Diagnosis and management of dementia in older people

John M Starr
Katherine E Walesby

Abstract

Inconsistencies between diagnostic criteria for different dementia aetiologies have led to the 5th edition of the Diagnostic and Statistical Disorder of Mental Disorders abandoning 'dementia' as a diagnostic term. Diagnostic criteria for dementia that remain are increasingly based on molecular rather than clinical features. In particular, dementias associated with fronto-temporal lobe degeneration are now classified as tau-positive or tau-negative, with specific genetic variants associated with subtypes of these two broad categories. Management guidelines for dementia in the community are well established, but this is not the case for acute hospital settings, where diagnosis can be more difficult and coexisting age-associated morbidities and informant history require specific attention. The management of behavioural and psychological symptoms of dementia in acute hospital settings can also be challenging – non-pharmacological and alternative pharmacological interventions are available that may avoid the need to prescribe antipsychotic drugs.

Keywords Acute hospital care; Alzheimer's disease; behavioural and psychological symptoms of dementia; dementia; fronto-temporal lobe degeneration; Lewy body dementia; vascular dementia

Key points

- A diagnosis of dementia is inadequate; aetiology should be determined to facilitate management
- Admission to acute hospital provides an opportunity to make a diagnosis of dementia and arrange appropriate follow-up
- Behavioural and psychological symptoms of dementia are common in hospital; consider pain, constipation and other physical factors as potential causes

Diagnosing dementia

Clinical diagnostic criteria for dementia require at least 6 months of memory decline interfering with everyday activities, a decline in other cognitive abilities and a decline in emotional control or motivation, or a change in social behaviour. Although depression can co-present with dementia, it can also be responsible for poor cognitive performance and is common in hospital settings. An informant history is invaluable, as may be the opportunity to reassess over time. As such, diagnosis in the community is often easier than in the acute hospital setting.

Moreover, making an early diagnosis is often not helped by the lack of universally agreed criteria. For example, for vascular dementia (VaD), the Neurological Disorders and Stroke –Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria[1] require a decline in memory and *two* other domains of cognitive function. However, the 10th revision of the International Classification of Diseases criteria requires a decline in both verbal and non-verbal memory, together with deficit in at least *one* other cognitive domain. The criteria in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders abandon the term 'dementia' and instead use 'major neurocognitive disorder'. This is precisely defined as the situation where cognitive test scores (complex attention, executive function, learning and memory, language, perceptual-motor, social cognition) fall below the third centile or two standard deviations below the population mean; there is therefore no requirement for any decline in memory for a diagnosis. Hence, any given patient with a specific profile of cognitive deficits may or may not be diagnosed with VaD depending on the criteria applied.

As a diagnosis of dementia in itself is inadequate, probable aetiology should also be determined.

Historically, the classification of dementia has been based on neuropathological features (Table 1). Alzheimer's disease (AD), the most common cause, has conventionally been a clinical diagnosis of exclusion. Recently, biomarkers (structural magnetic resonance imaging, molecular neuroimaging with positron emission tomography [PET], cerebrospinal fluid analyses) have been increasingly used to define AD diagnosis in research studies,[2] but this is rarely practicable in clinical practice. VaD is often difficult to diagnose formally, as clinical evidence of significant cerebrovascular disease, reasonably judged to be related aetiologically to the dementia, is required.

The classification of dementias related to fronto-temporal lobe degeneration (FTLD) is evolving along molecular biological lines depending on whether or not tau protein is involved in the neuropathology (Figure 1). Pick's disease was recognized in the 1990s as a tau-opathy associated with the microtubule-associated protein tau gene (*MAPT*). Subsequently, some cases of FTLD with clinical features similar to Pick's or progressive non-fluent aphasia (another manifestation of FTLD) were associated with progranulin gene (*PRGN*, also known as *GRN*) mutations found, like *MAPT*, on 17q21.

Soon after the discovery of PRGN-associated FTLD, a further molecular pathway associated with the transactive response DNA-binding protein 43 (TDP-43) was implicated in ubiquitin-positive inclusion body FTLD; various types have subsequently emerged (Figure 1). TDP-43 is likely to have messenger RNA regulation activity within the central nervous system, and

John M Starr *FRCPEd is Consultant Physician and Director, Alzheimer Scotland Dementia Research Centre, Edinburgh, UK. Competing interests: none declared.*

Katherine E Walesby *MRCP(UK) is Clinical Research Fellow Geriatric Medicine, Alzheimer Scotland Dementia Research Centre and the Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK. Competing interests: none declared.*

