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Definition, clinical features and neuroanatomical basis of dementia

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Introduction

Dementia is a frequent consequence of neurodegenerative diseases involving the cerebral cortex. Unlike stroke, encephalitis or head injury, which lead to relatively circumscribed and stable brain damage, degenerative disorders often affect many regions of the brain. The widespread changes in brain structure and the multiple signs of cognitive impairment that result from such changes have led to a conceptualization of the degenerative dementias, and especially of Alzheimer's disease, as 'diffuse' pathological processes, but this is not strictly true. The degenerative dementias, including Alzheimer's disease, do not affect the entire cerebral cortex equally. Instead, the degenerative dementias are associated with varied profiles of anatomic involvement, which can be tracked by quantitative histopathological and neuroimaging techniques. Association and limbic regions suffer the brunt of the damage.

It is widely accepted that cognition is supported by distributed neural systems, and that it is susceptible to dissociation by focal brain damage. Despite continued uncertainties about the physiology underlying normal cognition, locally and globally, the pathological functional anatomy of many cognitive disorders is beginning to be elucidated. Classic examples of such disorders and their anatomic correlates include anterograde declarative amnesia, which is due to lesions of the hippocampal formation and adjacent mesial temporal lobe structures; aphasia, which is due to lesions in the left perisylvian cerebral cortex; ideomotor apraxia, which is due to lesions of the left parietal lobe; and simultanagnosia, which is due to bilateral lesions of the dorsal occipital and parietal lobes. The clinical manifestations of degenerative processes clearly depend in part on which neural structures and systems are affected earliest and most extensively. It is now apparent that degenerative dementia can present with impairments resembling any of the classic 'focal' disorders listed above.

In this introductory chapter, we review the clinical features of the cortical dementias, including their profiles of cognitive impairment. We then review the evidence that the profile of involvement of association and limbic regions determines the profile of cognitive impairment. These relationships recapitulate many of the relationships that have been observed in focal, stable brain damage. The syndrome of primary dementia (dementia without other neurological signs) reflects relative sparing of primary motor and sensory cortex and of subcortical structures. The prominent amnesic component of Alzheimer's disease is accounted for by the early and salient involvement of mesial temporal structures. The data supporting this conclusion will be considered in some detail. Variant patterns of involvement of neocortical regions in Alzheimer's disease have predictably altered clinical correlates. Lesion-deficit correlation is a promising approach in the study of other degenerative diseases, such as frontotemporal lobar atrophy and dementia with Lewy bodies.

Since the first version of this chapter, remarkable progress has been made on several fronts in neuropathology and neurology. As the existence of this volume testifies, there now exists a greatly improved description of the neuropathology of dementia, due in part to increasing success in characterizing these disease processes at the molecular level, and in developing more specific staining techniques. This is particularly true for the frontotemporal

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lobar atrophies. At the same time, registries of research subjects with dementia and their associated autopsy series, have greatly extended the amount of data available for clinico-pathological correlation. These data have been leveraged in clinical research due to the universal availability of high resolution anatomic clinical imaging, which now routinely reveals a great deal of anatomic information in living patients with dementia (e.g. the degree of regional cerebral atrophy). Increasingly, sophisticated structural and functional imaging techniques are being used in clinical research, which are sensitive to losses of gray matter and metabolic activity early in the course of degenerative disease. Further, these quantitative techniques allow the investigation of the anatomic correlates of indices of impairment of particular aspects of cognition. These developments in the molecular biology and imaging of degenerative disease permit us to address the main questions of this chapter in greater detail than was previously possible.

Definitions and clarifications

The ICD-10 definition of dementia illustrates the prevailing concept of dementia. A diagnosis of dementia requires: (a) impairment in short- and long-term memory; (b) impairment in abstract thinking, judgement, higher cortical function, or personality change; (c) memory impairment and intellectual impairment, which cause significant social and occupational impairments; and (d) the occurrence of these traits when patients are not in a state of delirium.

As this set of criteria emphasizes, amnesia is a prominent feature of dementia, but the term implies broader cognitive impairment than amnesia *per se*. The paradigm on which this definition is based is Alzheimer's disease (AD), in which anterograde amnesia is one of the inaugural and salient features. Not all degenerative dementias share this profile, however, and although it is unusual for anterograde memory to be completely normal in a patient with any of the degenerative dementias, the clinical picture of dementia is sometimes dominated by other impairments, for example, in executive function or language, rather than memory. Consequently, a somewhat broader definition of dementia is a better foundation for developing a neurological clinical approach. In this perspective, *Dementia is an acquired and persistent impairment of intellectual faculties, affecting several cognitive domains, that is sufficiently severe to impair competence in daily living, occupation, or social interaction.*

Dementia implies involvement of multiple neural systems, supported by multiple anatomic structures. Isolated impairment of memory, language, visuospatial abilities or higher visual processes do not qualify *per se* as dementia, and are best denoted by the terms amnesia, aphasia or agnosia. Also, dementia implies a decline from a previously attained level of intellectual function (in contradistinction to developmental encephalopathies), but progressive impairment is not required to diagnose dementia. Dementia may be static, as it commonly is when closed head injury or large cerebral infarcts are the causes. Nevertheless, it is true that most dementing illnesses are progressive.

