Review

Dementia

Cunningham EL[1], McGuinness B[1,2], Herron B[2], Passmore AP[1,2]

ABSTRACT

Dementia is a clinical diagnosis requiring new functional dependence on the basis of progressive cognitive decline. It is estimated that 1.3% of the entire UK population, or 7.1% of those aged 65 or over, have dementia. Applying these to 2013 population estimates gives an estimated number of 19,765 people living with dementia in Northern Ireland. The clinical syndrome of dementia can be due to a variety of underlying pathophysiological processes. The most common of these is Alzheimer's disease (50-75%) followed by vascular dementia (20%), dementia with Lewy bodies (5%) and frontotemporal lobar dementia (5%). The clinical symptoms and pathophysiological processes of these diseases overlap significantly. Biomarkers to aid diagnosis and prognosis are emerging. Acetylcholinesterase inhibitors and memantine are the only medications currently licensed for the treatment of dementia. The nature of symptoms mean people with dementia are more dependent and vulnerable, both socially and in terms of physical and mental health, presenting evolving challenges to society and to our healthcare systems.

INTRODUCTION

Dementia is a clinical diagnosis requiring new functional dependence on the basis of progressive cognitive decline and representing, as its Latin origins suggest, a departure from previous mental functioning.

The incidence of dementia rises with age making it an increasingly common phenomenon within our aging population. The nature of symptoms mean people with dementia are more dependent and vulnerable, both socially and in terms of physical and mental health, presenting evolving challenges to society and to our healthcare systems. Despite the seemingly simple premise, the clinical diagnosis of dementia can be difficult with de novo functional impairment often obscured by physical frailty, comorbid psychiatric symptoms such as depression and a subtle but steady assuming of household responsibilities by spouses and family. Clinical and pathological criteria for the main dementia-causing diseases overlap significantly. The emergence of symptoms decades into the pathophysiological process hamper targeted disease therapy. A great number of research initiatives are underway to identify potential biomarkers of disease processes earlier. The association of both overt cognitive decline and underlying pathophysiological processes with normal aging complicate the process of identifying disease processes early within the spectrum of normal aging.

Once the diagnosis is established, prognostic measures are required, and are still lacking, as disease trajectories between individuals can vary greatly. Globally, governments are recognising these challenges. Investment and research infrastructure are beginning to reflect the scale of the need. Drugs conferring symptomatic benefit are available and memory service structures exist to diagnose dementias and guide management. The personal impact of dementia on patients and families is also being increasingly recognised, with discussion in the media surrounding famous sufferers and dramatisations in literature and film. Herein we attempt to describe the current landscape of dementia.

TABLE 1

Gender specific age-related prevalence (%) of dementia in the UK (estimates from Dementia UK 2014)

Age in years	Female	Male	Total
60 – 64	0.9	0.9	0.9
65 – 69	1.8	1.5	1.7
70 – 74	3.0	3.1	3.0
75 – 79	6.6	5.3	6.0
80 – 84	11.7	10.3	11.1
85 – 89	20.2	15.1	18.3
90 – 94	33.0	22.6	29.9
95+	44.2	28.8	41.1

EPIDEMIOLOGY AND SOCIO-ECONOMIC IMPLICATIONS

Dementia is often arbitrarily considered early (< 65yrs) or late-onset (> 65yrs), with the vast majority (>97%) of cases being of late-onset [1]. Table 1 shows the most recent age-related prevalence estimates for dementia in the UK, which equate to 1.3% of the entire UK population or 7.1% of those aged 65 or over [2]. Applying these to 2013 population estimates gives an estimated number of 19,765 people living

[1.] Centre for Public Health, Queen's University Belfast [2.] Belfast Health and Social Care Trust

Correspondence to: Dr Emma Cunningham

emmacunningham@doctors.org.uk

with dementia in Northern Ireland [2]. This compares to the 12,811 people registered with the Quality and Outcomes Framework for Northern Ireland (NI) with a diagnosis of dementia in 2013-2014 (http://www.dhsspsni.gov.uk/index/statistics/qof/qof-achievement/qof-lcg-13-14.htm).

The age-related incidence of dementia in the UK is falling, presumably as a result of better public health measures [3], meaning the increasing absolute numbers of people with dementia are based on the shifting population demographic, the aging population. Global estimates of a doubling in the dementia population every 20 years giving an estimated 115 million people with dementia by 2050 were revised further upwards in 2013, to take account of the likely further increases in lower and middle income countries [4].

Prognosis at the time of dementia diagnosis varies, with evidence that age at diagnosis, gender, comorbidities and disease severity can all affect life expectancy [5]. Whilst methodological variations limit the usefulness of the data available, median life expectancy from the time of diagnosis has been shown to range from 3.2 to 6.6 years, and from 3.3 to 11.7 years from dementia onset [5]. Local research has suggested a median survival of 5.9 years from diagnosis (unpublished data).

Transition into residential care as a result of the functional impairments of dementia is a prospect that worries many patients and a reality that many families face. It was estimated last year that 69% of all those living in residential care within the UK suffer from dementia [2].

It is perhaps no surprise then that dementia is expensive. The updated estimated cost to the UK economy of £26.3 billion per year published last year [2] took account of the role played by unpaid carers (£11.6 billion), social care costs were estimated at £10.3 billion and healthcare costs at £4.3 billion in comparison.

