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What's new in dementia?

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Dementia is a major public health issue globally,[1] consequent upon its increasing prevalence in ageing populations and the costs, societal and financial that this will generate. A National Dementia Strategy for England has been enunciated to be implemented over the next five years, one key strand of which relates to early diagnosis and intervention.[2] Many diseases, including vascular, structural, infectious, inflammatory, metabolic and endocrinological, and also neurodegenerative disorders, may be associated with cognitive deficits[3] which are sometimes reversible. It therefore behoves clinicians in many specialties to have some familiarity with the diagnosis of the dementia syndrome and its principal causes.

The journals are replete with new articles on dementia, but in many ways the generic skills for diagnostic assessment remain the same:

- a history, including collateral history from a knowledgeable informant – a patient attending the cognitive clinic alone, despite a request to bring an informant, is a highly sensitive sign of the absence of dementia[4]
- a neurological examination, including some form of cognitive assessment
- some focused investigations, as appropriate (neuroimaging, neuropsychology, neurophysiology, genetic testing with counselling)
- a diagnostic formulation.

Guidelines for dementia diagnosis have attempted to formalise this approach (Table 1).[5]

Alzheimer's disease

New diagnostic criteria for Alzheimer's disease (AD) have been developed which take a biological approach to disease definition, incorporating new knowledge from neuroimaging findings, cerebrospinal fluid biomarkers and deterministic genetic mutations (Table 2).[6]

Table 1. Recommended investigations in dementia.[5]

		Evidence level
Blood tests:		
• generally proposed as mandatory	• ESR, full blood count, electrolytes, calcium, glucose, renal and liver function tests, TSH	Good practice point
• often required	• Vitamin B12, serology for syphilis, HIV, Borrelia	Good practice point
Neuroimaging:		
• structural	• CT: to identify surgically treatable lesions and vascular disease	A
	• MRI: to increase diagnostic specificity	A
• functional	• SPECT and PET: may be useful in those cases where diagnostic uncertainty remains	B
Neurophysiology	• EEG: useful adjunct, especially if CJD or transient epileptic amnesia suspected	B
CSF	• Cell count, protein, glucose, protein electrophoresis in atypical presentations	Good practice point
	• Total tau, phospho-tau, Aβ42 as adjunct in cases of diagnostic doubt	B
Genetic testing:		
• known pathogenic mutations?	• In patients with appropriate phenotype or family history of autosomal dominant dementia	Good practice point
	• To be undertaken only in specialist centres, with appropriate counselling of patient and family care givers, and with consent	
• ApoE	• Not recommended as routine	B
Tissue biopsy	• For specific diagnosis of some rare dementias	Good practice point
	• To be undertaken only in specialist centres	

Aβ = amyloid β-peptide; ApoE = apolipoprotein E; CJD = Creutzfeldt-Jakob disease; CSF = cerebrospinal fluid; CT = computed tomography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission CT; TSH = thyroid-stimulating hormone.

These criteria, although still probabilistic, aim to supersede the old 'binary outcome' diagnostic approach:

1 Is there dementia?
2 Is it AD?

The hope is that earlier diagnosis, prior to development of dementia, will be possible. However, few UK centres currently have access to all the desired diagnostic modalities.

Key Points

- **Dementia is a global public health issue with increasing prevalence as populations age**
- **Cognitive impairment and dementia may be caused by diseases of vascular, inflammatory, infective, metabolic and endocrinological as well as neurodegenerative aetiology, and hence are of relevance to clinicians in many disciplines**
- **Common neurodegenerative causes of cognitive impairment and dementia include Alzheimer's disease (AD), Parkinson's disease dementia and frontotemporal lobar degenerations; prion disease remains rare**
- **Symptomatic pharmacotherapies for AD will be superseded, hopefully in the near future, by disease-modifying drugs targeted at pathogenetic pathways**
- **Attention to modifiable risk factors for the development of dementia, such as hypertension, hypercholesterolaemia and alcohol misuse, may be an appropriate primary prevention strategy for dementia**

KEY WORDS: Alzheimer's disease, dementia, Parkinson's disease, treatment

Pathology

The understanding of AD pathogenesis is still dominated by the amyloid hypothesis. This proposes that altered metabolism of the transmembrane amyloid precursor protein (APP) to produce amyloid β-peptides (Aβ) is the ultimate cause of AD. This has been reached in part from analysis of rare cases of autosomal dominantly inherited AD due to deterministic mutations in three different genes: APP, presenilin-1 (the most common) and presenilin-2, all of which alter Aβ production.[7] Collectively, these mutations may account for only 0.5% of AD.