Neuropathological features of different neurodegenerative causes of dementia

Neurodegenerative disorder	Neuropathological features	Contributory proteins, etc.
AD	Amyloid plaques Neurofibrillary tangles	β-Amyloid Predominantly three repeat tau isoforms. Both plaques and tangles incorporate other proteins, heparin sulphate, etc., as part of becoming insoluble
LBD	Lewy bodies	α-Synuclein Ubiquitin
Parkinson's disease	Lewy bodies	As above. Note ubiquitin is also thought to regulate β-amyloid concentrations
Progressive supranuclear palsy	Neurofibrillary tangles Possibly Lewy bodies in some cases	Tau α-Synuclein and ubiquitin
Corticobasal degeneration	Neurofibrillary tangles	Tau
Pick's disease/ *MAPT*-associated dementia	Neurofibrillary tangles	Tau
TDP-43-positive FTLD	Ubiquitin-positive inclusion bodies	Ubiquitin
PRGN FTLD	Ubiquitin-positive inclusion bodies	Ubiquitin
FUS familial ALS	FUS and ubiquitin-positive inclusion bodies	Ubiquitin FUS
C9ORF72 FTLD and ALS	Ubiquitin-positive inclusion bodies	Ubiquitin

Table 1

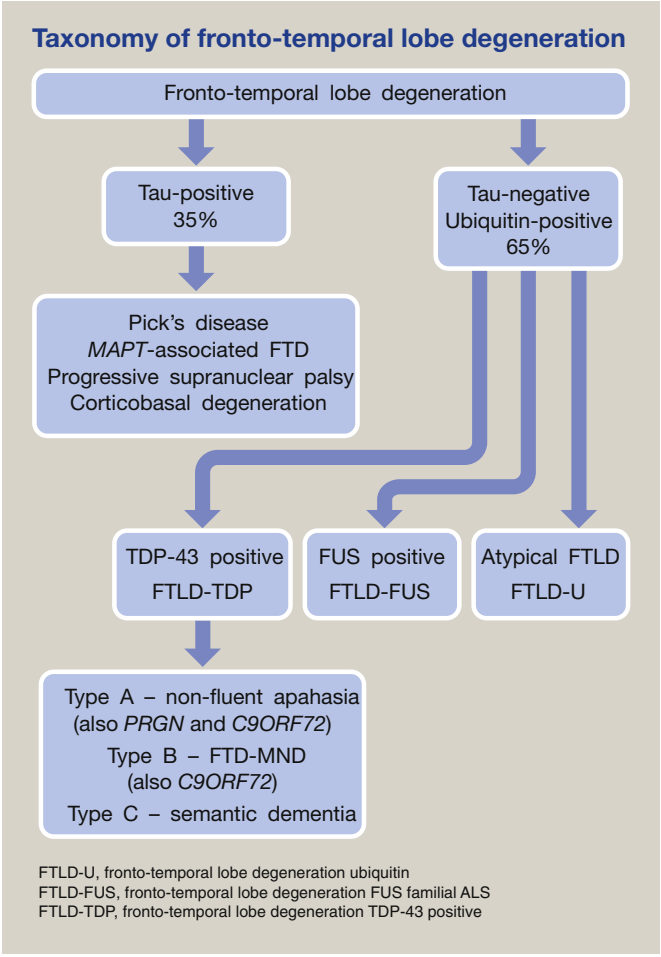

Figure 1

mutations in the *TARDBP* gene located on chromosome 1p36.22 are associated with amyotrophic lateral sclerosis (ALS, a form of motor neurone disease [MND]). The classification of TDP-43 subtypes is not yet agreed — a provisional classification (Figure 1) relates to neuropathological features, but phenotypic overlap remains so that type A occurs in 25% of corticobasal degeneration cases and type B in 25% of behavioural variant FTLD. TDP-43 immunoreactivity, distinct from neurofibrillary tangles, has also been demonstrated in AD, suggesting that this pathway may be of broader significance in neurodegenerative diseases.

More recently, the RNA-binding fused-in-sarcoma gene (*FUS*) on chromosome 16p11.2 has been implicated in a ubiquitin-positive, tau-negative form of ALS, familial ALS type 6, which accounts for about 4% of familial ALS. *FUS* moves between the nucleus and the cytoplasm, and it is thought that cellular stress, secondary to environmental toxins for example, predisposes *FUS* to relocalize into stress granules, with persistent cellular stress resulting in inclusion bodies. In 2011, the chromosome 9 open reading frame 72 gene (*C9ORF72*) was identified as the most common mutation found to date in familial ALS, familial fronto-temporal dementia and ALS-FTLD; it is also thought to account for about 4% of sporadic cases.

Diagnostic criteria for dementia with Lewy bodies (DLB) have also evolved. These comprise *core* features of:

- fluctuating cognition with changes in attention and alertness
- recurrent visual hallucinations
- parkinsonian features present for <1 year before cognitive changes

and *suggestive* features of:

- rapid eye movement sleep behaviour disorder,
- severe neuroleptic sensitivity
- low dopamine uptake in the basal ganglia on single-photon emission computed tomography or PET scanning.

At least one core feature plus another core or suggestive feature fulfils the diagnosis. Patients with parkinsonian features