CLINICAL DIAGNOSIS

The clinical syndrome of dementia, characterised by new functional dependence on the basis of progressive cognitive decline, can be due to a variety of underlying pathophysiological processes. The most common of these is Alzheimer's disease (AD; 50-75%) followed by vascular dementia (VaD; 20%), dementia with Lewy bodies (DLB; 5%) and frontotemporal lobar dementia (FTLD; 5%) (Figure 1). The significant clinical and pathological overlap between these processes mean their relative frequencies are estimates at best [1,6]. Less common causes (3%) include Huntingdon's disease, Creutzfeldt-Jakob disease, HIV/AIDS and multiple sclerosis. We will first consider the clinical and then the pathological properties of these diseases.

Cognitive impairments central to the diagnosis of dementia can be categorised into five main domains: memory; executive function; language; visuospatial abilities; personality and behaviour. As dementia, of any cause, progresses, cognitive impairments will broaden, involving more domains, and

deepen, causing increased functional impairment. It can thus be difficult to distinguish dementias of different aetiologies in the later stages. In the early stages however the pattern of prominent symptoms can help identify the most likely
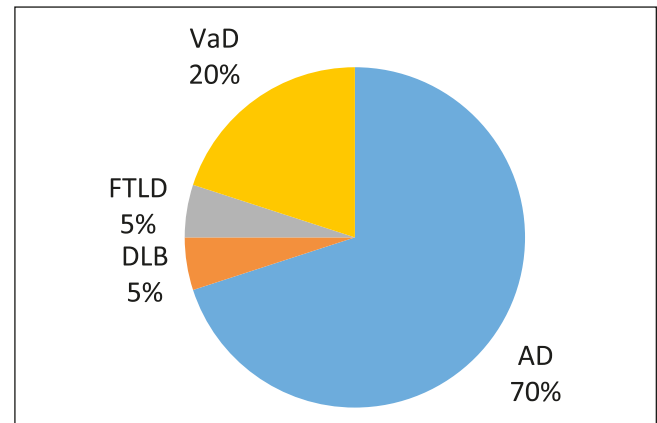

Fig 1. Pie chart showing estimated frequencies of dementia-causing disease processes

underlying disease process. Clinical criteria exist for all the main dementia sub-types, the main features of which are outlined in Table 2 [7-11]. All criteria require a diagnosis of dementia and include the caveats that there should not be a symptom pattern more in keeping with another of the dementias and that cognitive impairments should not be better explained by a psychiatric illness. Neuropsychiatric symptoms should be sought. Depression can be a cause or effect of cognitive impairments and often features such as hallucinations and delusions will not be volunteered unless specific enquiries are made.

AD, the most common cause of dementia, typically presents with short-term memory deficits, manifesting for example as repetitive questioning. Impairment in at least one other cognitive domain is required for a diagnosis of probable dementia due to AD (ADD). Atypical presentations of ADD include behavioural or language deficits suggesting frontal variants or prominent early visuospatial problems suggesting posterior cortical atrophy. The most relevant feature of a presentation of VaD is the temporal association of cognitive deficits with stroke and evidence of cerebrovascular disease on examination and imaging. The Lewy body diseases comprise DLB and Parkinson's disease (PD). Patients with DLB may go on to develop Parkinsonism. As a rule of thumb, if the emergence of dementia and physical PD symptoms are within one year the diagnosis is PD dementia (PDD), if cognitive symptoms predate physical symptoms and signs by more than one year the diagnosis is considered to be DLB. Early language or behavioural symptoms raise the prospect of FTLD. In the younger age groups, ie less than 65, the incidence of FTLD and ADD are almost equal, in contrast to the vastly lower incidence of FTLD in older age groups. The early symptoms of behavioural variant FTLD often raise the possibility of primary functional psychiatric diagnosis, complicating diagnosis.

It is relatively common to be presented with clinical

TABLE 2

Clinical diagnostic criteria for dementias

Disease	ADD	DLB	Behavioural variant FTLD	Primary progressive aphasia (FTLD)	VaD
Authors (year)	McKhann et al (2011)	McKeith et al (2005)	Rascovsky et al (2011)	Gorno-Tempini et al (2011)	Gorelick et al (2011)
Required symptoms	(Typical ADD) Memory deficits + deficits in at least one other cognitive domain	(Central features) Attentional deficits Executive dysfuction Visuospatial deficits (Core features, 2/3) Fluctuating cognition Visual hallucinations Parkinsonism (Suggestive features) REM sleep behavior disorder Neuroleptic sensitivity Positive DAT scan	Behavioural disinhibition Apathy or inertia Loss of sympathy or empathy Perseverative, stereotyped or compulsive/ritualistic behavior Hyperorality and dietary changes Executive dysfunction with relative sparing of episodic memory and visuospatial skills (3/6 required)	Language deficit most prominent symptom and accounts for functional decline No prominent memory, visuospatial or behavioural problems	Clear temporal relationship between vascular event and onset of cognitive deficits Cognitive deficits independent of motor/ sensory sequelae of vascular event

scenarios that do not wholly and exclusively fulfil a single diagnostic criteria. Reflecting the concurrent accumulation of pathophysiological processes within the brain, symptoms can represent overlapping disease processes and mixed pictures can be said to occur, this is most commonly the case with ADD and VaD.