Genetic susceptibility to AD is conferred by various genetic polymorphisms,[8] the most significant being the ε4 allele of the apolipoprotein E (ApoE) gene, although its presence is neither necessary nor sufficient for disease expression. Recent genome-wide association screens have identified other potential susceptibility genes, many of which may influence Aβ metabolism. Toxic Aβ, oligomers may produce effects on structural proteins of the neuronal cytoskeleton. Altered phosphorylation and aggregation of the microtubule-associated protein tau leads to impaired axonal transport, synaptic loss and ultimately neuronal death, and also to neurotransmitter deficits particularly in the basal forebrain cholinergic system. Tau pathology (neurofibrillary tangles) and synaptic loss correlate better with degree of dementia than amyloid plaque burden.

Current treatment

Despite advances in the mechanistic understanding of AD pathogenesis, treatment remains neurotransmitter-based.

Table 2. Proposed new diagnostic criteria for Alzheimer's disease (AD).[6]

Probable AD	
Diagnosis requires A plus one or more supportive features B–E	
Core criteria	
A	Early significant episodic memory impairment, including: • gradual and progressive change in memory function over >6 months • objective evidence of significantly impaired episodic memory on testing • episodic memory impairment, isolated or associated with other cognitive changes at AD onset
Supportive criteria	
B	Medial temporal lobe atrophy on MRI
C	Abnormal CSF biomarker: ↓Aβ42, ↑total tau, ↑phospho-tau
D	Specific pattern on functional neuroimaging with PET (*NB*: not SPECT)
E	Proven AD autosomal dominant mutation in the immediate family
Definite AD	Requires clinical features + neuropathological confirmation *or* clinical features + presence of deterministic genetic mutation

Aβ= amyloid β-peptide; CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography.

Cholinesterase inhibitors (ChEIs) and memantine are the only licensed treatments. Their use in the UK currently is 'guided' (= proscribed) by the National Institute for Health and Clinical Excellence (NICE), based upon an idiosyncratic calculus of cost-effectiveness. These agents are symptomatic; none of the three available ChEIs slows the conversion from mild cognitive impairment (a non-dementia prodromal form of AD) to dementia.

Disease-modifying treatments

Hopes for future treatment are based on early application of disease-modifying agents. Various candidates are undergoing investigation, only a few of which will be mentioned here.

- *Immunotherapies*, either active or passive, which target Aβ have proved potent in animal models but have faced significant issues relating to toxicity and lack of efficacy in transfer to the clinical arena.
- Trials of *passive immunotherapy* (bapineuzamab) continue, but only certain subgroups of AD patients may respond (eg those carrying the ApoE ε4 genotype).
- *Inhibitors of the secretase enzymes (β and γ)* which cleave APP to produce Aβ represent another potential method of disease modification, based on the amyloid hypothesis. One such agent, tarenflurbil, looked promising in phase 2 trials but failed at phase 3. Investigation of the γ-secretase inhibitor LY450139 (semagacestat) is ongoing.

Other disease-modifying approaches, independent of the theoretical underpinning of the amyloid hypothesis, include:

- tau aggregation inhibitors (methylthioninium chloride, 'Rember'), and
- dimebon, originally marketed as an antihistamine but which may act as a mitochondrial stabiliser.

Both these compounds have shown promise in phase 2 clinical trials; phase 3 trials are ongoing. The difficulties of demonstrating disease modification within the time span of a clinical trial are recognised and surrogate measures, such as structural or functional brain imaging, may be required.

