CLINICAL ISSUES IN THE DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF DEGENERATIVE BRAIN DISEASE

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The development of impaired cognition in older people is now of major concern for public health, therefore the physician must expect to be consulted increasingly by ageing people with early or subjective changes in mental function. They, and their families, will have urgent questions about the causes and prevention of further decrements in memory and reasoning; they are often fearful of the dire consequences of such changes on quality of life and the implied economic threats of dementia. Opportunities for assessment will also arise when patients present with a range of general medical problems and the physician should be alert to associated mental changes. Informant reports and shortened forms of cognitive testing are efficient methods of screening for all stages of dementia in clinical settings which may be used by all physicians.[1] Important advances have occured in the two major components of clinical assessment of patients who have progressive organic brain disease; in the diagnostic process (which is being influenced by developments in the neurobiological understanding of the dementias) and in the evaluation of risk factors which contribute to cognitive decline.

DIAGNOSIS

Accurate diagnosis is always essential in order to determine whether there is a treatable cause of any cognitive changes which are detected, even though the number of treatable causes which account for chronic cognitive changes is small.[2] The diagnostic process should also identify co-morbid psychiatric and medical conditions which may be treatable, and inform the counselling of patients and carers.

The clinical criteria of McKhann *et al*.[3] for probable and possible Alzheimer's disease are widely accepted, and broadly similar descriptions and diagnostic guidelines are available from the World Health Organisation (ICD-10)[4] and the American Psychiatric Association (DSM-IV).[5] Schedules for diagnosis have also been produced by expert groups for vascular brain disease,[6] Lewy Body dementia[7] and fronto-temporal dementia.[8] Such subtyping is not widely attempted but there is increasing evidence of the prognostic, therapeutic and preventive value of more certain clinical diagnosis, especially of cerebrovascular disease.[9] In the UK, ICD-10 diagnoses of dementia are collated by the Departments of Health but a detailed breakdown of returns for dementia is not available for Scotland. A comparison of diagnostic practice in England in 1995–96 from ICD-10 coding with the results of a contemporary epidemiological study suggests limited diagnostic specificity in comparison with what can be achieved with best clinical practice (see Table 1 and references 10,11).

Collecting information for diagnosis

The first interview has, as priorities, the collection of accurate historical information, and the gain of the trust and co-operation of the patients and their family, along with a preliminary understanding of interpersonal and environmental factors. It is vital to exclude delirium, which is a little understood 'syndrome of cerebral insufficiency'which is characterised usually by a history of sub-acute onset with marked fluctuations in the mental state.[12] The difficulty in focusing and sustaining attention and shifting attention, which indicates a fundamental disturbance of consciousness rather than the more stable dysfunction of higher cognition seen in the dementias, may be observed. The history will suggest vascular cognitive impairment if there is a sub-acute onset followed by a plateau or the classical stepwise decline associated with repeated cerebral infarction. The expectation of neuro-radiological findings of brain ischaemia is increased by a history of gait changes, nocturnal confusion and early onset of urinary incontinence.[13] This history will guide the physical examination to expect focal neurological signs and potential sources of thromboembolism.

Clinical features

The basis of all diagnostic schedules is the psychiatric definition of a dementia 'syndrome'. The cognitive deficits identified to confirm dementia should involve memory, and one or more of the other areas of cognition (e.g. language, visuo-spatial skills, abstract reasoning abilities). There should also be practical consequences of these deficits for

TABLE 1
Comparison between research-based and routine clinical diagnosis of subtypes of dementia in England.

Subtypes of dementia	Prevalence of research-based subtypes of dementia[1]	Case closures with primary diagnosis of dementia[2]
Unspecified	–	63%
Alzheimer's disease	75%	11%
Vascular dementia	17%	25%
Mixed	4%	–
Others	4%	0.7%

[1]Brayne *et al*., 1995[11]
[2]Department of Health, Mental Health Division, 1995–96

impairment of function in daily living; and the changes should occur progressively in an alert patient over a period of at least six months. This description is the essence of the McKhann criteria[3] for 'probable' Alzheimer's disease when other possible causes are excluded after investigation. In practice many patients are now referred at a much earlier stage of cognitive decline and so may not meet these criteria. Even when the problem is restricted to loss of memory for recent events, effort must be employed to determine possible or probable causes, because there is a substantially increased risk of dementia in patients with only mild or circumscribed cognitive impairment.[14] Clinicians are also increasingly asked to see elderly patients with persisting subjective complaints about their memory who may have a realistic awareness of cognitive decline. These patients justify assessment, as difficulties with concentration and registration often accompany emotional disorders, and older people may be aware of cognitive change before clinical screening tests detect such a decline.[15,16]

At least one third of people with dementia develop psychoses, and so the trigger for referral may sometimes be a neuropsychiatric symptom such as delusions, hallucinations, a misidentification syndrome or the disinhibition and behavioural changes of anterior cortical degeneration. In such cases, memory impairments may not be prominent even when florid symptoms lead to assessment[17] and associated neuropsychological dysfunction is often subtle and discrete, requiring specialist analysis.