Many people present with objective cognitive symptoms that fall short of the requirements for a diagnosis of dementia. Criteria exist then for the diagnosis of mild cognitive impairment (MCI) [12,13]. Creation of this diagnostic category has facilitated focused follow up demonstrating that 5-10% per year of those with MCI will progress to fulfill the diagnostic requirements of a dementia [14]. Such symptoms can also be due to psychiatric illness, drugs known to be deleterious to cognition or may be transient and regress spontaneously. As the use of biomarkers, outlined below, evolves, identification of those more likely to be in the prodromal stages of a dementia is improving, with some arguing that patients should be identified at the MCI stage as either prodromal dementia or not [15]. For now the diagnostic bracket of MCI, whilst disputed, remains.

Other diagnostic criteria exist. In addition to the criteria set out by McKhann et al in 2011 [7] an International Working Group has proposed diagnostic criteria for ADD intended for use primarily in research [15]. The older Hachinski [16] and NINDS-AIREN [17] scales are still used to define VaD. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders published in 2013 by the American Psychiatric Association [18] has introduced the terms major and mild neurocognitive disorders, which equate to dementia and MCI. Their criteria for the various subtypes equate broadly with the pre-existing clinical criteria.

Diagnosis and differentiation of dementias requires careful history taking and examination. Both patient and collateral histories are needed to establish a new functional dependence and to explore the progressive cognitive impairments as well as neuropsychiatric symptoms. Physical examination is required to examine for focal neurological or extrapyramidal signs. Cognition will be assessed informally during the course of the consultation but formal testing is required, and facilitates longitudinal monitoring. A suggested framework for assessment of patients presenting with cognitive complaints is outlined in Table 3.

Probably the most widely recognised formal cognitive test is the Mini Mental State Examination (MMSE), first proposed in 1975 [19]. Whilst assertions of copyright have impacted on its use in recent years the MMSE has become well and widely established, and provides a common language for those fluent in its use. The Montreal Cognitive Assessment, originally developed as a test for MCI, and also marked out of 30, has expanded into the space created by MMSE apprehension (www.mocatest.org). The Addenbrooke's Cognitive Examination-III (ACE-III) provides a more thorough assessment and marks are calculated for each domain, then tallied to give a total, out of 100 (http://www. neura.edu.au/frontier/research/test-downloads/). A growing variety of scales exist, none of which is perfect. Inter and intra-rater reliability can limit use and all scales are reliant on premorbid educational abilities. The important thing is to become familiar with a scale, ensure its consistent use within a service, and use it to monitor progression.

TABLE 3

Suggested foci of assessment of patients with cognitive symptoms

History	History from patient and informant Change from baseline Functional decline Past medical history Drug history Current home circumstances Alcohol and smoking Driving Family history	Some specific examples: repetitive questioning; inability to navigate journeys and less familiar environments eg shopping centres, own children's home; difficulty recognising previously familiar people; difficulty using new equipment eg new oven; word-finding difficulties; tendency to participate less in group conversations; less attention to personal hygiene/appearance; new short-temperedness with family Progressing to: agitation in the evening; not recognising home as own Specific safety concerns: problems in the kitchen; problems with cigarette disposal; wandering; handling of money
Physical examination	Extrapyramidal signs Focal neurological deficit(s) Ability to follow instructions Pulse Chest auscultation	
Cognitive examination and associated scales (52,53)	Formal cognitive testing (eg MMSE/ACEIII) Geriatric Depression Scale (or alternative) Activities of Daily Living Scale Neuropsychiatric Inventory	Neuropsychiatric Inventory includes delusions, hallucinations, agitation/aggression, apathy, disinhibition, sleep and appetite
Investigation	Bloods CT brain (or MRI if appropriate) ECG	

PATHOPHYSIOLOGY/ PATHOLOGICAL FEATURES

The disease processes underlying dementia are yet to be fully understood. With the (probable) exception of VaD, all involve a pathological accumulation of a native protein: in the case of AD it is the extracellular plaques of amyloid and the intracellular tangles of hyperphosphorylated tau; in DLB it is alpha-synuclein in the form of Lewy bodes; in FTLD several culprits have been identified including TDP-43 and the hallmark proteins of AD and DLB in a frontotemporal distribution. Examples of these lesions can be seen in Figures 2-5. It is important to remember that evidence of these processes is also found post-mortem in people who did not exhibit cognitive impairments prior to death, and that these patterns are not mutually exclusive, existing concurrently as they often do [20].

These pathological accumulations are associated with synapse and neuronal loss and atrophy which also demonstrate patterns in terms of distribution. Hippocampal atrophy within the medial temporal lobe for instance is associated with AD, in keeping with the early amnestic symptoms [21]

Genetic studies have contributed greatly to our knowledge of these disease processes. The observation that people with Down's syndrome (trisomy 21) almost invariably develop AD, led to the discovery of the first of three autosomal dominant genes associated with early-onset ADD [22]. Study of these genes, responsible for amyloid cleavage, have been integral to the understanding of pathological amyloid production. In contrast to the aberrant production of amyloid

proteins implicated in early onset ADD, late-onset ADD (LOAD) is thought to be more to do with faulty clearance of amyloid from the brain. Apolipoprotein E [23] and, more recently, TREM-2 [24,25] alleles have been identified as risk factors for LOAD. Their pathophysiological roles remain unclear: they are implicated in amyloid processing and neuroinflammation amongst other pathways. Neither are sufficient or requisite for LOAD and are therefore not tested for in routine clinical practice. Genome wide association studies in recent years have consistently identified several genes with significant but modest associations with LOAD[26] and examination of their relevant pathways, including immune response and inflammation, cell migration and lipid transport, have enhanced the evolving understanding of the ADD disease process.

