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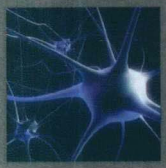
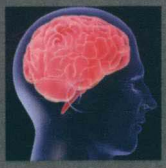
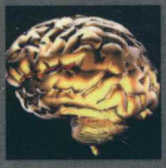
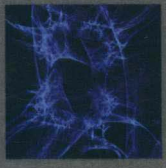

Alzheimer's Disease

Edited by
GUNHILD WALDEMAR
ALISTAIR BURNS

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Alzheimer's Disease

Second edition

Edited by

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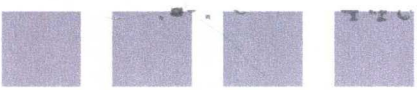

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Abbreviations

ABAD	Amyloid β-peptide binding protein alcohol dehydrogenase
ABC	ATP-binding cassette
ACP	Advance care planning
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease Assessment Scale
ADI	Alzheimer's Disease International
ADRT	Advance decision to refuse treatment
AICD	APP intracellular domain
APh	Anterior pharynx-defective phenotype
APOE	Apolipoprotein
APP	Amyloid precursor protein
AT	Assistive technology
BACE	β-site APP cleaving enzyme
BDNF	Brain-derived neurotrophic factor
BPSD	Behavioural and psychological symptoms of dementia
BRACE	Bristol Research into Alzheimer's Disease
CCT	Cranial computed tomography
CDK	Cyclin-dependent kinase
CDRSB	Clinical Dementia Rating scale–sum of boxes
ChEI	Cholinesterase inhibitor
CIBIC	Clinicians Global Impression of Change
CR	Complement component receptor
CREB	cAMP-response element binding protein
CSF	Cerebrospinal fluid
DAD	Disability Assessment for Dementia
DAT	Dopamine transporter scanning
DLB	Dementia with Lewy bodies
DSM	Diagnostic Statistical Manual of the American Psychiatric Association
EEG	Electroencephalography
EFNS	European Federation of the Neurological Societies
EPA	Enduring Power of Attorney
FAD	Familial Alzheimer's disease
FAQ	Functional Activities Questionnaire
FCSRT	Free and cued selective reminding test

FDG-PET	Fluoro-deoxy-glucose positron emission tomography
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GDS	Global Deterioration Scale
GFAP	Glial fibrillary acidic protein
GP	General practitioner
GSK	Glycogen synthase kinase
GWAS	Genome Wide Association Studies
HDL	High-density lipoprotein
ICT	Information and communication technologies
IDE	Insulin-degrading enzyme
IMCA	Independent Mental Capacity Advocate
iNOS	Inducible nitric oxide synthase
LMIC	Low- and middle-income countries
LPA	Lasting Power of Attorney
LRP	Low-density lipoprotein receptor-related protein
LTD	Long-term depression
LTP	Long-term potentiation
LXR	Liver X receptor
lyPPA	Logopenic variant progressive aphasia
MCA	Mental Capacity Act
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MOA	Monoamine
MOCA	Montreal Cognitive Assessment
mPTP	Mitochondrial permeability transition pore
MRCCFA	Medical Research Council Study on Cognitive Function and Ageing
MRI	Magnetic resonance imaging
NDMA	*N*-methyl-D-aspartate
NFT	Neurofibrillary tangles
NGF	Nerve growth factor
NHS	National Health Service
NIA–AA	National Institute on Aging–Alzheimer's Association
NICE	National Institute for Health and Care Excellence
NO	Nitric oxide
NPI	Neuropsychiatric Inventory
NSAIDs	Non-steroidal anti-inflammatory drugs
PCA	Posterior cortical atrophy
PEG	Percutaneous endoscopic gastrostomy
PEN	Presenilin enhancer

PET	Positron emission tomography
PHF	Paired helical filaments
PiB	Pittsburgh compound B
POA	Power of Attorney
PPA	Primary progressive aphasia
PPAR	Peroxisome proliferator-activated receptor
RCT	Randomized controlled trial
REM	Rapid eye movement
ROS	Reactive oxygen species
RXR	Retinoid X receptor
RYR	Ryanodine receptor
sCJD	Sporadic Creutzfeldt–Jakob disease
SES	Socioeconomic status
SIB	Severe Impairment Battery
SORL	Sortilin-related receptor
SPECT	Single photon emission computed tomography
SSRI	Selective serotonin re-uptake inhibitor
TACE	Tumour necrosis factor-α converting enzyme
TNF	Tumour necrosis factor
TREM	Triggering receptor expressed on myeloid cells
VASCOG	International Society of Vascular Behavioural and Cognitive Disorders
VLDL	Very low-density lipoproteins

