Dementia: Clinical Background

2

Contents

2.1 What Is Dementia?

Dementia refers to a clinical syndrome rather than a disease. Dementia is usually defined as an acquired condition involving multiple cognitive impairments that are sufficient to interfere with activities of daily living. It is usually but not necessarily progressive. Memory impairment is one of the most common deficits, but other domains such as language, praxis, visual-perceptive and most notably executive functions are often involved. With increasing loss of function due to these cognitive problems, there is progressive difficulty with activities of daily living. Many of the diseases that cause dementia have a relentlessly progressive course with an insidious onset; many have long durations (e.g. 5–10 years from diagnosis) and relatively prolonged end stage period where all self-care and -independence is lost. Dementia places tremendous burdens on patients, their families and carers and on health and social care systems. The most important causes of dementia have an age-related incidence. As a result, the prevalence and societal costs of dementia are predicted to rise dramatically over the coming decades.

2.2 Prevalence and Incidence

Of all diseases associated with age, dementia is the fastest growing entity (Fig. 2.1).

2.2.1 Prevalence

In 2000, prevalence data of 11 European population-based studies were pooled to obtain stable estimates of

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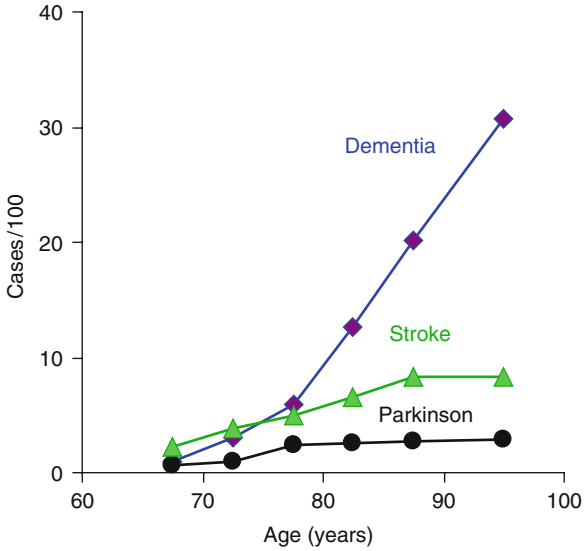

Fig. 2.1 Prevalence of three age-associated syndromes. Dementia shows the highest increase in numbers with advancing age (*Eurodem*)

prevalence of dementia in the elderly (>65 years). Age-standardized prevalence was 6.4% for dementia (all causes), 4.4% for AD and 1.6% for VaD. Prevalence of dementia was higher in women than in men and nearly doubled with every 5 years increase of age: from 0.8% in the age group 65–69 years to 28.5% over the age of 90 years (Fig. 2.2).

Prevalence rates for dementia have been compared among 12 population-based European studies.

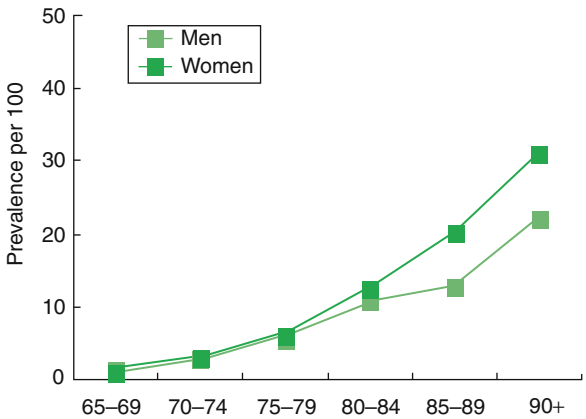

Fig. 2.2 Prevalence rates of dementia among men and women after the age of 65. (After Lobo et al. (2000) Neurology 54(11 Suppl 5):S4–S9)

Crude prevalence rates varied between 5.9% (Italy, the Counselice study) and 9.4% (the Netherlands, Rotterdam study). Again, an almost exponential increase with age and a female excess – mostly after age 75 – was described, independent of country. As the age distribution of the Western population shifts, the rapid increase of the prevalence of dementia with increasing age means that both the number of affected individuals and the affected proportion of the total population are increasing. This will be most prominent in Europe, where the median age of the population is higher than in any other part of the world.

