Practical neurology — 6

Memory loss

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MJA 2012; 196: 114–117
doi: 10.5694/mja11.11399

Previous article in this series "Recurrent unresponsive episodes and seizures" in MJA 2011; 195: 586–591

The grading system for recommendations in this article is described in MJA 2011; 195: 328

Alan's story

Alan, a 72-year-old retired solicitor, presented to his general practitioner with his wife. The couple were concerned about Alan's increasing forgetfulness. He had been losing objects about the house, particularly over the past year, and his wife had noticed that he was becoming more forgetful in conversations with family and friends. Despite this, Alan had continued to manage his daily routines well. He had also been responsible for managing his family's finances, and he had continued to drive and to play weekly games of bridge and golf. His medical history was unremarkable. He had no cardiovascular disease other than hypertension (treated since the age of 50 years) and had low levels of cholesterol and glucose. He had never smoked, he drank two large glasses of red wine (about 35 g of alcohol) per day, and he led a sedentary lifestyle.

On examination, Alan was in sinus rhythm and his blood pressure was 160/90 mmHg (lying and standing). He scored 28 points out of 30 on the Mini-Mental State Examination (MMSE), with points lost for date (2 days out) and recall of only two of three objects after 5 minutes. Results of the rest of the neurological examination were normal.

Due to the couple's concerns about the cause of the cognitive decline, Alan was referred to the local memory clinic, which was run by a geriatrician and psychogeriatrician. Assessment of his cognitive function showed that he had great difficulty in retaining new information. He also had mild depressive features (pervasive sadness, decreased pleasure in relationships and hobbies, and difficulty getting to sleep), which he attributed to a loss of life roles since retiring. He was prescribed citalopram 20 mg daily to treat his depression and a detailed neuropsychological assessment was organised for 2 months later. Other investigations included blood tests and a non-contrast computed tomography (CT) scan of the head (Box 1). Generalised cerebral atrophy was evident on the CT scan, but results of the blood tests were normal.

Two months later, Alan reported improved mood, but results of the detailed neuropsychological assessment showed that his performance on visual and verbal memory tests was 1.0 standard deviation below population norms, despite his overall cognitive abilities being mostly in the superior range. Alan and his wife were pleased about his improved mood, and they asked about other tests that could clarify his diagnosis and strategies for preventing further memory loss. Three-monthly follow-up visits with his GP were scheduled.

Summary

- Most older people with memory loss do not have dementia. Those with mild cognitive impairment are at increased risk of progressing to dementia, but no tests have been shown to enhance the accuracy of assessing this risk.
- Although no intervention has been convincingly shown to prevent dementia, data from cohort studies and randomised controlled trials are compelling in indicating that physical activity and treatment of hypertension decrease the risk of dementia. There is no evidence that pharmaceutical treatment will benefit people with mild cognitive impairment.
- In people with Alzheimer's disease, treatment with a cholinesterase inhibitor or memantine (an *N*-methyl-D-aspartate receptor antagonist) may provide symptomatic relief and enhance quality of life, but does not appear to alter progression of the illness.
- Non-pharmacological strategies are recommended as first-line treatments for behavioural and psychological symptoms of dementia, which are common in Alzheimer's disease. Atypical antipsychotics have modest benefit in reducing agitation and psychotic symptoms but increase the risk of cardiovascular events. The role of antidepressants in managing depressive symptoms in patients with mild cognitive impairment is uncertain and may increase the risk of delirium and falls.

APPROACH TO THE PROBLEM

Interpreting the clinical findings

Alan has evidence of mild memory impairment, but there is no clear decline in his general function or associated impairment of other higher cortical functions. Consequently, he does not fulfil standard diagnostic criteria for dementia[2] (Box 2). Yet, his memory loss and cognitive profile are not consistent with his educational attainment and occupation. Mild cognitive impairment (MCI) is a transitional zone between normal cognitive function and clinically probable dementia. Although diagnostic criteria vary for MCI, they are essentially common with regard to their aim and theoretical framework in referring to a cognitive state which is "at risk" of dementia — most commonly that of Alzheimer's disease. If Alan's performance on memory tests had been more than 1.5 standard deviations below population norms, he would have fulfilled the criteria for a tentative diagnosis of "amnestic MCI".[3] (Seven per cent of the general population would score lower than 1.5 standard deviations below the norms on these tests, and 16% below 1.0 standard deviations.) People with MCI are thought to convert to dementia at a greater rate than their peers, and there is some evidence that people with deficits in multiple cognitive domains (memory, language, praxis, executive functions, etc) are at greater risk. Nonetheless, a large proportion of people with MCI will never develop dementia, and many may improve.