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Alzheimer's Disease

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Chapter 1

Dementia disorders: an overview

Roland Zahn and Alistair Burns

Key points

- Dementia is a clinical syndrome which comprises three domains: cognitive impairments, behavioural symptoms, and impairments of activities of daily living
- Dementia may be caused by a wide range of brain disorders and systemic conditions. Alzheimer's disease (AD) is the most frequent cause of dementia
- Clinical interview, neuropsychological assessments, brain imaging, routine blood tests, and neurological examination are the most important instruments for differentiating between the causes of dementia

1.1 What is dementia?

Dementia is a clinical syndrome operationally defined as cognitive impairment in at least two domains interfering with activities of daily living (Diagnostic Statistical Manual of the American Psychiatric Association: DSMIIIR and DSMIV-TR). Dementias are called major neurocognitive disorders in DSM-5, where impairment in only one domain documented by concern of patient or informant and neuropsychological tests, as well as interference with independence in everyday activities, is required. Classically, dementias referred to global cognitive impairment and always included prominent memory impairment. With the improvement of treatment, management, and diagnostic procedures, dementia disorders are detected at earlier stages and therefore the symptoms can often be focal rather than global. Dementia syndromes can also start with other symptoms than memory, for example language problems.

Although dementia in elderly people has been recognized by clinicians since a long time, it was only at the turn of the twentieth century that different causes and forms of dementia became suspected. This was possible due to following up patients with dementia syndromes during the course of their illness until death and then microscopically investigating silver-stained slices of their brains post-mortem.

In 1906, Alois Alzheimer described neurofibrillary tangles and senile plaques in the brain of patient Auguste D. who had suffered from a progressive dementia, which we now call Alzheimer's disease (AD) in recognition of this discovery. Despite these early case reports, it was not until the end of the twentieth century that sensitive clinical criteria were formulated that predict a probable post-mortem neuropathological diagnosis of AD. The sensitivity of clinical criteria for probable AD is very good (sensitivity above 80% with a specificity of about 70%). This means that the clinical diagnosis of AD is correct in most patients but that we may still diagnose somebody with probable

AD when neuropathology would show a different cause. Conversely, there are some patients with atypical symptoms who exhibit AD-typical neuropathological changes post-mortem, however with an atypical regional distribution leading to atypical symptoms. This differential diagnostic challenge will become increasingly important in the future when costly disease-modifying treatments become available, especially in case these treatments have serious side-effects.

1.2 How frequent is dementia?

The prevalence of dementia increases with age, doubling with every five-year increase. Between 65 and 69 years of age the prevalence of dementia is estimated at 1.3% in the United Kingdom, rising up to 32.5% in people older than 95 years. Estimates of frequency of subtypes of dementia should be interpreted with caution because the clinical information available in large epidemiological studies is often insufficient for accurate differential diagnosis. Frontotemporal dementia (FTD) may be as likely as AD in patients younger than 65 years, but most people with dementia are late-onset patients (around 98% of all dementia patients in the United Kingdom). At least 60% of dementias are caused by AD and the proportion is higher if cases with additional vascular changes are considered (i.e. 'mixed dementia').

1.3 Different forms of dementia and their diagnosis

One of the most important diagnostic instruments is the interview with a caregiver of the patient. In this interview it is important to ask for the first and most prominent symptom, the 'lead' symptom of the disease which often dates from many years earlier. Further, it is crucial to ask about the course of the problem, whether it started slowly or suddenly and at what pace the progression was noted.

Time course and lead symptoms indicate which diseases one needs to consider and rule out. As a general rule, one should be alarmed when there is a sudden or subacute onset, i.e. if the dementia syndrome has developed within weeks from normal functioning. Particular diagnostic attention should also be paid to rapidly progressing dementia syndromes in which there is marked decline within three to six months after onset. In both subacute onset or rapid decline, one needs to initiate a more detailed diagnostic assessment. This includes usually an analysis of the cerebrospinal fluid (CSF) to determine cell count and 14-3-3 protein sensitive to Creutzfeldt–Jakob disease (CJD) and the exclusion of encephalopathies caused by autoimmune or inflammatory diseases. A magnetic resonance imaging (MRI) examination including axial and coronal T1-, T2-, fluid-attenuated-inversion-recovery, and diffusion-weighted images is needed in these patients. Electroencephalography (EEG) usually shows general slowing in encephalopathy patients. In CJD there are often characteristic triphasic complexes.