Definitions of dementia traditionally and explicitly exclude the sort of fluctuating encephalopathy which alters the level of consciousness and is known as a 'confusional state.' Although such fluctuating conditions are usually due to a metabolic disturbance, this exclusion criterion is problematic now that it has become clear that a fluctuating sensorium is a prominent feature in dementia with Lewy bodies (DLB). Finally, it must be stressed that dementia is a clinical term, not a pathological term. It is possible to have neuropathological changes of a particular degenerative disease without dementia. For example, pathological changes characteristic of AD may be associated with clinical mild cognitive impairment or with no demonstrable cognitive impairment. It is also possible to meet criteria for dementia without neuropathological changes in the brain, for example, in certain metabolic conditions or as a consequence of depression.

Objective memory or other cognitive impairment, which is not sufficiently severe to impair activities of daily living is defined as mild cognitive impairment (MCI) (Peterson *et al.*, 1999). Most cases of MCI are cases of mild and more or less circumscribed amnesia, but other forms of MCI exist, for example mild and more or less circumscribed anomia, and the mild impairments of executive dysfunction that presage frontotemporal dementia. However, these conditions are rarely recognized, and have hardly been studied. To our knowledge, no early autopsies of such cases have been reported. In the remainder of the chapter, we will use the terms amnesic MCI and MCI more or less interchangeably.

Current data suggest that patients with formally defined MCI worsen to the point of being classifiable as demented at a rate of approximately 10–15% per year (Morris *et al.*, 2001). Ultimately, more than half of these patients may develop dementia, though some do not, even after many years of follow-up. Mild cognitive impairment may be the earliest overt manifestation of AD in many patients. (But it is not

simultaneous with the appearance of the neuropathology of AD, which may precede symptoms by a number of years.) Whether all or most patients with AD pass through such a phase of 'amnesic MCI' remains to be determined; however, it is likely that amnesic MCI is the ordinary presentation of AD (Morris *et al.*, 2001). Since the previous version of this chapter, MCI has become a focus of intense research interest.

The observation that there are graded degrees of vulnerability to degenerative processes across brain regions and cortical laminae, and the fact that these diseases have presymptomatic phases, raise the question of what determines the transition from unaffected status to the status of MCI and to the status of dementia? What is the anatomic basis for the development of dementia? We review the evidence bearing on these questions for several degenerative conditions. The neuropathological basis of Alzheimer dementia will be discussed in the most detail, but we will also consider frontotemporal lobar degeneration (FTLD), Lewy body diseases; and Creutzfeldt–Jakob disease.

Clinical evaluation of dementia

In order to provide context for a discussion of the anatomic basis of the dementias, we will review briefly the contemporary clinical approach to dementia. We then provide an overview of the clinical features of the degenerative disorders which cause dementia. The reader is referred to the appropriate chapters in this volume for a fuller consideration of these topics.

General clinical approach

Neurologists and other clinicians are often called on to evaluate progressive or suspected progressive impairments of cognition. The first task of a clinician confronted with a patient suspected of dementia is to establish whether the patient's intellectual ability has been diminished relative to its prior level, and whether the patient's capacity to function in his/her accustomed occupational and social settings has been impaired. The clinician must decide whether the patient has apparently normal cognition, mild cognitive impairment, or dementia based on the formal evaluation of mental status (in the office and/or neuropsychology laboratory), coupled with estimation of the patient's premorbid intellectual abilities. Interviewing a relative, friend or companion is a necessary component of the evaluation, since the value of the self-report of the patient, which is usually crucial information in a medical encounter, is attenuated in this setting. Both overestimation and underestimation of the severity of one's own cognitive impairment are common. The former is common in normal ageing, adjustment disorders and depression. The latter arises when patients have poor insight into, or even unawareness of, their illness (anosognosia), which is very common in AD and FTLD.

Mild cognitive impairment is most often evident on tests of anterograde episodic memory, and on timed tests. Anterograde memory impairment in isolation is a common profile. The differential diagnosis in such cases includes other processes that preferentially affect mesial temporal lobe structures, such as epilepsy, anoxia, carbon monoxide intoxication, herpes simplex encephalitis, and paraneoplastic limbic encephalitis. However, a good history usually excludes most of these processes, and careful neuropsychological evaluation may demonstrate minor degrees of impairment in other domains of cognition.