A consensus conference in 2005 under the auspices of Alzheimer Disease International estimated that 24.3 million people worldwide suffer from dementia, with 4.6 million new cases of dementia every year (one new case every 7 s) (Ferri et al. 2005). A recent update by ADI in 2009 estimated that 35.6 million people worldwide will be living with dementia in 2010. This number was estimated to nearly double every 20 years, to 65.7 million in 2030, and 115.4 million in 2050 (www.alz.co.uk). Much of the increase is clearly attributable to increases in the numbers of people with dementia in low and middle income countries. Rates of increase are not uniform and are driven by the population structure and life-expectancy changes; numbers in developed countries are forecasted to increase by 100% between 2001 and 2040, but by more than 300% in India, China and their south Asian and western Pacific neighbours.

2.2.2 Incidence

In the same collaborative effort that pooled prevalence data of European studies, data on incidence of dementia of eight population-based European studies were compared and pooled. In total, there were 42,996 person-years of follow-up with 835 new dementia cases. Of these, 60–70% were diagnosed with AD and 15–20% with VaD. Incidence rates of dementia increased exponentially with age from 2.4 per 1,000 person-years in the 65–69 age group to 70.2 per 1,000 person-years in the 90+ age group. Rates among women were higher, especially above the age of 80 (Fig. 2.3). The rates continue to increase with age in women, whereas the increase plateaus in men at age 85.

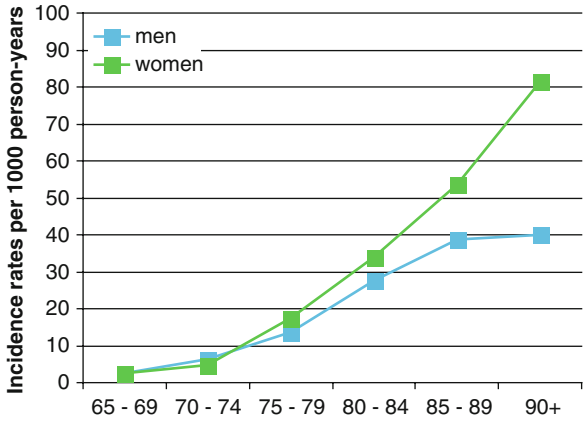

Fig. 2.3 Pooled incidence rates of dementia by sex. (Data from Fratiglioni et al. (2000) Neurology 54(11 Suppl 5):S10–S15)

2.3 Nosological Approach

As mentioned above, dementia is a syndrome, not a disease, and has many and varied causes. The diagnostic workup is meant to identify the underlying cause with a particular emphasis on picking up treatable conditions. Diagnosis is critically dependent on careful history taking from patient and informant followed by clinical and cognitive examination supported by ancillary investigations, of which neuroimaging is one of the most important. The a priori chance of a particular disease being present is dependent on age. The younger the patient, the greater the chance that one of a wide range of underlying pathologies is the cause of the cognitive problems. Diseases like FTD and HD tend to occur more often before the age of 70; genetic forms of AD almost exclusively occur at young ages and rare metabolic causes are more likely in early adulthood (see Table 2.1). In the older patient, AD, DLB and vascular disease are by far the most common pathologies. Mixed disease is very common: notably, AD with vascular disease has been shown to be the most prevalent in post-mortem series of older individuals (>85 years).