1 Useful investigations to assess people with complaints of cognitive decline[1]

Blood tests

- Full blood count, erythrocyte sedimentation rate, and tests for electrolyte levels, renal function, liver function, thyroid function, vitamin B_{12} levels, red cell folate levels and calcium levels
- Syphilis serology testing, especially in areas where syphilis is endemic
- HIV serology testing if appropriate

Imaging

- Computed tomography or magnetic resonance imaging scans of the head to exclude intracranial lesions, hydrocephalus, subdural or extradural haematomas, cerebral infarction or haemorrhage ◆

DIFFERENTIAL DIAGNOSES

Most older people with memory loss do not have dementia. Depression is clearly a possible diagnosis in Alan's case, as depressive symptoms can mimic dementia. People who have a first episode of depression in late life have a higher risk of risk of developing dementia. Although consumption of large amounts of alcohol may be associated with alcohol-related dementia, consumption of small amounts is associated with decreased risk of dementia.[1] In Alan's case, a lack of rapid onset, lack of other neurological signs and relatively normal results of brain imaging rule out encephalopathy, brain tumour and stroke.

APPROPRIATE USE OF INVESTIGATIONS

Alan underwent detailed neuropsychological testing because of his difficulty in retaining new information, and because of the couple's strong concerns about cognitive decline. He also had blood tests and a CT scan to exclude the presence of reversible causes of dementia or cognitive impairment, such as communicating hydrocephalus, hypothyroidism, and renal and liver dysfunction (Box 3). Although such investigations rarely lead to interventions that result in the reversal of cognitive deficits, they are considered best practice[4] and can be routinely organised by GPs. The management of depression may mitigate some of the apparent cognitive deficits. Of people who present with reversible dementia and show improvement, almost half are affected by depression or adverse effects of medications.

There are currently no laboratory and imaging tests that are helpful in predicting the course of MCI or useful for identifying people who will develop dementia. There is some interest in tests that may indicate an increased risk of Alzheimer's disease (eg, low amyloid-β1-42 or increased total tau protein in the cerebrospinal fluid, or bilateral reduction of glucose metabolism in temporal and parietal regions), but these have no clinical utility at present. Although positive results of such tests may be associated with an increase in risk of dementia, this increase has not been quantified in specific clinical situations, such as Alan's.

2 *International statistical classification of diseases and related health problems 10th revision* criteria for dementia[2]

Dementia (F00–F03) is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. This syndrome occurs in Alzheimer's disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain. ◆

FINAL DIAGNOSIS

Alzheimer's disease

Alan was seen at the memory clinic 1 year later. He reported walking for 30 minutes with his wife daily, and felt that he had good energy and was in good spirits. His blood pressure was 130/80 mmHg lying and 120/80 mmHg standing. He reported good adherence to antihypertensive medication. His MMSE score was 27/30 (one point less than previously but within measurement error). A neuropsychological review revealed a stable cognitive profile — slightly better visual memory, slightly worse verbal memory, and the other cognitive functions remaining mostly in the superior range. Alan's improvement was attributed largely to his regular physical activity. He elected not to return to the memory clinic for the time being, but chose to continue to be seen by his GP at 3-monthly intervals.

A further review at the memory clinic 2 years later revealed some functional decline: Alan had been managing his finances less efficiently (he had had trouble keeping track of his investments and bills), and he had recently got lost in his own neighbourhood when driving home from a night out playing bridge. His ability to play bridge had deteriorated and his MMSE score was 24/30. Neuropsychological testing revealed decline in visual and verbal memory, impaired verbal fluency and set-shifting (the ability to flexibly move from one pattern of thinking to another), and decreased working memory. A new CT scan of the head, organised by his GP, showed no obvious changes compared with the earlier scan.

A diagnosis of dementia of the Alzheimer's type was made. An electrocardiogram showed no evidence of bradycardia or conduction defects, which would be a relative contraindication to cholinesterase therapy. He was commenced on donepezil 5 mg at night. After 2 weeks, some initial mild nausea had abated but he had been troubled by vivid nightmares. Donepezil administration was changed to mornings and 2 weeks later the dose was increased to 10 mg. After 2 months of donepezil therapy, Alan and his wife felt that he may be slightly better — with slightly more energy and better concentration. His MMSE score was 26/30, and he was returned to the care of his GP.

