the population have motivated the preparation of a dementia-friendly community. Alzheimer's Disease International has defined a framework for dementia-friendly communities that includes the four components of people, organisations, partnerships, and communities and advocates timely diagnosis and post-diagnostic support by primary health care and appropriate professionals.⁵³ The World Alzheimer Report 2016 criticised the over-specialisation of overall dementia care and emphasised the role of primary care in early detection, diagnosis, disclosure, treatment, collaboration with social care, and continuing support to patients' families.⁵⁴ We propose that the medical community, government, universities, NGOs/charities, and industry in Hong Kong/China should collaborate closely to develop measures to cope with the medical and social impacts of AD.

Increase public awareness

The general public should be educated about the symptoms of dementia, including AD, to increase their awareness. Mass media, such as soap operas and television programmes, could be used for public education, while health care professionals will be key supportive information providers.

Early detection

Health education allows people to be familiarised with the symptoms of AD and initiate assessment when they suspect that their relatives have the disease, which facilitates early detection. Training for medical professionals needs to be focused on enhancing the perceptions of suitability and ability to arrive at a diagnosis and the value of doing so in a timely manner.⁵⁴

Prevention

The benefits of healthy diet, regular physical activity, sufficient sleep, and cognitive stimulation for cognitive health should be promoted. The public should also be aware that diseases such as T2DM and depression can increase the risk of developing AD. The Department of Health and NGOs could collaborate on promotion of preventive measures.

Diagnosis with genetic biomarker consideration

Identification of blood-based biomarkers may provide insight into the development of AD. Systematic and large-scale research is worthy of support, especially that on the identification of biomarkers that are unique to the Chinese population. Collaborations between academic institutions and industry will speed up research progress. A carefully designed plan should also be developed to ensure the appropriate utilisation of these biomarkers and environmental factors for early detection. Governmental support is essential to push forward the utilisation of research findings on AD diagnosis.

Potential therapeutics

Compounds targeting A β pathology, tau pathology, mitochondrial dysfunction, and neuroinflammation have entered clinical trials.⁵⁵ Keeping track of these trials can help to bring the latest information to the local community. Identification of genetic markers, aberrant gene expression patterns, and epigenetic profiles could provide insight on the aetiology of AD and thus may provide novel therapeutic targets. For example, a recent study using an AD mouse model revealed that interleukin-33 treatment could reverse synaptic plasticity and cognitive deficits.⁵⁶ Treatment with interleukin-33 reduced soluble A β and amyloid plaque deposition and decreased proinflammatory response in the brain. It may serve as a therapeutic candidate.

Continuous integrated care

A system of continuing care in the context of function preservation and living support must be easily accessible to patients with AD. It should guide the standards of patient care at different phases of the disease condition. A comprehensive integrated care programme can assist patients with AD in slowing down cognitive decline and preservation of function. It can also reduce unnecessary hospitalisation. Non-government organisations can help to moderate continual care pathways, such as caregiver training and support, day care, and residential services. Support and care for families and caregivers should also be readily available. Mutual help among patients, their families, and caregivers can enhance their coping ability with situations related to the condition.

An example: “Project Sunrise”

The myth of the inadequacy of primary care for dementia care in Hong Kong surrounds the accuracy of diagnosis, missing secondary diagnoses, accessibility of medicine, investigations, caseload, time, and remuneration. In the past 3 years, the Hong Kong Alzheimer’s Disease Association has

spearheaded a project named “Project Sunrise” at Tsuen Wan and Kwun Tong. The project trains family physicians in diagnosis of early AD and alerts them about unusual presentations that warrant further investigation and referrals. The resulting shortening of the period from seeking medical attention to diagnosis and initiation of treatment was demonstrated to be 2.1 months. The crux of the project lies in a pre-diagnostic assessment protocol and capacity building of primary care doctors and related health care professionals. Community awareness and training and service industries to be alerted about the needs of persons with dementia are other important elements of the project, which aspires to the dementia-friendly community concept. A Mental Health Review led by the Food and Health Bureau has investigated dementia-related needs and provided 10 recommendations in its 2016 report.⁵⁷ Moving forward, the task is shifting from secondary to primary care, and when a broad-based primary foundation is built, we will enter the era of task sharing, when early diagnosis and treatments are initiated promptly in the community. Longer-term case management for people with dementia and care paths to facilitate appropriate care can then be provided.

Supplementary information

Online supplementary information (Appendix) is available at www.hkmj.org.

Author contributions

Concept and design of study: CSM Au, JYN Lau, DLK Dai.

Acquisition of data: YN Chang, T Chung.

Analysis and interpretation of data: A Yee, NBY Tsui, LT Lau.

Drafting of the article: A Yee.

Critical revision of important intellectual content: M Fok, LT Lau, G Cheng, RYC Kwan, AYM Leung, JYN Lau, DLK Dai.

Acknowledgements

We thank Maggie Lee of Hong Kong Alzheimer’s Disease Association for discussion input; Prof Claudia Lai of the School of Nursing, The Hong Kong Polytechnic University for research coordination; Prof Terry Lum and Dr Gloria Wong of the Sau Po Centre on Ageing, The University of Hong Kong for discussion input about non-pharmacological interventions for Alzheimer’s disease; and Ms Polly Chan, Ms Connie Leung, Mr Nelson Li, and Ms Rebecca Shiu of Yan Oi Tong for valuable discussion about the potential roles of non-governmental organisations/charities in Alzheimer’s disease research.

Declaration

JYN Lau is the managing director of Avalon Genomics and a shareholder of its parent company, Avalon Biomedical Management. He is also an executive of Athenex Corporation and a board member of C-Mer Eye Care Holdings Limited, Porton Fine Chemicals, Aiviva, and Avagenex. All other authors have disclosed no conflicts of interest. All authors had full access to the data, contributed to the study, approved

the final version for publication, and take responsibility for its accuracy and integrity.

Funding/support

This work was supported by the Moonchu Foundation, a private donation from CSM Au, and The Hong Kong Polytechnic University (grant account number: 5.ZJL7).

Ethical approval

The Macau database was established with ethics approval from the Clinical Research Ethics Committee of the University Hospital, Macau University of Science and Technology. All subjects were recruited with written informed consent. All experiments were performed in accordance with the relevant guidelines and regulations.

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