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Neuroimaging in Dementia

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Preface

This book is inspired by the previous work entitled 'Magnetic Resonance in Dementia' published in 2002 with our dear colleague and friend, Jaap Valk. We were encouraged by many positive reactions from colleagues in different disciplines including radiology, neurology, psychiatry and geriatrics. Since then, so many developments have taken place that a completely new title was needed. First of all, there are new diseases, or new insights into existing disorders presenting with dementia. Secondly, a vast amount of new imaging studies on dementia disorders have become available. Thirdly, image processing techniques have made their entrance into clinical practice and have now been fully integrated. To reflect the incorporation of these developments and the more extensive coverage of other imaging modalities such as PET, we have chosen a new title, 'Neuroimaging in Dementia'.

Preparing a completely new book with a new team of authors also provides an opportunity to reorganise the material presented in our previous title. "Neuroimaging in Dementia" provides a consistent focus on MRI appearance as the guiding principle. In this vein, the classification of dementia has also been revised to follow the MRI appearance as strictly as possible. To enhance legibility and to be as clinically useful as possible, many tables and boxes are included. Last, but not least, a considerable number of new MRI and PET images has been introduced to the backbone of this book to create a true imaging atlas of dementia alongside the text.

We trust you will find this title informative and hope that it will find a place in your daily practice of managing patients with dementia.

Amsterdam — Frederik Barkhof and Philip Scheltens
London — Nick C. Fox
Porto — António Bastos-Leite

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List of Abbreviations

ACA	Anterior cerebral artery
AChEI	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADC	Apparent diffusion coefficient
ADEM	Acute disseminated encephalomyelitis
AGD	Argyrophilic grain disease
ALD	Adrenoleukodystrophy
AMN	Adrenomyeloneuropathy
ANA	Anti-nuclear antibodies
APBD	Adult polyglucosan body disease
APOE	Apolipoprotein E
APOEe4	Apolipoprotein E4 allele
APP	Amyloid precursor protein
ARWMC	Age-related white matter changes
ASA	Arylsulfatase A
ASL	Arterial spin labelling
AVM	Arteriovenous malformations
BBSI	Brain-boundary shift integral
BOLD	Blood oxygen-level dependent
BSE	Bovine spongiform encephalopathy
CA	Cornu ammonis
CAA	Congophilic amyloid angiopathy
CACH	Childhood ataxia with central hypomyelination
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBD	Corticobasal degeneration
CBF	Cerebral blood flow
CBS	Corticobasal syndrome
CHMP2B	Charged multivesicular body protein 2B
CJD	Creutzfeldt-Jakob disease
CKD	Chronic kidney disease
CNS	Central nervous system
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
Cr	Creatine
CRP	C-reactive protein
CSF	Cerebrospinal fluid

CT	Computed tomography
CTX	Cerebrotendinous xanthomatosis
DAI	Diffuse axonal injury
DAVF	Dural arteriovenous fistula
DIR	Double-inversion recovery
DIS	Dissemination in space
DIT	Dissemination in time
DLB	Dementia with Lewy bodies
DMN	Default-mode network
DNTC	Diffuse neurofibrillary tangles with calcification
DPHL	Delayed posthypoxic leukoencephalopathy
DRPLA	Dentatorubral-pallidoluysian atrophy
DSA	Digital subtraction angiography
DSC	Dynamic susceptibility contrast
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
EEG	Electro-encephalography
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyograph
EPI	Echo-planar imaging
ESR	Erythrocyte sedimentation rate
FA	Fractional anisotropy
FBD	Familial British dementia
FD	Fabry's disease
FDD	Familial Danish dementia
FDG	Fluorodeoxyglucose
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FFI	Fatal familial insomnia
FLAIR	Fluid attenuation inversion recovery
FMR1	Fragile X mental retardation gene-1
fMRI	Functional magnetic resonance imaging
FSE	Fast spin echo
FTD	Frontotemporal dementia
FTDP-17	Frontotemporal dementia with parkinsonism linked to chromosome 17
FTLD	Frontotemporal lobar degeneration
FUS	Fused-in-sarcoma
FXTAS	Fragile X-associated tremor/ataxia syndrome
GALC	Galactocerebrosidase
GCA	Global cortical atrophy
GE	Gradient echo
GFAP	Glial fibrillary acid protein
GFR	Glomerular filtration rate
GLD	Globoid leukodystrophy
GM	Grey matter
GRN	Progranulin
GSD	Glycogen storage disorder
GSS	Gerstmann-Sträussler-Scheinker
HAART	Highly active anti-retroviral therapy