Other symptoms of Alzheimer's disease

Clinical features of AD other than cognitive decline may require intervention. The ubiquity of behavioural and psychological symptoms of dementia (BPSD) has been increasingly recognised.[9] This is not least because they, rather than cognitive impairments, are the most common antecedents of nursing home placement, the most costly aspect of AD care. Treatment of BPSD remains difficult. Because antipsychotic medications are associated with an excess mortality secondary to cerebrovascular disease, behavioural rather than pharmacotherapeutic approaches are now recommended. Epileptic seizures, once thought mere epiphenomena of AD, may in fact be an integral part of disease phenotype related to Aβ and contribute to cognitive decline. Antiepileptic drug treatments might therefore be both symptomatic and disease-modifying.[10]

Parkinson's disease dementia and dementia with Lewy bodies

Observational studies have suggested that most individuals with Parkinson's disease will develop cognitive problems over time, sometimes amounting to dementia (PDD), new diagnostic criteria for which have been produced.[11] The clinical and neuropsychological phenotype of PDD overlaps with that of dementia with Lewy bodies (DLB), with fluctuating attention, visual hallucinations and visuoperceptual deficits common to both. The two presentations reflect differing initial anatomical distributions of neuropathological changes based on the α-synuclein protein. Since cholinergic deficits greater than those in AD are common to both PDD and DLB, beneficial response to treatment with ChEIs is not surprising, although in the UK these medications are currently licensed only for the treatment of PDD. The potentially severe adverse effects of neuroleptic medications in DLB mandate early identification of this condition and avoidance of neuroleptics.[12]

Frontotemporal lobar degeneration syndromes

Research into the frontotemporal lobar degeneration syndromes continues apace.[13] Classification and nomenclature continue to evolve[14,15] in a manner potentially bewildering to the non-initiate, based on:

- the disparate clinical phenotypes: behavioural, linguistic, parkinsonian movement disorder, clinical or subclinical motor neurone disease
- pathological substrates: tauopathy, TDP-43 proteinopathy
- underlying genetic mutations: tau and progranulin genes.[7]

This expanding knowledge base hopefully represents the prelude to a biological understanding of these conditions for which no treatments, other than symptomatic control of aberrant behaviours, exist as yet.

Vascular cognitive impairment

Vascular cognitive impairment is heterogeneous with respect to clinical and neuropathological features.[16] The old dichotomy of vascular dementia (VaD) and AD as distinct disorders is now being superseded by a more 'integrative' approach to aetiology, with a continuum running from pure AD to pure VaD through entities such as 'AD with vascular lesions' and 'VaD with AD changes'. Various lines of evidence support this conceptualisation:

- the shared vascular risk factors for AD and VaD
- evidence for cholinergic deficits in VaD
- neuropathological studies showing that mixed AD/vascular pathology is the rule in demented elders
- evidence for the synergistic modulation of AD-related clinical expression by vascular lesions

- the modest efficacy of ChEI in VaD (a treatment not currently sanctioned by NICE in the UK).

Certainly finding a few peripheral punctuate high-signal lesions of vascular origin on magnetic resonance imaging of the brain of a demented patient does not automatically justify a diagnosis of VaD.

Prion disease

Although numerically extremely rare, the prion diseases continue to garner significant attention, both scientific and popular, in part because of the public health implications of the epidemic of variant Creutzfeldt-Jakob disease (human bovine spongiform encephalopathy), the ultimate extent of which remains uncertain.[17]

HIV-associated dementia

HIV-associated dementia has shown a dramatic decline in incidence since the advent of highly active antiretroviral therapy with nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors, but the prevalence of HIV-associated neurocognitive disorders is increasing because of improved life expectancy. In addition to viral burden, persistent neuroinflammation and AD-like neurodegenerative changes may contribute to these cognitive problems, requiring additional therapeutic approaches.[18]

Alcohol-related dementia

Distinct from the amnesia of Wernicke-Korsakoff syndrome related to thiamine deficiency, alcohol may also induce a dementia syndrome, perhaps consequent upon synaptic and neuronal loss. With changing drinking habits (the 'binge culture'), concerns have been expressed about the possibility of increased numbers of alcohol-related dementia cases in the future.[19]

Conclusions

Dementia syndromes will be of increasing importance with the ageing of the population. Understanding of the pathophysiology of neurodegenerative dementias has unequivocally advanced in the past 10 years but this has yet to be translated into significant, disease-modifying therapeutic interventions. Primary and secondary prevention measures, perhaps facilitated by predicting risk of dementia in 20 years' time based on factors such as age, education, blood pressure, cholesterol and obesity,[20] may be a more appropriate public health strategy emphasising a lifelong, lifestyle approach to cognitive well-being.

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