The nosological approach is facilitated by the use of clinical criteria, which are detailed in the remaining chapters of this book, where the diseases

Table 2.1 Differential diagnostic considerations in a patient presenting with dementia at young age (arbitrarily defined as onset before age 65). Note the wide variety of diseases in this age group and the particular emphasis on the use of imaging

Disease	MRI findings	Clinical clues	Additional tests
AD	Posterior cingulate atrophy, medial temporal atrophy	Family history, visuospatial and apraxia > memory	CSF (abeta and tau); FDG-PET; amyloid PET
FTLD	Frontotemporal atrophy Temporal atrophy (asymmetrical or symmetrical)	Family history, language, behaviour	FDG-PET
CBD	Frontoparietal atrophy; may be asymmetrical	Asymmetrical Parkinsonism, dyspraxia and myocolonus; alien limb	CSF; Dopamine imaging
SVD	Strategic infarcts, lacunes, WMH	TIA; stroke	Vascular risk factors
Vasculitis	WMH, patchy enhancement, multifocal diffusion restriction	TIA, multifocal	ESR and CRP elevation; CSF, DSA, serology
MS	Disseminated WM lesions, black holes; Gad-enhancement	Relapses; other neurological findings	CSF oligoclonal bands
CJD	Abnormal DWI basal ganglia or neocortex	Myoclonus; cerebellar ataxia	EEG, CSF tau and 14-3-3-protein
Paraneoplastic or limbic encephalitis	Temporal lobe lesions; thalamic swelling	Subacute onset; other neurological findings	CSF antibodies
Infectious	WM lesions, enhancement	Fever, HIV, Lues	Serology, CSF, culture
Metabolic	WM lesions, GM lesions, lactate in spectroscopy, diffusion restriction	Stroke-like episode	CSF, serology, muscle biopsy, genetics

Source: Modified from Ridha B, Josephs KA (2006) Neurologist 12:2–13

Note the wide variety of diseases and the particular emphasis on the use of imaging. For abbreviations see list on page XV

Table 2.2 Listing of the clinical criteria for the various dementia syndromes

Dementia type	Presenting symptom	Criteria	Year published	Imaging included
AD	Memory	NINCDS-ADRDA DSM IV Dubois	1984 1994 2007	No No Yes, MRI/PET
VaD	Memory Memory Unspec Dysexecutive	NINDS-AIREN DSM IV SCADDTC SIVD	1993 1994 2002 2000	Yes, CT/MRI No Yes, CT/MRI Yes, MRI
DLB	Fluctuating, Executive Dysfunction	McKeith	2005	SPECT and MRI
FT(L)D	Behaviour, Language	Neary McKhann	1998 2001	Supportive No
CJD sporadic	Various	Masters	1979	No
CJD variant	Psychiatric	Will	2000	Yes, MRI
PSP	Falls, Parkinsonism	Litvan Williams	1996 2005	No No
CBD	Limb Dyspraxia	Boxer	2006	No
NPH	Gait	Vanneste	2000	Yes, CT/MRI
Huntington	Chorea	CAG repeats	1993	No
MSA	Parkinsonism	Gilman	2008	MRI, PET supportive

The table illustrates that for some diseases in time neuroimaging features have been added to the strictly clinical features. For abbreviations see list on page XV

presenting with dementia are discussed. In Table 2.2, the main disease categories and their published clinical criteria are listed with the use of imaging highlighted. From the table, it may be inferred that for the majority of diseases, no specific imaging criteria have been formulated; however, it is also notable that more recent revisions of criteria are increasingly including imaging (for positive as well as negative predictive value).

2.3.1 Genetic/Protein Classification

Several genes have been implicated in the origin of dementia syndromes. Some diseases are almost exclusively genetic, like HD, while in AD, genetic forms account for <5% of all cases. While the gene product is known for many of the genes, effective therapy has not evolved. In Table 2.3 the known genes and location are listed.

2.3.2 Clinical and Pathological Uncertainty

Using clinical criteria various levels of diagnostic certainty may be reached. For instance, the NINCDS-ADRDA criteria for probable AD have a diagnostic sensitivity and specificity compared to the pathological diagnosis, ranging between 50% and 90%, mainly depending on the setting (clinical expertise) and the age of the patients studied. This diagnostic uncertainty applies to other clinical criteria as well. Of note is that when imaging is included in the criteria such as in the NINDS-AIREN a higher degree of specificity (>90%) is reached. In general, the use of imaging has shifted from excluding disorders that may mimic a dementia