These methods are being applied across the dementia spectrum and similar pathways are implicated in DLB, FTLD and VaD [27,28]. FTLD in particular has myriad of increasingly recognized heritable components.

Animal models, often based on these predisposing genetic mutations, continue to provide basic science research opportunities. Improving chemistry techniques, such as proteomics and metabolomics are also being used to study the disease using human-derived samples such as blood and cerebrospinal fluids.

BIOMARKERS

The search for biomarkers further informs our understanding of these disease processes and offers the opportunity to identify them prior to symptom emergence. A biomarker has
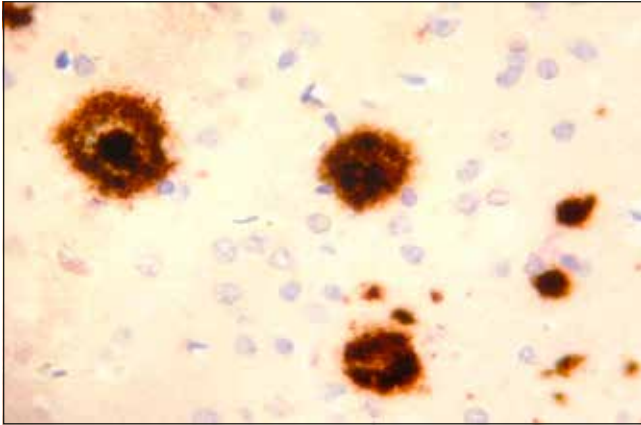
Fig 2. An immunohistochemical section taken through the cortex in a case of ADD. An antibody to Beta A4 amyloid is applied to the tissue and detects this antigen which in turn stains the antigen brown.
This shows a dense deposition of amyloid throughout the cortex as dense core (DC) and diffuse (D) plaques.
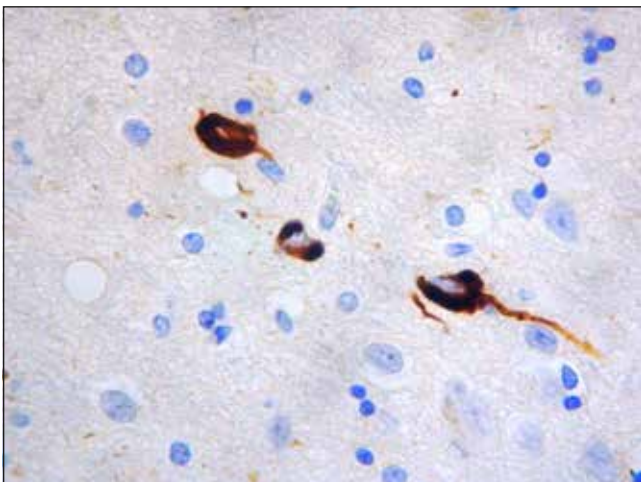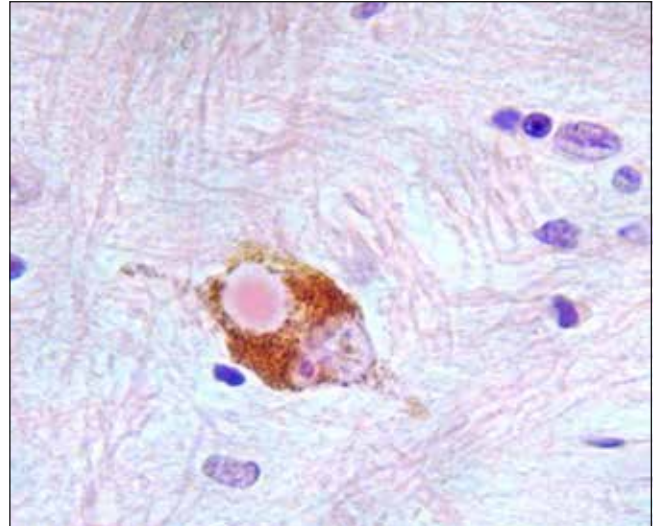

Fig 4. A pigmented neuron from the substantia nigra. A single Lewy Body is present. This patient also had diffuse cortical Lewy bodies characteristic of Pure Lewy Body Dementia
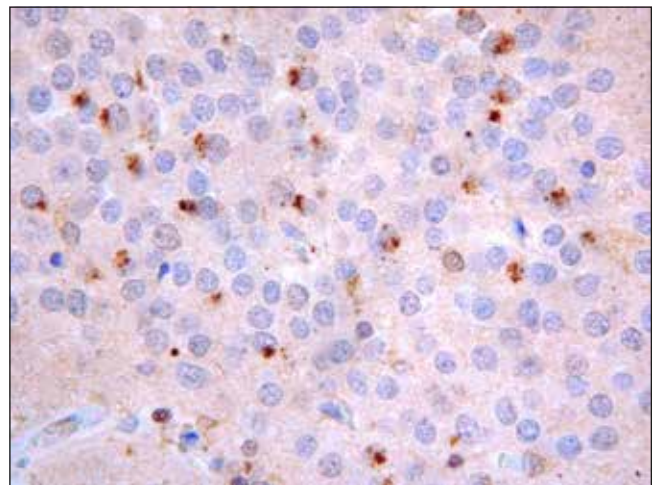

Fig 3. Neuronal tangles stained with an antibody to Tau (T)

Fig 5. A section from the hippocampal dentate fascia showing dot like deposition of ubiquitin.
This is characteristic of Frontotemporal Lobar Dementia with Ubiquitinised inclusions (now called TDP).

been defined as a 'characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [29]. Research into ADD is currently the main focus and biomarkers are generally considered as representing the underlying AD process (evidence of amyloid and tau accumulation) or neurodegeneration (markers of synapse/neuronal loss or atrophy) [7,15].