In the clinical history and blood tests it is also important to look for signs of an occult cancer (e.g. increased blood sedimentation rate) which may in rare cases lead to autoimmune reactions with antibodies directed towards neural tissue, or could cause brain metastases which do not necessarily show up on a cranial computed tomography (CCT) without contrast. In those cases an MRI should be considered. When cognitive impairment is slowly progressive, the neurological exam is otherwise normal and routine diagnostic assessments do not contradict a neurodegenerative disorder, then the diagnosis of a probable cause of dementia is guided by lead symptoms and the neuropsychological test profile (for an overview see Figure 1.1). In neurodegenerative dementias,

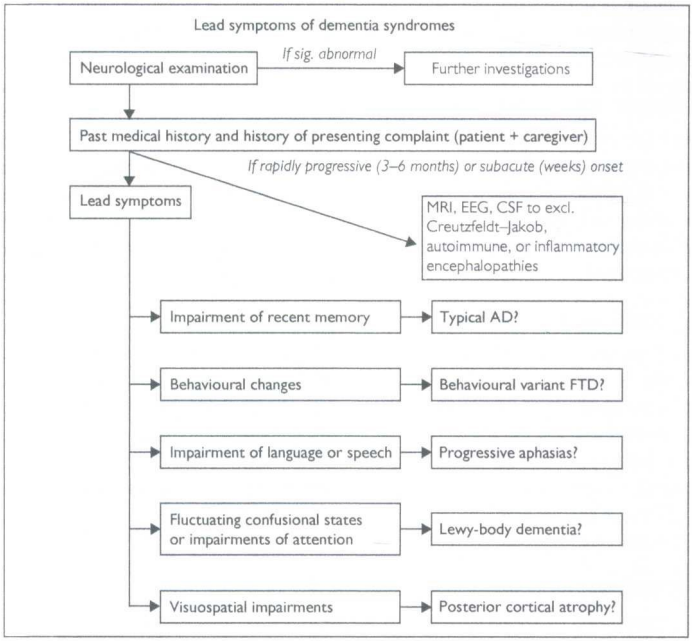

Figure 1.1 'Lead' symptoms are the most prominent and first symptoms to appear in the course of a dementia syndrome. Lead symptoms differ because neurodegeneration starts in different regions of the brain before spreading to other parts. Often they need to be explored retrospectively. This overview considers progressive cognitive disorders in which neurological symptoms (e.g. rigor, akinesia, muscle fasciculations, gaze palsy, orthostatic dysregulation and bladder incontinence, hyperkinetic movements, abnormal pupillary responses) are not prominent. If such symptoms are present, other forms of dementia need to be considered which are not discussed here. A CCT without contrast is needed in all patients to exclude haematoma, larger tumours, and normal pressure hydrocephalus. The degree of large or small vessel disease needs to be assessed on CCT. Neuropsychological test examination is necessary to identify characteristic profiles of impairment for different forms of dementia and to get objective confirmation of clinical reports. Other causes of dementia syndromes need to be considered if the clinical history or routine laboratory points to complex-partial seizures, chronic alcoholism, autoimmune disorders, signs of occult cancer or renal or liver failure, electrolyte changes, thyroid dysfunction, vitamin B12 and folate deficiencies. 'Lead' symptoms point in the direction of possible syndrome diagnoses. A syndrome is a combination of clinical symptoms and/or criteria which is defined in order to correspond most closely to a specific disease (i.e. aetiology). Here, we give an overview of which syndrome diagnoses one needs to consider for slowly progressive cognitive disorders in which the neurological exam and CCT appears normal or only shows atrophy and minor vascular changes. In order to establish a clinical syndrome diagnosis, one needs to check consensus criteria for the particular diagnosis (see suggested readings). As discussed in the text, it is impossible to find a one-to-one correspondence between a clinical syndrome diagnosis and a neuropathologically defined disease, but there are probabilistic associations.

the non-contrast CCT can appear normal or may show atrophy or small-vessel disease affecting less than one-quarter of the white matter. Differential diagnostic specificity increases when looking at regional distribution of abnormalities on structural T1-weighted MRI, diffusion tensor-weighted MRI, 18-fluoro-deoxy-glucose positron emission tomography (FDG-PET), amyloid-beta (Aβ) biomarkers in CSF or amyloid

PET. Quantitative analysis of images is more sensitive and specific but rarely practiced in clinical settings (e.g. see Figure 1.2). See Chapter 5 for a detailed overview of the diagnosis of AD.

1.3.1 Impairment of recent memory

The lead symptom of impairment of recent memory is characteristic of typical AD. Patients cannot remember important events, such as family gatherings, which happened weeks or days ago. Old memories, such as childhood events, are relatively spared in the beginning of the disease. Impairments of recent memory are associated with the degree of damage to the medial temporal lobe and posterior cingulate cortex which are affected early in the course of typical AD (see Figure 1.2).

