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Update on Dementia

Introduction

Dementia is a loss of global cognitive function in a previously unimpaired person beyond what might be expected for normal ageing. It is normally required to be present for at least 6 months for a diagnosis to be made. Dementia can result in significant psychiatric, social and physical disability. There are numerous causes, a small percentage which are reversible. This article concentrates on the more common aetiologies and discusses their management. This includes aids to diagnosis, pharmacological intervention and newer disease modifying therapies.

The Problem

There are currently 750,000 people in the UK with dementia. This is expected to increase to around 1.7 million by the year 2051. The cost is around £25 billion per year. (1) Dementia is not merely a memory problem but also can affect behaviour, thoughts, feelings and activities. As the disease progresses, patients may suffer from neglect and increasing physical problems leading to institutional care.

In February 2009, the National Dementia Strategy was published by the Department of Health. (2) This aims to improve early diagnosis and support services for patients and carers. Early diagnosis is vital and referral to specialist services is an important part of this strategy. Currently only a third of people with dementia receive a diagnosis.

Differential diagnosis

There are many causes of cognitive impairment, too many for the scope of this paper.

The short-term syndrome of delirium (lasting days or weeks) can be confused with dementia. Fluctuations in alertness or consciousness may indicate delirium. Patients can display hyper- or hypomotor activity. Dementia is a common predisposing risk for delirium. Visual hallucinations may also be present. (3)

Depression is common in older people. The presence of low mood with global memory loss and poor concentration is often present. There may be associated biological features such as weight loss, early waking and withdrawal.

Mild cognitive impairment (MCI) is seen as a prodrome to the development of dementia. It is characterised by the mild episodic impairment of anterograde memory with no effect on activities of daily living (ADL'S). 50% of patients with MCI develop dementia. Verbal fluency is assessed by naming as many objects with the same letter in 60 seconds. This test has been shown to be the most sensitive for identifying patients with MCI who may develop Alzheimer's disease.

Causes of Dementia

Mixed dementias are common which often leads to difficulties when drug treatments are being considered.

There are 10% reversible causes of dementia that include vitamin deficiencies and metabolic disorders.

Alzheimer's disease (AD)

AD is the commonest cause, affecting 60% of dementia sufferers. It is a neurodegenerative type dementia. The average time to diagnosis is 1-2 years. The onset is insidious with the patient lacking insight.

Anterograde memory is affected first, speech and language problems develop and conversation is often repetitive. Semantic fluency (the naming of animals) is more impaired than verbal fluency. The ability to learn new skills becomes lost and disorientation in time and then place is common. (4), (5).

Vascular Dementia (VaD)

This encompasses a number of forms of dementia, usually in patients with Cerebrovascular disease and have vascular risk factors.

Symptoms depend on the area brain involved, either from a single sudden event or more insidious in patients with small vessel disease.

Patients complain of a general slowing of thought processes and memory. Disturbances in speech (verbal fluency) gait and perception are all common. Depression is more common due to retained insight.

Dementia with Lewy bodies (DLB)

DLB is the second most common form of neurodegenerative type dementia. In DLB, symptoms of depression with altered perception occur early. This is followed by a progressive dementia with inattention, fluctuating cognition and hallucinations. Parkinsonism develops later, usually after one year.

Idiopathic Parkinson's disease (IPD)

The overall prevalence of dementia in IPD is 30-40% with over 80% showing some degree of cognitive impairment after 8 years of the disease. It is usually differentiated from DLB by the initial predominance of motor symptoms. Executive function is most notably affected. (6) Parkinson's plus syndromes such as Progressive Supranuclear palsy and Corticobasal degeneration also coexist with dementia.

Frontotemporal Dementia (FTD)

This condition includes a number of subtypes of dementia affecting the frontal and temporal lobes. FTD tends to present with behavioural disturbance and personality change. Mini mental state examination (MMSE) is often preserved, as it is not good at identifying central executive function. (7) It is the second most common cause of dementia in the young.

There are a number of sub types, which are dependent on the area of the cortex involved including Primary progressive aphasia and Frontal dementia.

Diagnosis

History taking is vital and this includes collateral input from carers and family.

Cognitive assessment tools.

There are many tools that can be used in everyday practice.

The Mini-mental state examination (MMSE)

It is probably the oldest and most commonly used. It can be used to monitor cognition over time. The MMSE has 82% specificity in detecting dementia. It assesses attention and concentration, orientation, short and long-term memory, language and executive function. (8)

A score of 26-30 may be normal. 20-25 indicated mild impairment whereas 10-20 represents moderate dementia.