Low amyloid beta and high tau in cerebrospinal fluid (CSF) and high levels of intracerebral amyloid as measured by positron emission tomography (PET) scanning predict the subsequent development of ADD [30]. The downstream markers of neurodegeneration - hippocampal atrophy on MRI and decreased uptake of a radiolabelled glucose tracer (18-fluorodeoxyglucose, FDG) as measured using PET scanning (FDG-PET) have also been shown to increase diagnostic accuracy when used to supplement clinical measures [30].

The occurrence of these pathophysiological processes in cognitively normal people, especially with increasing age,

complicates the interpretation of these biomarkers. Several studies of cognitively normal patients are ongoing and a recently published cross sectional study of 985 participants showed that over the age of 85 more people had biomarker changes in keeping with ADD than did not [31]. There are significant variations in neuroimaging techniques across centres and also in the sampling, handling and analysis of CSF [21,32,33]. Worldwide research collaborations, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), are in place to try and accelerate our understanding of the pathophysiological processes underlying dementia, and hence the interpretation of biomarker findings, in both cognitively normal and impaired participants. Global standardisation initiatives are also ongoing with regard to MRI and PET imaging and CSF amyloid and tau. Biomarkers are beginning to be used in clinical practice [34] but the likelihood, and benefit, of more widespread adoption is dependent on these issues being resolved.

INVESTIGATION

Initial investigation of patients presenting with cognitive impairment centres on the exclusion of reversible causes of cognitive impairment. The National Institute of Clinical Excellence (NICE) recommends blood tests (full blood picture, urea and electrolytes, calcium, glucose, liver function tests, thyroid function tests and vitamin B12 and folate) and structural brain imaging (preferably MRI but CT will suffice) [35]. In addition to ruling out tumours, subdural haematomas, stroke and normal pressure hydrocephalus, CT, and to a greater extent MRI, can also provide information regarding chronic ischaemia, infarcts and focal atrophy. Functional imaging, such as single-photon emission computed tomography (SPECT) and FDG-PET are recommended to help differentiate between the dementia sub-types where appropriate. Figures 6&7 show normal compared to reduced uptake in keeping with ADD on FDG-PET. Dopamine transporter (DAT) scanning has shown high sensitivity and specificity for DLB and is the investigation of choice when trying to differentiate between DLB and other dementias [36].

RISK FACTORS

In tandem with the laboratory science methods outlined above, observational studies have informed our understanding of the risk factors for dementia, as well as the natural history and prognosis of the diseases. Age is the main risk factor for dementia. Established modifiable risk factors for dementia include: depression, diabetes, (midlife) hypertension, (midlife) obesity, smoking, alcohol abuse, high cholesterol, coronary heart disease, renal dysfunction, low unsaturated fat intake and inflammation [37]. It has been argued that the decrease in age-related dementia incidence seen in the UK is due to better public health measures and thus amelioration of these factors [3]. There is in addition increased focus on recognised protective factors such as: cognitive activity, physical activity, healthy dietary pattern and low/moderate alcohol intake [37].

MANAGEMENT – NON-PHARMACOLOGICAL

Management will be guided by the nature and severity of the symptoms and any safety concerns. Vascular risk factors should be addressed. Patients and relatives should be offered information and explanations. The Public Health Agency (www.publichealth.hscni.net) have developed a booklet 'Communicating effectively with a person living with dementia' available via their website. The Alzheimer's Society have local offices and provide information and support (www.alzheimers.org.uk). Patients and carers should be referred to a social worker if a carer's assessment is felt appropriate and to facilitate access to services such as Day Centres and social services care provision. As a result of the NI Dementia Strategy a navigation service for all those diagnosed with dementia is being established in all Trusts; this will ensure patients and carers have a consistent contact point throughout their journey. Moderate physical exercise should be encouraged where possible. No formal cognitive training services are currently being offered consistently though

supportive evidence is emerging and may translate into service provision. Where appropriate patients can be referred to community mental health teams. Transition into residential care is influenced by social circumstances, dementia severity and the behavioural and psychological symptoms of dementia (BPSD) eg aggression. Non-pharmacological measures are recommended as first line therapy for BPSD but there is as yet no consensus regarding the most effective measures. All patients should be advised to inform the Driver & Vehicle Agency and their insurer of a diagnosis of dementia. If there are concerns regarding a patient's ability to drive they should be advised to stop driving. Where patients lack capacity to manage their own affairs and assets a referral to the Office of Care and Protection (www.courtsni.govuk/en-GB/Services/OCP/) may be warranted. A draft Mental Capacity Bill (NI) (working title) is due to be introduced to the NI Assembly this year having already been consulted upon. It is likely this will have significant impact on how healthcare decisions are made for people who lack capacity.