Making the diagnosis of Alzheimer's disease

It took 3 years for Alan to "convert" to dementia, which is typical. The yearly conversion rate for people who present with MCI to memory clinics is about 15%.[5] People with MCI who do not present to memory clinics show a lower conversion rate, and as many as 20% of them improve or no longer fulfil the research criteria for the diagnosis of MCI after 1 or 2 years.[6,7]

The clinical assessment of a patient with cognitive impairment demands a structured approach. The first objective is to determine the pattern of cognitive and behavioural deficit. While the MMSE is the most widely known and "tolerably useful" brief structured method of assessing cognitive function, it is insensitive to MCI and strongly influenced by educational level, culture, anxiety and neurological impairment, particularly language and deafness. Moreover, it tends to focus on memory, language

3 Potentially reversible causes of cognitive impairment or dementia

- Depression
- Adverse effects of medications, especially those with anticholinergic or psychotropic properties (eg, anticonvulsants and benzodiazepines)
- Communicating hydrocephalus
- Sleep apnoea
- Hypothyroidism
- Metabolic abnormalities, such as hypercalcaemia, renal dysfunction and liver dysfunction
- Vitamin B_{12} and other vitamin deficiencies
- Neurosyphilis (especially in areas where syphilis is endemic)
- HIV infection ◆

and literacy skills, at the expense of non-dominant visuospatial skills and, apart from the mental tracking associated with the "serial sevens" task, includes no assessment of judgement and reasoning (and social behaviour) processed in the frontal lobe. Thus, the MMSE often needs to be supplemented by other tests and supporting history from a reliable family observer. The second objective is to determine any involvement of the nervous system more generally (eg, impaired vertical gaze, dysphasia, tremor, bradykinesia, pyramidal signs). Finally, the general examination should not be overlooked as clues to aetiology of cognitive impairment may lie outside the nervous system (eg, liver disease, sleep apnoea, drugs).

Alzheimer's disease, vascular dementia, frontotemporal dementia and dementia with Lewy bodies are the most common dementias, both in older people and younger adults. Although all have some impairment of episodic memory, there is wide variation in the degree of associated changes in behaviour, personality and language abilities, as well as the course of these conditions due to differences in the underlying neuropathological conditions. The current view is that people with the clinical picture of Alzheimer's disease present with overlapping neuropathological conditions (eg, neurofibrillary tangles and senile plaques together with cerebrovascular changes), but the insidious onset and lack of focal neurological signs in Alan's case make a predominant vascular dementia less likely. The absence of visual hallucinations, fluctuating course and extrapyramidal signs suggest that the diagnosis of dementia with Lewy bodies is improbable.

MANAGEMENT

Managing MCI and the risk of dementia

No medication has been shown to definitely alter the prognosis of MCI. A Cochrane review has shown no overall effect for donepezil, the cholinesterase inhibitor that is most widely used (Level A evidence).[8] Although there is insufficient evidence from randomised controlled trials (RCTs) to support the systematic use of certain interventions to prevent dementia, data from cohort studies and RCTs are compelling in indicating that treatment of hypertension and increased physical activity decrease the risk of dementia (Level B evidence).[1] There is also observational evidence that cessation of smoking potentially decreases the risk of dementia (Level C evidence).[1] The evidence regarding cognitive stimulation in the prevention of dementia is far from compelling.[1]

FACT OR FICTION?

Fact: It is *true* that lifestyle modifications, particularly increased physical activity, reduce the risk of dementia.
Fiction: It is *not true* that cholinesterase inhibitors alter the progression of Alzheimer's disease. ◆

4 Neuropsychologist assessing a patient with memory problems

Role of memory clinics

Memory clinics funded by state health services, such as the Cognitive, Dementia and Memory Service throughout metropolitan and regional Victoria, are becoming increasing available. These clinics not only allow team-based multidisciplinary assessment of people with memory loss (typically with a geriatrician, psychogeriatrician, neurologist, neuropsychologist, nurse, social worker, occupational therapist and speech pathologist [Box 4]) and management of people with dementia, but also provide links to other service providers such as home and community care providers and community supports such as Alzheimer's Australia support groups. Memory clinics operate within a shared-care model, with a GP providing ongoing medical care and liaising with other specialists. There is some evidence that memory clinics improve the quality of life of carers and improve the assessment of people with dementia.[5] Although there are few such clinics in rural settings, some clinics have extended their reach using telehealth.