Table 2.3 Genetic causes of dementia

Disease/phenotype	Gene	Gene product	Chromosome	Age at onset (typical)
AD	PSEN 1 PSEN 2 APP	Amyloid Amyloid Amyloid	14 1 21	30–55 variable 45–65
HCHWA	APP Cystatin C BRI2	Amyloid Variant cystatin C ABri and ADan	21 20 13	<65 variable variable
CJD, FFI, GSS	PRNP	Prion protein	20	variable
FTD (esp bvFTD), CBS, PSP	MAPT	Tau	17	25–65
FTD, PNFA	Progranulin, GRN	TDP43 + ve intranuclear inclusions in neurons	17	35–90
BvFTD, FTD-MND	TARDBP (TDP-43); CHMP2B; VCP	Idem; Ubiquitin	1, 3, 9	Very variable and rare
CADASIL	Notch3	Notch protein	19	25–65
Huntington's disease	IT-15	Huntingtin	20	Variable (CAG repeat length)

For abbreviations see list on page XV

syndrome or may be (surgically) treatable to using it to identify specific abnormalities that may aid the clinician to diagnose underlying disease, i.e. to increase specificity over sensitivity. One has to bear in mind that the ultimate 'gold standard' for diagnosis does not exist. In many criteria, a definite diagnosis is often designated as either being made post-mortem or on the basis of genetic information. The former is obviously too late to be helpful in the clinical situation and usually becomes available many years after the first clinical manifestation. The latter may be available during the clinical workup, and probably better serves to inform the clinician about the underlying pathology than anything else. In this respect, certain tau mutations leading to an unexpected clinical diagnosis of AD or vice versa presenilin mutations with unexpected clinical FTD presentation are particularly informative. However, one has to be careful about generalising from familial to sporadic cases. The future of clinical diagnosis making lies within the realm of making a diagnosis at protein level, regardless of the clinical presentation. Possibly, molecular imaging (e.g. demonstrating amyloid deposition rather than a given clinical presentation) will allow a more rational approach towards disease modifying treatment; other imaging of specific pathological markers (e.g. tau) would be very valuable in differential diagnosis. Until that is possible, clinical and radiological information has to be pooled to make the best possible judgement to enable treatment and management of the patient.

2.4 Differential Diagnosis

In the twentieth century the perspective on dementia evolved tremendously. Before 1900, there was very little in the way of specific diagnoses, but with much effort from clinicians to recognize subtypes and help from pathologist, geneticists, neuro-imagers and others, it is now possible to make a list of differential diagnoses and to have a fair chance of predicting pathology in a number of conditions.

Memory deficits, a key feature of the DSM IIIR definition of dementia is no longer essential for dementia and a number of criteria for different diseases causing dementia incorporate the different cognitive profiles expected in the different disorders. This shift in conceptual thinking is illustrated in Table 2.2.

2.4.1 Diagnostic Evaluation

A full diagnostic evaluation is warranted in every patient who present with cognitive or behavioural complaints. Current EFNS and AAN guidelines stipulate what tests are evidence based and need to be done. Below, the main ancillary investigations are summarised. Note that in general the tendency is to move away from excluding other (brain) diseases, towards finding specific clues to make a diagnosis. Imaging has taken the lead in this, followed closely by CSF examinations and to a lesser extent EEG.

2.4.1.1 Laboratory Tests

These should be used to explore whether the patient has co-morbidity, risk factors for dementia, and risk for delirium or has a primary cause for dementia. For this matter, the following tests are generally proposed as mandatory: full blood count and erythrocyte sedimentation rate (ESR), electrolytes, calcium, glucose, renal, liver and thyroid function tests. More extensive tests will be required in individual cases (and places), like serological test for syphilis and vitamin B12 levels, HIV and Borrelia. Patients should be treated for co-morbidity, especially thyroid and vitamin B12 deficiency.

2.4.1.2 Cerebrospinal Fluid (CSF)

Like imaging, CSF provides a 'window on the brain' as biochemical changes, such as extracellular aggregation of beta amyloid in plaques and formation of tau tangles, are reflected in it. A 50% decrease of CSF Aβ42 is seen in patients with AD or MCI in comparison to age-matched controls. The decrease has been associated with enhanced Aβ42 deposition in the brain. With specificity set at 90% the mean sensitivity is 86% in comparison to normal aging. In the differential diagnosis between AD and other dementias, CSF Aβ42 is only moderately specific, with reduced levels also seen in DLB and to a lesser extent also in FTLD and VaD.