The diagnosis of Alzheimer's disease should be a positive one rather than one made by exclusion. It is the most common form of dementia associated with neuropathological changes which confirm the diagnosis.[18] Typically, a gradual onset is seen with progressive decline in cognition but with sparing of sensory and motor functions until late in the illness. Memory deficits (episodic, prospective, semantic) are a common early feature of the cognitive profile and are succeeded by regional neuropsychiatric changes. The temporal lobes, hippocampal formation, and the parieto-occipital association cortices are more susceptible to this form of neurodegeneration, so dysphasia, dyspraxia and visuo-spatial dysfunctions may emerge.[2] Focal neurological signs are absent until the latest stages of decline when frontal release signs may appear. Dementia associated with cortical Lewy bodies is a variant of dementia with prognostic and therapeutic implications. The diagnosis of this variant in a patient with dementia requires the presence of two of three core symptoms: fluctuations in cognition with variations in alertness (and no cause for delirium), recurrent detailed visual hallucinations and spontaneous motor features of Parkinsonism.[7] The diagnosis is supported by other features including exquisite and dangerous sensitivity to neuroleptic drugs which lends practical force to the subtyping.

Assessing cognitive functions

A short test of mental function should be performed as part of the initial assessment. The Mini Mental State Examination (MMSE) is flawed but has the virtues of common usage and simplicity.[19] The maximum score is 30 and it can be administered quickly with little experience. Orientation, aspects of memory and understanding as well as a simple visuo-spatial constructional test are covered. Premorbid intellect and educational attainment bias the score, and professional patients may score well above the cut-off point of 23 when there is already very substantial cognitive decline. Conversely, an MMSE score in the low twenties in an old person with little secondary education and sensory impairments may not be significant.[20] A decrease in score of about three points per year is typical in Alzheimer's disease and the test can be shortened for busy clinicians with little reduction in specificity.[1,21] In addition to quick screening measures, a compact but more comprehensive neuropsychological battery is very valuable if available. This might include tests of executive functions, abstract reasoning, memory, language and visual perception. These can further refine the diagnosis where specific regional syndromes such as frontotemporal or other lobar dementias, and slowly progressive isolated cognitive degenerations are suspected in the clinic.[22]

Laboratory screening investigations

Chui and Zhang[23] prospectively studied the results from the evaluation of memory-impaired patients referred to a university clinic. Laboratory tests changed the diagnosis in 9% and had management implications in 13% of patients. Admittedly, the finding of thyroid, haematological and infective (treponemal) abnormalities raised the possibility of co-morbid rather than primary metabolic or infective cognitive impairment. The authors make the point that treatment of co-morbid disorders is part of good patient management, even when these disorders have been previously diagnosed and treated. Screening should include haematology with ESR and B_{12}, biochemistry with serum calcium, phosphate, and liver function tests, thyroid function and urinalysis.

The E4 allele of the lipoprotein ApoE is more common in patients with Alzheimer's disease, and individuals homozygous for E4 have an increased risk of the disease without earlier onset. However, many people will reach old age unimpaired with two copies of the gene and without cognitive decline. Therefore predictive power of knowing E4 status is not sufficient to currently support the clinical use of genetic screening.[24] Detailed clinical assessment including suitable neuropsychological testing remains the most sensitive method of detecting early cases.

Neuropsychological testing

A comprehensive psychometric assessment by an experienced psychologist who will relate the clinical findings to the patient's problems in daily living, is of value. This assessment can have diagnostic implications; and in one study when combined with standard assessments it changed the diagnosis in 11% of cases.[23] The findings were of particular value in distinguishing between mild cognitive impairment and early dementia, especially when relative preservation of memory suggested non-Alzheimer dementia.

Collaboration with a clinical psychologist provides an important baseline for the assessment of progressive change and the clarification of regional neuropsychological dysfunction in the atypical syndromes. The findings also provide some objective means of monitoring the effects of cholinesterase inhibitors and other longer-term preventive interventions. A comprehensive neuropsychological profile assessment is not always available but it will indicate the abilities which are both lost and preserved. This may help the patient and carers adopt strategies to cope with demanding tasks, and improve the rapport between patient and carers as understanding develops.