Managing Alzheimer's disease

Having made a diagnosis of probable Alzheimer's disease, there is good evidence from RCTs and meta-analyses that the use of cholinesterase inhibitors (which increase the availability of central acetylcholine) is associated with symptomatic benefits, including improvements in memory and general mental functioning, and enhanced quality of life.[9] The cholinesterase inhibitors donepezil, galantamine and rivastigmine are all subsidised by the Pharmaceutical Benefits Scheme (PBS) for the treatment of mild to moderate Alzheimer's disease, defined by an MMSE score ⩾10.

Treatment with memantine, a moderate affinity *N*-methyl-D-aspartate receptor antagonist that also provides symptomatic relief and enhances quality of life, can be initiated for people with moderate Alzheimer's disease (MMSE score 10–14); however, memantine does not currently qualify for a PBS benefit if it is prescribed concurrently with a cholinesterase inhibitor. None of these agents alter the progression of the disease. Also, these agents can only be prescribed on the PBS for more than 6 months if there is objective evidence of improved cognitive performance during the initial 6 months of treatment, which is defined as a 2-point increase in MMSE score (or a 4-point decrease on the cognitive section of the Alzheimer Disease Assessment Scale[10] or, in specific circumstances, improvement on the Clinician's Interview-Based Impression of Change[11]).

Two years after Alan was diagnosed with Alzheimer's disease (5 years after his initial presentation), he was re-referred to the memory clinic because of delusions. He believed that his wife had been unfaithful (which his wife denied) and he had demonstrated increasing verbal aggression. There had been one incident where he pushed his wife. His MMSE score was 16/30. On general physical examination, there was evidence of an enlarged liver and subsequent investigations revealed metastatic adenocarcinoma of the bowel. He required several hospital admissions for assessment and management of the adenocarcinoma, including surgery for impending bowel obstruction. A program of non-pharmacological intervention — mainly identifying and avoiding triggers of behavioural disturbance and distress — was introduced by the local community mental health team for older adults. While he was in hospital, Alan received support during delirious episodes from the hospital liaison psychogeriatric team. His subsequent decline was rapid, he was managed between home and hospice care, and he died 6 months later from advanced bowel cancer and associated severe cognitive decline.

Alan was 78 years of age at the time of his death and had lived with the diagnosis of Alzheimer's disease for 2.5 years. The median duration of survival for people with dementia is 4.5 years from the time of diagnosis,[12] but this is highly variable and some people survive for as long as 20 years. Physical complaints are a major problem for the majority of people with dementia. Many people with dementia die from other causes, as in Alan's case, but the presence of dementia is a contributing factor. In Australia, Alzheimer's disease and dementia (with advanced debility) is the third leading cause of death in women and the sixth leading cause of death in men.[13]

Nine in 10 people with Alzheimer's disease will develop behavioural and psychological symptoms of dementia (BPSD) during the course of their illness.[14] There is some evidence that atypical antipsychotics such as risperidone may be effective in decreasing agitation and psychotic symptoms, but their use increases the risk of cardiovascular events and death (Level A evidence).[14] The efficacy of antidepressants in treating depressive symptoms associated with dementia or MCI has not been established and antidepressants may increase the risk of delirium and falls. Hence, non-pharmacological interventions (eg, identifying and avoiding situations that trigger distress) should be considered before psychotropic medications for the treatment of BPSD (Level C evidence). The presence of pain can also exacerbate behavioural symptoms in people with dementia. In addition, people with dementia seem to be particularly susceptible to the development of delirium, which may be triggered by infections, metabolic imbalances, and a wide range of drugs (particularly sedatives and analgesics).

SUPPORT FOR CARERS

A major determinant of quality of life and ability to remain at home for people with dementia is the continuing support of a carer. Support for carers, such as timely access to information and services, enables people with dementia to maintain maximum quality of life in non-residential care settings. Aged Care Assessment Teams are often a helpful starting point for access to these services. The Australian Government, as part of the Dementia Initiative, has funded the Dementia Behaviour Management Advisory Service, a nationwide network of services that provide advice for patients and their carers, and the *Dementia resource guide* (http://www.health.gov.au/internet/main/publishing.nsf/Content/ageing-dementia-info-hp.htm). In addition, Alzheimer's Australia provides support groups and various other types of support — such as counselling services — in each state (http://www.fightdementia.org.au).

Competing interests: No relevant disclosures.

Provenance: Commissioned; externally peer reviewed.

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