1.3.2 Behavioural changes

The lead symptom of behavioural changes with intact recent memory and visuospatial skills is characteristic for the behavioural variant of frontotemporal dementia. Patients often show socially inappropriate behaviour (e.g. touching strangers), obsessive–compulsive behaviours (e.g. hoarding, repetitive behaviours, clock watching), and changes in food preference (e.g. preference for sweet foods). Neuropathology often shows classic Pick bodies in these patients. In some patients, standard neuropsychological tests can be normal, but caution is needed when making a diagnosis without neuropsychological or neuroimaging confirmation.

1.3.3 Impairment of language or speech

The lead symptom of language impairment with intact non-verbal memory and visuospatial skills is characteristic of fluent and non-fluent forms of progressive aphasia. The fluent form is called semantic dementia because patients do not only lose the ability

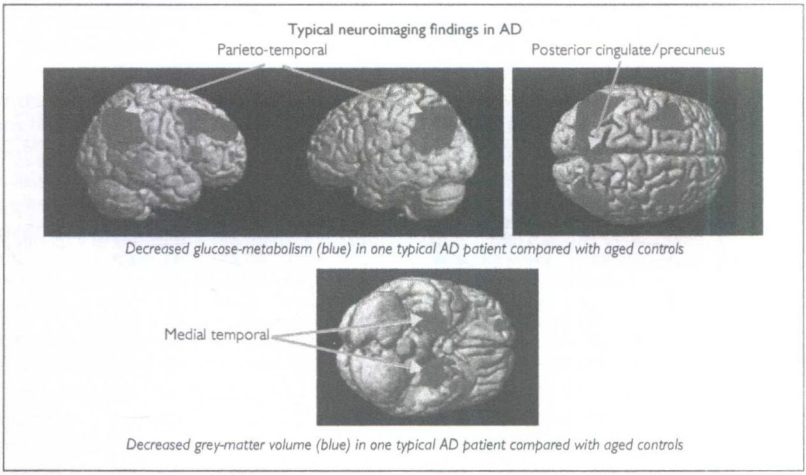

Figure 1.2 Brain regions typically involved in patients with mild to moderate stages of AD are depicted: medial temporal lobe, posterior cingulate/precuneus and parieto-temporal cortex.

Data from unpublished single case analysis using Statistical Parametric Mapping Software (<http://www.fil.ion.ucl.ac.uk/spm/>, group results and methods further described in Zahn, *et al.*, *Psych. Res.: Neuroimaging* (2005). 140: 115–31).

to understand the meaning of words but also of non-verbal material such as pictures. Both forms are classified as forms of frontotemporal lobar degeneration, often confirmed by neuropathology. However, non-fluent patients frequently turn out to have AD with atypical distribution on neuropathology. Patients with progressive aphasia usually show intact delayed recall of geometric figures (e.g. a circle) from memory which distinguishes them from patients with typical AD on neuropsychology.

1.3.4 Fluctuating confusional states or impairments of attention

Fluctuating confusional states warrant exclusion of autoimmune, inflammatory, paraneoplastic (i.e. antibodies against neural tissue in patients with occult cancer) as well as toxic and metabolic causes. The picture can occur together with visual hallucinations and neuroleptic hypersensitivity or Parkinsonian features in Lewy-body dementia. Multiple strokes or small vessel disease within the basilar artery territory also need to be considered.

1.3.5 Visuospatial impairments

Some patients show predominantly visuospatial and apraxic difficulties due to atrophy of the occipital or parietal lobes (posterior cortical atrophy). Most of these patients show AD-typical neuropathology with atypical distribution.

1.3.6 Vascular dementia

The diagnosis of vascular dementia or 'major vascular cognitive disorder' according to the International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) criteria can only be made based on neuroimaging showing either multiple large vessel disease-related strokes, an extensive single infarct or haemorrhage in critical areas (usually thalamus or basal ganglia), multiple lacunar infarcts or haemorrhages in these areas, or extensive and confluent white matter lesions (more than one-quarter of the total white matter had been previously suggested). Despite these criteria, we have seen patients with extensive haemorrhages to basal ganglia and thalamus on MRI scans who showed mild cognitive impairments but no major changes in functioning after recovering from the acute phase. Milder cerebrovascular changes often contribute to the cognitive decline in AD and the distinction between 'mixed' dementia versus pure AD is gradual. White matter hypodensities on CCT do not need to be vascular; they can also point to other white matter diseases and should be carefully evaluated in marked cases. CSF analysis may be needed for differential diagnosis against inflammatory causes of white matter diseases.

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