HAND	HIV-associated neurocognitive dysfunction
HCHWA	Hereditary cerebral hemorrhage with amyloidosis
HCV	Hippocampal volume
HD	Huntington' s disease
HDL	Huntington's disease-like
HIV	Human immunodeficiency virus
HIVE	Human immunodeficiency virus encephalitis
HLA	Human leukocyte antigen
HMPAO	Hexamethylpropylene amine oxime
HSE	Herpes simplex encephalitis
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus type-1
IBMPFD	Inclusion body myopathy associated with Paget's disease and frontotemporal dementia
ICA	Independent component analysis
^{123}I-MIBG	Iodine-123 metaiodobenzylguanidine
IRIS	Immune reconstitution inflammation syndrome
IVL	Intravascular lymphomatosis
KSS	Kearns-Sayre syndrome
LB	Lewy bodies
LBD	Lewy body dementia
LE	Limbic encephalitis
LPA	Logopenic aphasia
MAO	Monoamine oxidase
MAPT	Microtubule-associated protein tau
MBs	Microbleeds
MCA	Middle cerebral artery
MCI	Mild cognitive impairment
MCP	Middle cerebellar peduncles
MD	Mean diffusivity
MELAS	Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
MGC	Multinucleated giant cells
MID	Multi-infarct dementia
MLD	Metachromatic leukodystrophy
MNGIE	Mitochondrial neuro-gastrointestinal encephalopathy
MPR	Multi-planar reconstruction
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MS	Multiple sclerosis
MSA	Multiple system atrophy
MT	Magnetization transfer
MTA	Medial temporal lobe atrophy
MTR	Magnetization transfer ratio
NAA	N-acetyl aspartate
NAL	Neuroaxonal leukodystrophy
NBIA	Neurodegeneration with brain iron accumulation
NFT	Neurofibrillary tangles

NIFID	Neuronal intermediate filament inclusion disease
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NMDA	N-methyl d-aspartate
NMO	Neuromyelitis optica
NPH	Normal pressure hydrocephalus
OPCA	Olivopontocerebellar atrophy
PAS	Periodic acid-Schiff
PC	Phase-contrast
PCA	Posterior cerebral artery
PCR	Polymerase chain reaction
PD	Parkinson's disease
PDD	Parkinson disease dementia
PET	Positron emission tomography
PIB	Pittsburgh compound B
PKAN	Pantothenate kinase-associated neurodegeneration
PML	Progressive multifocal leukoencephalopathy
PNFA	Progressive nonfluent aphasia
PPA	Primary progressive aphasia
PRES	Posterior reversible encephalopathy syndrome
PSEN	Presenilin
PSP	Progressive supranuclear palsy
PWI	Perfusion-weighted imaging
REM	Rapid eye movement
ROI	Region-of-interest
RPLS	Reversible posterior leukoencephalopathy syndrome
RRMS	Relapsing/remitting multiple sclerosis
SAE	Subcortical arteriosclerotic encephalopathy
SCA	Spinocerebellar ataxia
SCP	Superior cerebellar peduncle
SD	Semantic dementia
SIVD	Subcortical ischemic vascular dementia
SLE	Systemic lupus erythematosus
SPECT	Single-photon emission computed tomography
SPM	Statistical parametric mapping
SSPE	Subacute sclerosing panencephalitis
SVD	Small vessel disease
SVD	Subcortical vascular dementia
SWI	Susceptibility-weighted imaging
TBI	Traumatic brain injury
TEA	Transient epileptic attacks
TGA	Transient global amnesia
THC	Tetrahydrocannabinol
TSE	Transmissible spongiform encephalopathy
TSE	Turbo spin echo
VaD	Vascular dementia
VBM	Voxel-based morphometry
VCP	Valosin-containing protein

VGKC	Voltage-gated potassium channel
VLCFA	Very-long-chain fatty acids
VRS	Virchow-Robin spaces
VWM	Vanishing white matter
WE	Wernicke's encephalopathy
WK	Wernicke-Korsakoff's syndrome
WM	White matter
WMC	White matter changes
WMH	White matter hyperintensity
WML	White matter lesions

How to Use This Book? 1

Contents

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1.1 General Background

The focus of this book is on the practical use of neuroimaging in dementia in a clinical diagnostic setting. We felt that there are many publications that describe the imaging findings of a particular disease, but you first need to know what the diagnosis is in order to look up articles describing those findings. As well as offering a summary of the findings in the most relevant conditions causing cognitive decline we wished to provide a guide to interpreting a particular imaging finding. The organization of the book therefore takes as departure point the dominant imaging findings and incorporates the clinical features along the way. The topic of vascular dementia does not easily fit with this approach due to its heterogeneous appearance; however, it does form a natural bridge between primary white and grey matter disorders. The 'route map' aims to direct the reader towards additional tests (imaging and non-imaging) and clinical features in a practical way.