People with dementia are frequently admitted acutely to hospital, most commonly following a fall, and it is estimated that up to one quarter of in patients in UK hospitals, at any one time, have dementia [38]. This is important as caring for patients with dementia requires modification of communication, diagnostic and, at times, management approaches. Patients
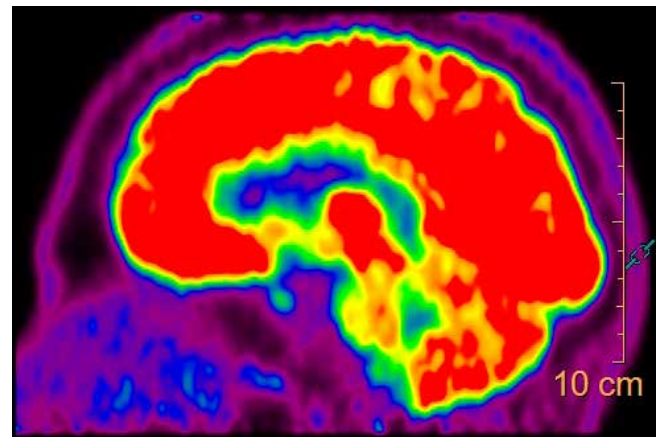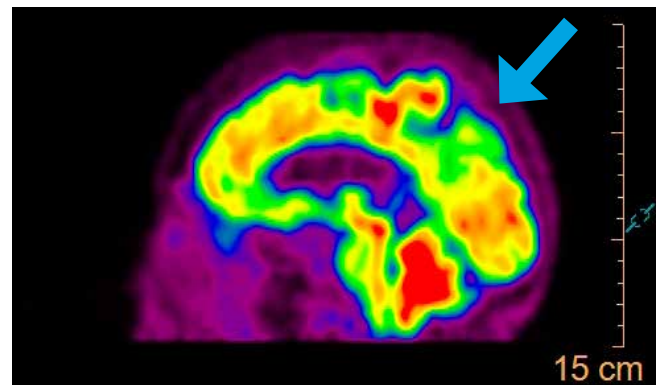

Fig 6.

Fig 7.

Figures 6 and 7 show normal and reduced uptake on FDG-PET scanning respectively. The decreased uptake in the temporoparietal and precuneus (arrow) regions, typical of ADD, can be seen.

TABLE 4

Acetylcholinesterase inhibitors and memantine

Generic name	Brand name	Dosing schedule
Donepezil	Aricept	5mg od, titrated up to 10mg od after 4 weeks if tolerated
Galantamine	Reminyl	XL preparation available for od administration, 8mg daily initially, titrating up by 8mg after 4 weeks if tolerated to maximum of 24mg od
Rivastigmine Rivastigmine patch	Exelon	1.5mg bd titrating up by 1.5mg bd at intervals of at least 2 weeks; usual range 3-6mg bd 4.6mg/24 hours titrating up to 9.5mg/24 hours after 4 weeks if tolerated
Memantine	Ebixa	5mg od, titrated up by 5mg per week to maximum dose 20mg od

may have difficulties articulating symptoms. Constipation and acute urinary retention for example should be actively sought out. Disorientation and agitation may develop and both environmental (eg clear signage and clocks) and attitudinal (eg repeated reassurance, clear explanations, good lighting, involvement of families) approaches can ameliorate this. Dysphagia is a common occurrence as dementia progresses and patients may require dietary modification and assistance at meal times. Dyspraxia can hinder personal care, with considerate assistance required. Patients with dementia are more likely to develop delirium which can further complicate care needs [39]. Rehabilitation attempts can be hampered by cognitive impairments but dementia should not be a contraindication to rehabilitation as evidence for benefit exists. Discharge planning is required, often with inclusion of families. More than one third of patients with dementia admitted to hospital from their own homes will be discharged to an institutional setting [38]. A scheme has been introduced to increase the understanding, and identification, of dementia within hospital settings (http://butterflyscheme.org.uk).

MANAGEMENT – PHARMACOLOGICAL

Offending medications, in particular those with anti-cholinergic properties should be reconsidered and stopped where possible. It is important to note that even over the counter medications can affect cognition [40]. An association with benzodiazepines has been suggested by observational work and these too should be reconsidered [41].

Acetylcholinesterase inhibitors and memantine, an NMDA receptor antagonist, (Table 4) are the only medications currently licensed for the treatment of dementia. All three acetylcholinesterase inhibitors (AChEi) have a license and are recommended by NICE for the treatment of ADD with rivastigmine additionally approved for the treatment of PDD [42,43]. Memantine is approved for the treatment of moderate ADD where AChEi are contraindicated or not tolerated and as an adjunct to AChEi therapy in severe disease [43]. Evidence exists to suggest a moderate improvement in cognitive function with these drugs [44,45]. These drugs are not licensed for use in VaD. In clinical practice it can be difficult to distinguish whether there is an ADD component and these medications are often offered as a therapeutic trial. There is no evidence to support the use of AChEi or memantine in FTLD; [46,47] AChEi usually make symptoms of FTLD worse as the underlying pathological process is different to that of ADD.

Mild, moderate and severe disease severity categories are often used but are arbitrary by nature. As a rule of thumb NICE considers corresponding cut-offs by MMSE of 21-26, 10-20 and less than 10 [35] but in practice this is only a single facet of the assessment outlined in Table 3.