Addenbrooke's Cognitive Examination Revised (ACE-R)

The ACE-R encompasses the MMSE and includes further tests on antegrade and retrograde memory as well as attention, fluency, language and visuospatial skills in more detail. Scores are out of 100 with sub scores across the above domains (9). It also includes the Clock Drawing Test (CDT) (10). Patients are asked to draw numbers on a pre-drawn circle to form a clock face. Ten minutes after eleven has been shown to be the most sensitive time. The CDT evaluates frontal lobe and visuospatial function which are not accurately assessed by the MMSE.

Cambridge Cognitive Examination (CAMCOG) using CANTAB

CANTAB is an exciting new tool in the assessment of cognitive function. It uses touch screen technology and has a large database to compare results. It is available in many different languages, which makes it easy to use in our multi-cultural society.

There are many other tools that are used including AMTS (abbreviated mental test score), CASI (cognitive abilities screening instrument), GOPC (general practitioner assessment of cognition) and so on.

Investigations

The cognitive assessment tools are obviously useful in assessing cognitive impairment but a mixed neurodegenerative and vascular picture are often present. Imaging can play an important role in differentiating the different types of dementia. A routine blood screen is required and this includes FBC, U/E, LFT's, Calcium, TSH, Glucose, B12, Folic acid, Syphilis serology and occasionally HIV status.

Imaging

CT and MRI are used commonly. They can rule out any reversible causes. Vascular changes may be present which would support an underlying VaD.

There are a number of changes seen in Alzheimer's disease, which include Hippocampal atrophy and median Temporal lobe atrophy (10). Fronto-Temporal atrophy on MRI suggests FTD.

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) show parieto-temporal hypoperfusion in AD whereas occipital hypoperfusion is more predominant in DLB. Fluorodeoxyglucose (FDG) is a defining biomarker in clinical dementia. PET/CT using FDG has a major role in characterising AD, DLB and FTD.

CSF examination

CSF examination has been the focus in research on diagnostic biomarkers for AD. The three markers, total tau (T-Tau), phospho-tau (P-tau) and the 42 amino acid form of β - amyloid have been evaluated in many studies. These biomarkers should reflect the central pathogenic processes in the brain i.e the synaptic and axonal

degeneration, the aggregation of β -amyloid ($A\beta_{42}$) with subsequent deposition in plaques, and the hyperphosphorylation and ubiquitination of tau and subsequent formation of tangles.

In summary, there is a moderate to marked increase in total tau and phospho-tau with a moderate to marked decrease in $A\beta_{42}$. The diagnostic performance of these CSF markers seems to be highest in the differentiation between AD and normal ageing, depression, alcohol dementia and Parkinson's disease. (11)

Treatment

Concentrating on pharmacological interventions but recognising the valuable input of carers, support groups, exercise programmes etc provide.

Cholinesterase inhibitor therapy.

NICE has recently changed its guidelines in relation to the use of Donepezil, Galantamine and Rivastigmine(12). Treatment should be commenced with the lowest cost drug. Mild AD (MMSE 21-26) is now an indication for treatment. The Cochrane review of Cholinesterase inhibitors concluded that trials have shown modest benefits on patient's cognition and global clinical state (13). There is no evidence to suggest a difference of efficacy between the three drugs.

However, a decrease in a MMSE score of 1 may be the difference in keeping patients in their own home or ending up in institutionalised care.

There is no evidence of benefit in patients with MCI or VaD.

The most common side effects are nausea, vomiting and diarrhoea. They should be used with caution in patients at risk of

gastrointestinal bleeding as well as left bundle branch block and unexplained syncope. Urinary retention, cardiac conduction disturbances including prolonged QTc are less common.

Memantine is N-methyl-d-aspartate (NMDA) receptor antagonist, which blocks the action of glutamate. It is recommended by NICE for the treatment of severe AD (MMSE <10) and moderate disease if Cholinesterase inhibitors are not tolerated. It is also useful in behavioural and psychological problems associated with dementia. The combination with Cholinesterase inhibitors is currently undergoing a trial by the Medical Research Council and Alzheimer's society.

Other drugs

Anti- psychotics are often used in patients with dementia. In the UK, around 144,000 sufferers are unnecessarily prescribed anti-psychotics. Low doses are advised after evaluating the risks and benefits. Anxiolytics are avoided as they can cause agitation. Anti-depressants are useful in treating the cognitive and behavioural symptoms of depression in Alzheimer's disease. Trazadone, a tricyclic related antidepressant, is often useful for treating agitation.

The Future

Disease modifying drugs aiming to immunologically remove cerebral amyloid and phosphorylated tau are under consideration. Monoclonal antibodies against beta amyloid are also under investigation (15).

Dementia is a complex disease, which has major implications for patients, carers and family. Early referral and diagnosis is essential for both Pharmacological and non-Pharmacological treatment.

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