CSF tau levels are on average increased 2–3 times in AD and MCI in comparison to controls. Tau is thought to reflect the amount of neuronal degeneration in chronic neurodegenerative disorders. With specificity set at 90%, mean sensitivity is 81% for AD. Elevation of CSF tau is also observed in CJD and after acute stroke; in VaD and FTLD it may also be elevated. The concentration of CSF phosphorylated tau (e.g. p-tau181 or p-tau231) reflects the phosphorylated state of tau protein, and thus the formation of tangles. CSF levels of p-tau in AD patients can be increased by an order of magnitude compared to controls. Increased levels of p-tau are considered to be more specific for AD (Box 2.1).

Assessment of 14-3-3 protein in the sporadic form of CJD has a sensitivity and specificity well above 90%. False positive test results have been noted in patients with encephalitis, cerebral infarcts, metastases, paraneoplastic syndromes and rapidly progressive AD, making it likely that the protein is a marker of brain cell death rather than for CJD.

2.4.1.3 Electro-Encephalography (EEG)

Generalised slowing of background rhythm on EEG is a frequent finding in AD and DLB. These changes are not specific for AD and can also be found in other diffuse encephalopathies (Box 2.2). In FTD patients, the EEG is generally normal. Typical sharp wave complexes are relatively specific for CJD, particularly for the sporadic form. Another possible important finding is temporal epileptic activity which can cause transient epileptic amnesia, a rare cause of memory deficits. In the Box 2.2 the main EEG findings in various dementias are listed.

Box 2.1 Levels of CSF markers in some dementias

	Aβ1-42	Total tau	Ptau-181
AD	↓↓	↑↑	↑/↑↑
DLB	↓	=/↑	=
VAD	=/↓	=/↑	=
FTLD	=/↓	=/↑	=
CJD	↓	↑↑↑	=
Normal aging	=	=	=

↑ mildly elevated, ↑↑ elevated, ↑↑↑ strongly elevated, = normal CSF markers in the most prevalent dementia syndromes. (Courtesy of Dr. N.S.M. Schoonenboom). For abbreviations see list on page XV

Box 2.2 EEG characterisctics in the most prevalent dementia syndromes. Note that for FTLD in particular EEG is normal, while in CJD it has the highest diagnostic yield

	AD	FTLD	VaD	Delirium	DLB	CJD
Decreased alpha rhythm	+	-	0	++	+	+
Decreased alpha reactivity	+	-	0	+	+	+
Asymmetric alpha rhythm	-	--	+	-	-	-
Theta waves	+	-	0	++	+	+
Temporal slow waves	0	0	++	0	++	0
Focal abnormalities	-	-	+	-	0	0
Sharp waves	-	--	+	+	0	0
Periodic discharges	--	--	0	+	0	++
FIRDA	--	--	0	++	+	0

-- never occurring, - incidental, 0 sometimes, + frequent, ++ almost always, *FIRDA* frontal intermittent delta activity. (Courtesy Prof C.J. Stam)

2.5 Multidisciplinary Integration

The diagnosis of a patient with (suspicion of) dementia may require input from many disciplines: clinicians (e.g. geriatricians, neurologists, psychiatrists), psychologists, neurophysiologists as well as radiologists and nuclear medicine specialists. The increasing need for an earlier and more specific diagnosis to guide management and treatment poses a burden on the diagnostic skills of the team involved.

The appropriate use of neuroimaging covered in this book may help to advance diagnosis and alleviate burden for the patient and carer. This book aims to take an approach that fits with clinical reality – that one is presented with patients with clinical and imaging features rather than diagnoses. The arrangement of the book aims to help the reader to move from imaging and clinical features to a diagnosis; and to be accessible to all those seeking to improve diagnosis in dementia.

Suggested Reading

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