AChEi therapy exerts its benefit by raising pathologically low levels of the neurotransmitter acetylcholine. Potential adverse events include risk of bradycardia and syncope, potential worsening of obstructive airways disease and gastrointestinal disturbance. Assessment should therefore include an ECG and chest auscultation, with severe sinus bradycardia or evidence of a significant cardiac conduction defect or significant audible wheeze all contraindications to AChEi therapy. The possibility of reduction in the dose of beta-blocker or rate-limiting calcium channel blocker could be considered prior to initiation of an AChEi. An anti-emetic, usually domperidone, can be prescribed on an as required basis for the first few weeks to alleviate nausea. The British National Formulary recommends nocte administration of donepezil but it is acceptable to take it in the morning. The decision to continue or terminate drug therapy, in the setting of inevitable cognitive decline, can be difficult. The DOMINO-AD [48] study showed that continuation of donepezil therapy, even in severe disease, was associated with significant cognitive benefit.

Souvenaid is a food for special medical purposes with evidence for improved memory function in early ADD [49]. It is not available on prescription and requires a recommendation from a healthcare professional.

BPSD is an umbrella term for a variety of symptoms including apathy, agitation, disinhibition and sleep disturbance. These can be particularly distressing for carers and often precipitate admission to institutional care. Atypical antipsychotics are sometimes employed to combat BPSD but are associated with significant side effects including an increase in mortality and so should be carefully considered [50]. Only risperidone has a license for the treatment of BPSD and short-term treatment (<6 weeks) is recommended [42]. Depression is a common symptom (see the upcoming review in this Journal regarding diagnosis and treatment of depression).

Many pharmacological avenues are being explored in an effort to find new effective, safe drugs for dementia. Efforts

are hampered by the as yet incomplete understanding of the pathophysiological processes being targeted. Drugs targeting amyloid production and amyloid plaque clearance have failed on safety and efficacy grounds. Anti-tau agents are currently being studied. Apart from Souvenaid the much vaunted dietary supplements have yet to be supported by consistent evidence. Safety concerns are being addressed, and emerging pathophysiological insights exploited, by attempts to reposition existing drugs within the dementia field, for example metformin [51].

CONCLUSION

Significant advances have been made in our understanding of dementia in recent decades. Dementia presents laboratory, clinical, societal and economic challenges. Diagnosis remains clinical, supplemented by improving biomarkers. Dementia causing diseases overlap in their pathophysiology and phenotypes. The only licensed drugs to date provide symptomatic benefit. Disease-modifying drug development is reliant on early identification of disease processes prior to symptom emergence, where it is currently felt best therapeutic window exists. Both biomarker and drug development depend on better understanding of underlying pathophysiological processes. The wide-reaching benefits of improved public health measures have yielded a decrease in age-related incidence but the ongoing demographic shift means efforts on all fronts must be redoubled if we are to diagnose, treat, understand and care for those of us who develop dementia. The importance of dementia as a global priority is recognised in the declarations of the G8 Dementia Summit in 2013, committing the G8 nations to the improvement in the quality of life for people with dementia and their carers and identification of disease-modifying therapies by way of a co-ordinated and funded international research framework.

CONFLICTS OF INTEREST

ELC has received a contribution towards conference fees from Lundbeck

BMcG has received honoraria and assistance with travel from Nutricia

BH has nothing to declare

APP has received honoraria and assistance with travel from Pfizer/Eisai, Shire, J&J, Novartis, Lundbeck and Nutricia

REFERENCES

1. Knapp M, Prince M. *Dementia UK: full report*. London: Alzheimer's Society; 2007.

2. Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera A, *et al*. Dementia UK: Update. London: Alzheimer's Society; 2014.

3. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet*. 2013;**382(9902)**:1405-12.

4. Prince M, Guerchet M, Prina M. *Policy Brief for Heads of Government: The Global Impact of Dementia 2013 - 2050*. London: Alzheimer's Disease International; 2013.

5. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry*. 2013;**28(11)**:1109-24.

6. Prince M, Jackson J. *World Alzheimer Report 2009*. London: Alzheimer's Disease International; 2009.

7. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr. CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Demen*. 201;**7(3)**:263-9.

8. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, *et al*. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;**65(12)**:1863-72.

9. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, *et al*. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;**134(Pt 9)**:2456-77.

10. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, *et al*. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;**76(11)**:1006-14.

11. Gorelick PB, Scuteri AC, Black SE, DeCarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;**42(9)**:2672-13.

12. Petersen RC MJ. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol*. 2005;**62(7)**:1160-3.

13. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, *et al*. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Demen*. 2011;**7(3)**:270-9.

14. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand*. 2009;**119(4)**:252-65.

15. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, *et al*. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurology*. 2014;**13(6)**:614-29.

16. Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, *et al*. Cerebral blood flow in dementia. *Arch Neurol*. 1975;**32(9)**:632-7.

17. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, *et al*. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;**43(2)**:250-60.

18. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.

19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975 ;**12(3)**:189-98.

20. Wharton SB, Brayne C, Savva GM, Matthews FE, Forster G, Simpson J, *et al*. Epidemiological neuropathology: the MRC Cognitive Function and Aging Study experience. *J Alzheimers Dis*. 2011;**25(2)**:359-72.

21. Frisoni GB, Jack Jr. CR, Bocchetta M, Bauer C, Frederiksen KS, Liu Y, et al. The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: Evidence of validity. *Alzheimers Dement*. 2015;**11(2)**:111-25.