Neuroimaging

The detection of focal neurological signs and gait disturbances, together with atypical and sub-acute symptom development, indicate the need for CT scanning which is usually the most quickly available imaging technique. A CT scan will exclude 'silent' cerebral infarction, normal pressure hydrocephalus, tumour or a chronic subdural haematoma. The study by Chui and Zhang (with the reservation that their assessments were likely to be of younger and less deteriorated patients than in routine practice) showed that diagnosis was changed following a CT or MRI scan in 28% of patients with memory impairments.[23] Apart from three cases (of 119) with potentially treatable lesions, 22 cases had cerebral infarcts, half of which were previously undiagnosed. Management was changed in 15% of cases, usually by the need for careful evaluation and treatment of cardiovascular risk factors. A third of the sample had one or more indications for brain imaging from the history and examination but were found to be false positives with diffuse cerebral atrophy or mild white matter changes. Focal signs and gait disturbance were the most frequent false positive indicators. This inevitably reduced the sensitivity of the scanning investigations.

In vascular brain disease both CT and MRI are informative, but MRI is more sensitive for white matter anomalies, and ischaemic patterns of white matter change can, to an extent, be distinguished from so-called age-related changes. Imaging findings are required for diagnostic rigour in vascular dementia as the presentation and clinical assessment are often atypical. Findings such as 'silent' infarction, extensive rarefaction of white matter or focal atrophy may support a diagnosis of vascular dementia. Conversely, the absence of lacunar or focal infarction may support a diagnosis of Alzheimer's disease.[25]

Structural and functional imaging are beginning to contribute to the diagnosis and monitoring of organic brain disease in other ways. Radiological evidence of cortical or subcortical atrophy supports a diagnosis of Alzheimer's Disease, but the findings can overlap with those of normal ageing. Appropriately, weighted high-resolution three-dimensional MRI images can be acquired in a few minutes; the technique of automated image volume subtraction can then detect small areas of atrophy in serial scans, giving global and regional rates of change. The method increases diagnostic accuracy in the earliest stages of Alzheimer's disease, and will be valuable when applied to the assessment of preventive treatments.[26]

The studies of the OPTIMA research group (Oxford studies to investigate memory and ageing) have shown that atrophy of the medial temporal lobe is much more rapid in older people with probable Alzheimer's disease than in controls, and is highly predictive of histological confirmation of the diagnosis. In their selected series, the combination of structural and functional (SPECT) scanning predicted pathological diagnosis with a sensitivity of 90% and a specificity of 97%.[27]

Cerebral HMPAO-SPECT is a relatively cheap and widely available technique. The typical finding in 'probable Alzheimer's disease' is hypoperfusion in the posterior association cortex which may or may not be symmetrical. Sometimes lateralised isolated perfusion deficits are reported, and, while these are not uncommon in Alzheimer's disease, if a global review of a patient suggests the possibility of clinically atypical vascular brain disease or lobar atrophy then structural imaging should be performed. When the scattered perfusion deficits said to be typical of vascular brain disease are found using HMPAO-SPECT, with supportive evidence of focal ischaemia from the history and examination, then structural scanning may not be necessary. Where the history and examination are compatible with Alzheimer's disease however, diagnostic clarification of scattered perfusion deficits suggests the need for structural scanning. SPECT findings can often be useful to distinguish between different types of degenerative dementia.[28]

ASSESSMENT OF RISK FACTORS

Paradoxically, while the definition of Alzheimer's disease in life has traditionally depended upon the exclusion of cerebrovascular disease, the clinical phenotypes may be identical, and the changes in the ageing brain associated with vascular risk may include Alzheimer neuropathology.[29] Data on vascular risk factors, therefore, should be gathered in all patients, supplemented by physical examination and investigation as appropriate (see Table 2).

General advice on stopping smoking, weight reduction, increasing exercise and improving dietary intake, together with the detection and effective treatment of diabetes and the indicated use of lipid-lowering drugs, are important. Elderly people are at risk of a range of dietary deficiencies and although the evidence for this is not so far sufficiently robust, supplementation of a dietary intake often short of fresh fruit and vegetables with the antioxidant vitamins A, C and E, may contribute to maintaining cognitive performance.[30]

Memory disorders and loss of insight may limit compliance with all of these interventions, but liaison with other specialists and with the primary care team in the management of associated medical disorders can slow the progression of cognitive impairment and perhaps delay the onset of dementia. The development of hypertension, independent of control, predisposes to cognitive decline and dementia but effective management of raised blood pressure, anticoagulation of suitable patients with atrial fibrillation and the use of anti-platelet therapies may all be helpful in the prevention of vascular brain disease.[31]

