UNIT NO. 1

OVERVIEW OF DEMENTIA

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ABSTRACT

Dementia represents a late stage of disease along the continuum of cognitive impairment. With the prevalence of cognitive dysfunction rapidly rising, there is an urgent need for early diagnosis and intervention. A thorough history, cognitive evaluation along with suitable investigational studies is necessary for early diagnosis. The ability to diagnose dementia at the earliest stages has been greatly improved with the use of biomarkers such as medial temporal atrophy on MR imaging and cerebrospinal fluid beta amyloid levels. The management of dementia requires a multidisciplinary approach. While acetyl cholinesterase inhibitors can slow cognitive deterioration, newer disease modifying drugs which target the underlying pathology are at advanced levels of testing.

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INTRODUCTION

Dementia is a brain disorder that affects millions of people, mostly older adults. Dementia should be viewed as a "late stage" in the continuum of cognitive difficulties and hence clinicians should aim to identify the prodromal stages of dementia. The diagnosis of dementia requires the presence of dysfunction in memory and other cognitive domains which are progressive, resulting in a decreased level of function[1]. At the stage of dementia the pathological changes in the brain are often well established and profound. Alzheimer's disease (AD) is the most common cause of dementia and the pathological hallmarks of AD include Beta-amyloid plaques and neurofibrillary tangles.

There is evidence to show that these pathological changes begin many years prior to the onset of dementia[2]. The challenge for physicians would be to identify subtle changes in cognition when the pathological changes are only beginning to develop. These earlier stages of disease have been described using several terminologies including mild cognitive impairment (MCI) and cognitively impaired not demented (CIND)[3,4]. It is crucial that clinicians are able to identify these earliest stages of cognitive impairment as intervention is most likely to be effective when initiated at this early stage.

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EPIDEMIOLOGY

In Singapore the prevalence of dementia and cognitive disorders is likely to increase rapidly over the coming years. We have the fastest ageing population in the Asia-Pacific region with15-20% of the total population being above the age of 65 by the year 2030. At the present time it is estimated that we have about 25 thousand patients with dementia and this number is set to increase to 53 thousand by 2020[5-7]. The prevalence of MCI is presently unclear but based on western prevalence rates of 18.5% at age 50-60 and 35-38% at age greater than 60, it is estimated that we currently have 75-100 thousand subjects with MCI[8-9].

ETIOLOGY AND RISK FACTORS

Dementias are largely neurodegenerative conditions including Alzheimer's disease, Frontotemporal dementia (FTLD), dementia associated with Parkinsonism and Creutzfeldt-Jakob disease. However reversible causes such as normal pressure hydrocephalus, neurosyphilis, B12 deficiency, folate deficiency and Hashimoto's encephalopathy need to be considered and excluded. AD represents the most important cause of dementia followed by vascular dementia. The main pathological hallmarks of AD are the Beta-amyloid plaques and neurofibrillary tangles. The risk factors for the development of this pathology include advanced age, family history, vascular risk factors and APOE4 genotype[10-11]. It is also increasingly evident that AD and vascular pathology often coexist and manifests as mixed dementia. Optimization of vascular risk factors such as diabetes mellitus and hypertension is believed to slow the amyloid cascade resulting in stabilization of cognitive function among patients with vascular cognitive impairment.

CLINICAL PRESENTATION

Evaluation of a patient with cognitive symptoms must begin with a thorough history and physical examination. Short term memory is often affected early in the course of dementia and patients may present with difficulty remembering names, misplacing their personal belongings or for being repetitive. Long term memory is often relatively preserved in the early stages of dementia. Problems with visuospatial function may manifests with patients having difficulty finding their way about even in familiar environments.

As the dementia progresses, deficits in language emerge

with most patients having difficulty finding words and may resort to using alternative words which are simpler. Problems with comprehension are often observed in the moderate to severe stages of dementia. Difficulties in executive function manifests with problems in planning, organizing and judgement. Patients may have difficulty with routine tasks such as cooking and driving and are often unable to acquire new skills such as computing. It is always preferable that the cognitive symptoms are corroborated by a family member.

Cognitive evaluation across a range of domains including memory, language, visuspatial function and executive function needs to be performed. Cognitive tests such as the mini mental state examination (MMSE), frontal assessment battery (FAB) and the Montreal cognitive Assessment (MoCA) are valuable in identifying deficits across domains[12,13]. Adequate emphasis on mood and behaviour is also crucial. Screening for depression with standardized questionnaires should be routinely performed.

While clinicians need to be familiar with the typical manifestation of AD, which represents the most important cause of dementia, it is also important to recognize the manifestations of the less common causes of dementia. Patients with frontotemporal dementia for instance may have relatively preserved short term memory but may present with behavioral changes in the form of disinhibited behavior or alternatively they may present with a progressive aphasia. Patients with dementia with Lewy body classically present with vivid visual hallucinations, fluctuating cognition and extrapyramidal features such as tremors or bradykinesia.

INVESTIGATIONS

We are now fortunate to have a wide range of investigational tools including CT brain, MRI brain, PET scans, cerebrospinal fluid (CSF) studies and genotyping. With the availability of such tools which have been demonstrated to have reliable sensitivity and specificity the diagnosis of dementia and MCI should move away from being a "diagnosis of exclusion" to a "diagnosis of inclusion". Structural brain imaging with MRI is useful to evaluate for hippocampal atrophy which is the hallmark of AD while disproportionate atrophy of the frontal lobes may be indicative of frontotemporal dementia[14]. MRI is also valuable in demonstrating white matter disease and lacunar infarctions which are suggestive of vascular dementia. Special MRI sequences such as the diffusion weighted imaging (DWI) can demonstrate diffusion abnormalities which are highly specific for Creutzfeldt-Jakob disease. CSF studies of beta amyloid, total tau and phospho-tau have been demonstrated to have a high specificity for the diagnosis of AD. CSF examination is also valuable in managing reversible conditions such as encephalitis and autoimmune encephalopathies. PET scans also can help distinguish between AD and FTLD based on the pattern of glucose hypometabolism.

MANAGEMENT

Management of cognitive disorders requires a multidisciplinary approach including pharmaceutical and non-pharmaceutical management of the patient, caregiver support and provision of long term nursing care. The mainstay of phameucitical management includes acetyl cholinesterase inhibitors[15]. Patients who are initiated on AchEIs should be offered the highest tolerable dose for an adequate length of time. Switching from one AchEI to another or switching from an oral formulation to a patch delivery may need to be considered for patients who develop intolerable side effects.

Memantine, a NMDA receptor antagonist may be useful for patients with moderate to severe AD. In view of the increased risk of cardiovascular and cerebrovascular events with both typical and atypical antipsychotics, these drugs should be reserved for patients with severe behavioral symptoms. Several disease modifying agents are now in phase 3 clinical studies. They target the amyloid cascade or the production of tau and preliminary studies have demonstrated promising results.

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LEARNING POINTS

- **Cognitive dysfunction manifests along a continuum ranging from mild cognitive impairment to dementia.**
- **The strongest risk factors for AD are age, family history and APOE genotype.**
- **While dementia is often secondary to a neurodegenerative pathology, other reversible causes such as normal pressure hydrocephalus needs to be excluded.**
- **Investigational tools such as MRI and CSF studies can help establish a diagnosis of mild cognitive impairment and early dementia.**
- **Disease modifying agents are at advanced stages of investigation and have shown promising preliminary findings.**