22. Chouraki V, Seshadri S. Genetics of Alzheimer's Disease. *Adv Genet*. 2014;**87**:245-94.

23. Verghese PB, Castellano J, Holtzman DM. Apolipoprotein E in Alzheimer's Disease and other neurological disorders. *Lancet Neurology*. 2011;**10(3)**:241-52.

24. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, *et al*. TREM2 Variants in Alzheimer's Disease. *N Engl J Med*. 2013;**368(2)**:117-27.

25. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, *et al*. Variant of TREM2 Associated with the risk of Alzheimer's disease. *N Engl J Med*. 2013;**368(2)**:107-16.

26. Lambert J, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, *et al*. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*. 2013;**45(12)**:1452-8.

27. Beecham GW, Hamilton K, Naj AC, Martin ER, Huentelman M, Myers AJ, *et al*. Genome-wide association meta-analysis of neuropathologic features of Alzheimer's disease and related dementias. *PLoS Genetics*. 2014;**10(9)**:e1004606.

28. Ferencz B, Gerritsen l. Genetics and Underlying Pathology of Dementia. *Neuropsychol Rev*. 2015; **25(1)**:113-24.

29. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;**69(3)**:89-95.

30. Vos SJ, Verhey F, Frölich L, Kornhuber J, Wiltfang J, Maier W, *et al*. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain*. Epub ahead of print. Feb 17 2015. DOI. 10.1093/brain/awv029.

31. Jack CR Jr, Wiste HJ, Weigand SD, Rocca WA, Knopman DS, Mielke MM, *et al*. Age-specific population frequencies of cerebral beta-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *Lancet Neurol*. 2014;**13(10)**:997-1005.

32. Carrillo MC, Blennow K, Soares H, Lewczuk P, Mattsson N, Oberoi P, *et al*. Global standardization measurement of cerebral spinal fluid for Alzheimer's disease: an update from the Alzheimer's Association Global Biomarkers Consortium. *Alzheimers Dement*. 2013;**9(2)**:137-40.

33. Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous Sr. MD, Jagust WJ, *et al*. The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement*.2015;**11(1)**:1-15.

34. Bocchetta M, Galluzzi S, Kehoe PG, Aguera E, Bernabei R, Bullock R, et al. The use of biomarkers for the etiologic diagnosis of MCI in Europe: An EADC survey. *Alzheimers Dement*.2015;**11(2)**:195-206.

35. National Collaborating Centre for Mental Health. *Dementia: The NICE–SCIE Guideline on supporting people with dementia and their carers in health and social care*. National Clinical Practice Guideline; 42. Leicester: The British Psychological Society and Gaskell; 2007.

36. McCleery J, Morgan S, Bradley K, Noel-Storr A, Ansorge O, Hyde C. *Dopamine transporter imaging for the diagnosis of dementia with Lewy bodies*. Cochrane Database of Systematic Reviews; **2015(1)**: 010633.

37. Deckers K, van Boxtel MP, Schiepers OJ, de Vugt M, Muñoz Sánchez JL, Anstey KJ, *et al*. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry*. 2015;**30(3)**:234-46.

38. Lakey L. *Counting the cost: Caring for people with dementia on hospital wards*. London: Alzheimer's Society; 2009.

39. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;**383(9920)**:911-22.

40. Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, *et al*. Cumulative use of strong anticholinergics and incident dementia: A prospective cohort study. *JAMA Int Med*. 2015;**175(3)**:401-7.

41. Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, *et al*. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ*. Epub ahead of print. Sep 9 2014; 349. DOI. 10.1136/BMJ.G5205.

42. Joint Formulary Committee. *British National Formulary (BNF) 69*. London: BMJ Publishing Group and Royal Pharmaceutical Society; 2015.

43. NICE Clinical Guideline; 42. *Dementia: supporting people with dementia and their carers in health and social care. (Incorporating NICE technology appraisal guidance 217; 2011)*.

44. London: National Institute for Health and Care Excellence; 2013.

45. Birks J. *Cholinesterase inhibitors for Alzheimer's disease*. Cochrane Database of Systematic Reviews; 2006(1): 005593.

46. McShane R, Areosa Sastre A, Minakaran N. *Memantine for dementia*. Cochrane Database of Systematic Reviews; 2006(2):003154.

47. Li Y, Hai S, Zhou Y, Dong B. Cholinesterase inhibitors for rarer dementias associated with neurological conditions. Cochrane Database of Systematic Reviews: 2015(3);009444.

48. Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, *et al*. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2013;**12(2)**:149-56.

49. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, *et al*. Donepezil and Memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;**366(10)**:893-903.

50. Ritchie C, Bajwa J, Coleman G, Hope K, Jones R, Lawton M, *et al*. Souvenaid®: a new approach to management of early Alzheimer's disease. *J Nutr Health Aging*. 2014;**18(3)**:291-9.

51. Ballard C, Waite J, Birks J. *Atypical antipsychotics for aggression and psychosis in Alzheimer's disease*. Cochrane Database of Systematic Reviews: 2006(1); 003476.

52. Corbett A, Pickett J, Burns A, Corcoran J, Dunnett SB, Edison P, *et al*. Drug repositioning for Alzheimer's disease. *Nature Rev.Drug Discov*. 2012;**11(11)**:833-46.

53. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*.1994;**44(12)**:2308-14.

54. Yesavage JA, Sheikh JI. Geriatric Depression Scale (GDS). *Clin Gerontol*. 1986;**5(1-2)**:165-73.