Etiological, pathogenetic and clinical information are given as a reference, mainly as a background to understand and interpret imaging findings, not to provide an encyclopaedic text on all aspects on dementia – the interested reader will easily find her/his way to dedicated textbooks on genetics, biochemistry, histopathology and others.

Structural MR imaging is the lead theme largely because of its central position in clinical practice in many countries. Each chapter contains suggestion about the imaging strategy (e.g. which sequences to apply) and interpretation (e.g. salient features to look for) within a given clinical context (e.g. young age at onset). When appropriate, suggestion are provided for non-conventional MR techniques, such as diffusion-weighted

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MR, indications for nuclear medicine techniques (e.g. PET), or other diagnostic tests, such as CSF analysis.

1.2 Main Classification System

There are many ways to classify dementing disorders, e.g. sporadic/inherited, cortical/subcortical, all of which have their limitations. Classification according to histopathology (e.g. with or without certain type of inclusion bodies) is conceptually attractive, but clinically not very useful. By contrast, structural (MR) imaging is often performed in the work-up of a patient presenting with cognitive decline (even if only to exclude surgical pathology) and provides an increasingly useful angle of thought – or point of departure.

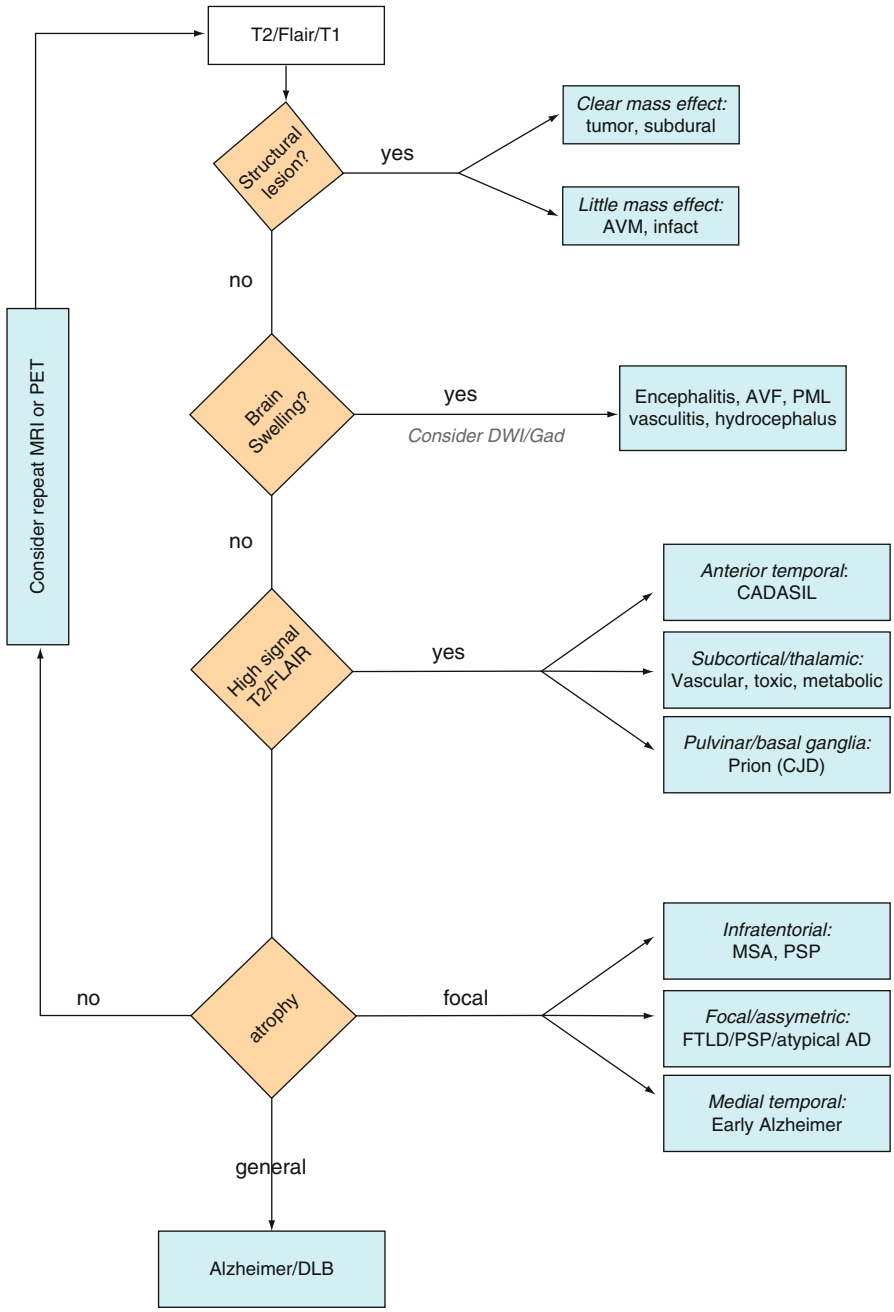
Our classification system is based roughly on four dominant imaging patterns:

- Primary grey matter loss – neurodegenerative diseases such as Alzheimer
- Vascular dementia – combined white and grey matter damage
- Primary white matter disorders – e.g. HIV encephalitis and metabolic disorders
- Disorders associated with brain swelling

While the lead theme of dominant neuroimaging finding may be useful in many circumstances, there are many patients in whom a clinical clue (e.g. visual hallucinations) can be more relevant than the non-specific imaging findings (diffuse cortical atrophy in case of Lewy body dementia). Other clinical settings, e.g. rapidly progressive cognitive decline, may lead to a differential diagnosis that may run across the disease clusters as reflected by the main chapters. Such alternative slicing patterns are presented throughout the book.

1.3 A Route-Map or Classification Tree

A key goal of imaging is to exclude a neurosurgically treatable cause of dementia (see e.g. Practice Parameter AAN); an MR scan performed for such an indication will include a T2-weighted sequence (e.g. FLAIR) which provides a useful starting point for our purpose.



The flow diagram above provides an example of how a series of assessments can be used to lead into the main diagnostic groups as represented in this book. It should be noted that although a 'main finding' may be a key pointer there can be considerable overlap of findings. Incidental white matter lesions for example will present in many elderly subjects, and occur with increased frequency in patients with Alzheimer's disease. Additionally, combinations of pathology are the rule rather than the exception in the very old, especially Alzheimer's and Vascular dementia.

Dementia: Clinical Background

2

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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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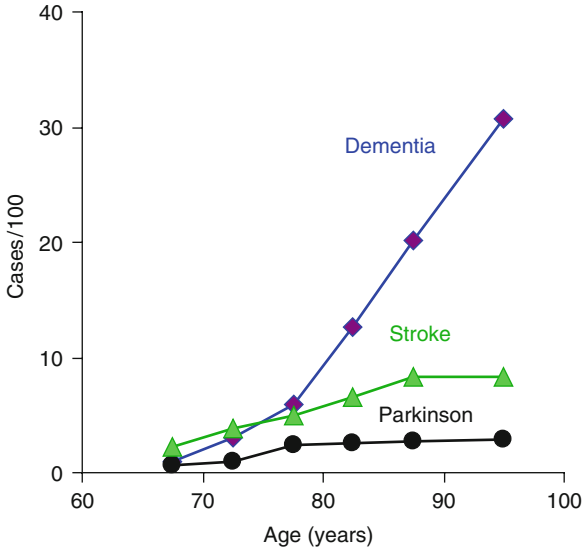

Fig. 2.1 Prevalence of three age-associated syndromes. Dementia shows the highest increase in numbers with advancing age (*Eurodem*)

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.

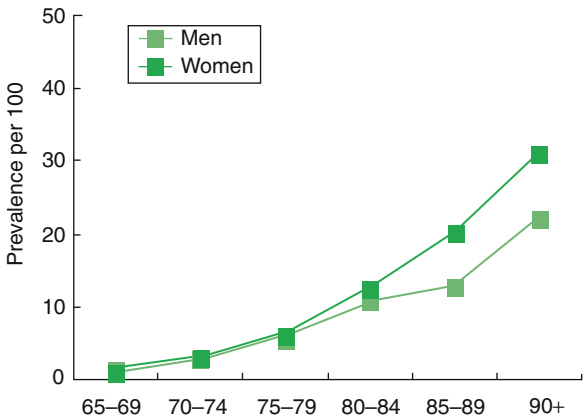

Fig. 2.2 Prevalence rates of dementia among men and women after the age of 65. (After Lobo et al. (2000) Neurology 54(11 Suppl 5):S4–S9)

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.

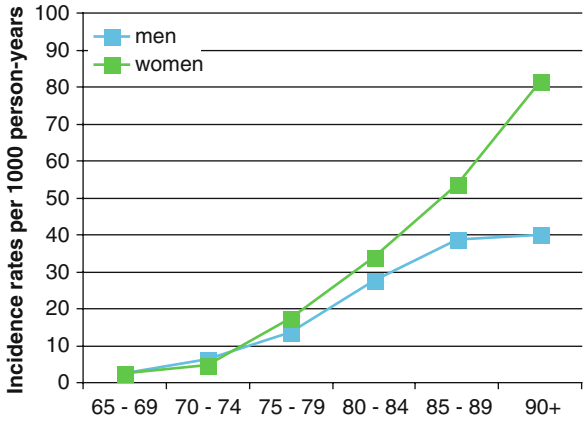

Fig. 2.3 Pooled incidence rates of dementia by sex. (Data from Fratiglioni et al. (2000) Neurology 54(11 Suppl 5):S10–S15)

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