THERAPY

Planned and co-ordinated inter-agency assessments, and interventions are, of course, essential to meet the needs of those experiencing dementia and their carers. Such procedures should always be founded on a diagnostic formulation. The detection and treatment of co-morbid medical illness has been emphasised, but the high prevalence of depressive and anxiety states in association with dementia also influences management. Co-morbid emotional disorders should be treated assertively. The treatment of other non-cognitive behavioural and psychological symptoms in dementia has been the subject of a recent Scottish Intercollegiate Guidelines Network (SIGN) publication,[32] but the evidence for efficacy of current pharmacological treatments is weak. Neuroleptic prescribing is often unmonitored with the potential for harmful short-and long-term side-effects.[33]

The aetiology of Alzheimer's disease is unknown, but a consistent finding is degeneration of cholinergic neurones in the basal forebrain. One therapeutic strategy, therefore,

TABLE 2
Some risk factors for cognitive decline.

Risk factors	Vascular brain disease	Alzheimer's disease
Clinical		
hypertension	+++	+
atrial fibrillation	+++	–
diabetes	+++	+
smoking	+++	–
head injury	–	+
poor diet	+++	–
Social / developmental		
sex	M	F
social deprivation	+++	–
educational attainment	–	+
premorbid brain size	–	+

has been to stimulate cholinergic function with the aim of improving cognitive performance. Cholinesterase-inhibitors prevent the hydrolysis of acetylcholine and prolong its survival in the synaptic cleft. At present there are two cholinesterase-inhibitors available for use in Alzheimer's disease in the UK: donepezil (Aricept) and rivastigmine (Exelon). The Scottish National Medical Advisory Committee has affirmed the principles of its English equivalent for prescribing these (and presumably future) drugs targeted at dementia symptoms. Specialists in old age psychiatry, medicine for the elderly or neurology, should initiate treatment after 'accurate' diagnosis. This advice has resource consequences for the lead service in each Health Board and Trust, including the establishment of the interdisciplinary organisation and training required to ensure an appropriate standard of assessment and monitoring. Debates about efficacy and cost, and a delay in producing central guidance have led to a suspicion in some areas of 'postcode prescribing', although most Health Boards are now funding the drugs on the basis of local shared-care protocols.

A substantial database now exists for the two available drugs from controlled trials. Donepezil is a piperidine-based specific and reversible inhibitor of acetylcholinesterase licensed for symptomatic treatment of mild to moderate Alzheimer's disease (MMSE score guide 16–24) with the caveats expressed above. In trials, improvement is obtained in the detailed cognitive section of the Alzheimer's disease Assessment Scale. The improvements are modest however, equivalent to a six-month delay in the expected progress of the dementia.[34] While most patients begin to decline as expected on the drug, responders show maintained improvement compared with anticipated deterioration over two years.[35] Rivastigmine is a carbamate-based pseudo-irreversible cholinesterase inhibitor with cortical selectivity which has relatively few peripheral cholinergic side-effects and few potential drug interactions.[36] Cholinesterase-inhibitors have now been shown to have interesting and important effects on psychological and behavioural non-cognitive symptoms in Alzheimer's disease and Lewy Body dementia.[37]

Clinical experience from prescribing cholinesterase-inhibitors is still limited, but anecdotal reports of striking and maintained responses are documented amongst patients who respond and show benefit. Personal experience with patients who had detailed psychometric assessment before, and three months after, treatment with donepezil, suggests that the increased volition, recall and alertness reported by some patients and their carers is not reflected by any consistent improvement in standard cognitive test scores. It may be that the frontal and subcortical cholinergic effects of the drug in responders are not adequately delineated by the tests used. Our own studies have shown significant effects on regional cerebral blood flow in a proportion of patients with Alzheimer's disease.[38]

Existing guidance suggests withdrawal of both of these drugs after three months in non-responders, although many physicians will wish to see evidence of decline before withdrawal. Judgement will be complicated in individual patients by real variations in the natural history of the disease (particularly where there are co-morbid factors). Discontinuation after long-term therapy raises ethical issues and, even when no clinical benefit is apparent, can lead to a catastrophic further decline.

CONCLUSION

A diagnostic instrument should be developed urgently to cover the dementia subtypes which must be valid but sufficiently simple to be used in routine assessments. A clear trend exists towards a more sophisticated neuro-psychiatric evaluation of cognitive impairments, and the equally important psychological and behavioural non-cognitive symptoms which appear in the course of the dementias. This is amply justified by emerging evidence concerning the prediction and prevention of cognitive decline in old people and the advent of new pharmacological therapies. Accurate diagnosis and informed management will increasingly depend on collaboration between specialists.

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