When dementia is present, the clinician should attempt to classify it as primary dementia, dementia 'plus' or secondary dementia. The syndrome of dementia without any abnormal signs on neurological examination is sometimes called primary dementia. Its presence implies that the brunt of the pathological process falls on association and limbic regions rather than on the primary cortices and subcortical regions.

In other patients the neurological examination discloses dementia 'plus' elementary neurologic signs (e.g. dementia plus evidence of cerebrovascular disease, dementia plus parkinsonism, or dementia plus gait impairment). In each case, the additional neurological findings constitute an important diagnostic clue. In many of these diseases, the brunt of the pathological process is suffered by subcortical structures (white matter or grey matter) rather than association and limbic regions, and the cognitive profile will often be dominated by slowed cognition, apathy and poor problem solving rather than signs of cortical dysfunction, such as amnesia, agnosia or aphasia.

Secondary dementia is dementia caused by potentially treatable medical or surgical conditions, such as medication effects, depression, metabolic derangements or surgically approachable structural problems, such as chronic subdural hematoma or orbitofrontal meningioma. Secondary dementia is generally identified by its association with past medical or psychiatric history, laboratory evaluation and structural imaging.

The clinician should be prudent with respect to secondary dementia. The differential diagnosis of dementia is potentially vast, but the majority of possible conditions are neither reversible nor treatable given our current

knowledge. Although secondary dementia is not nearly as common as the leading degenerative conditions, some of these cases are treatable with a high degree of efficacy. Therefore, the clinician often concentrates on potentially treatable causes of dementia rather than adopting the wider point of view necessary to achieve a precise diagnosis. These include primary affective disorders, especially major depression ('pseudodementia of depression') and medication encephalopathy. Metabolic disorders (thyroid disease, hypovitaminosis B12, hypercalcemia, etc.), alcoholism, neurosyphilis and certain structural alterations (chronic subdural hematoma, normal pressure hydrocephalus, brain tumours) are also sought.

Since the 1990s, it has become clear that the profile of cognitive impairment across cognitive domains is also helpful in diagnosis. In some cases, the impairment predominantly affects one domain (e.g. progressive non-fluent aphasia). In others, several aspects of cognition are affected, and on occasion, it is mainly the speed and efficiency of cognition that is affected. The latter pattern is commonly a consequence of subcortical disease. Secondary dementia usually has a subcortical profile, not a focal or broad cortical profile. As noted, AD usually presents as a primary dementia with salient anterograde amnesia, and other impairments. In practice, many clinicians begin to suspect an alternative diagnosis when impairments in some domains are found to be 'disproportionate' to anterograde memory impairment, i.e. when there is a deviation from the Alzheimer profile. Some of these non-Alzheimer profiles have been tentatively codified with diagnostic criteria, particularly those with salient executive or language dysfunction.

Specific laboratory investigation of dementia still has limited diagnostic value, except for structural imaging, which is useful in most, if not all, patients to detect surgically approachable structural lesions that may cause or contribute to dementia (e.g. hydrocephalus), as well as evidence of cerebrovascular disease and asymmetric atrophy. Imaging is especially helpful in the evaluation of patients with suspected frontotemporal dementia. Executive function is difficult to evaluate in the clinic, but frontotemporal atrophy in these cases is usually obvious on MR images. As for functional imaging, its role is still being defined. Blood biomarkers have yet to be developed, and CSF biomarkers described to date have not been demonstrated to be sufficiently sensitive and specific to be useful. Genetic testing is becoming more important, but commercial tests are available only for the most common inherited form of AD (i.e. presenilin-1) and Huntington's disease.

The main causes of dementia

Alzheimer's disease

The most common aetiology of dementia is AD ease. The inaugural manifestation of AD is, almost always, memory impairment. More precisely, it frequently presents with an insidious anterograde amnesia for factual material. (Note that some diagnostic criteria, such as ICD-10 imprecisely equate anterograde memory impairment with 'short-term' memory impairment.) The constellation of primary dementia featuring anterograde memory impairment more or less corresponds to what has been termed the 'dementia of Alzheimer type'. Some perceptive families also note, in retrospect, that patients with AD have had subtle alterations in personality and affective symptoms. Once manifest, the disease pursues a slowly progressive but relentless course over 8–12 years, without remission. Memory difficulty becomes more pronounced. Visuospatial disorientation, and impaired word-finding appear within the first 3 years or so. Other cognitive deficits (loss of semantic memory, aphasia, apraxia, executive impairment) ensue, combined with a striking lack of insight into the presence and/or degree of impairment (anosognosia). Gait impairment and other motor signs do not appear until the final stage of the disease, when cognitive dysfunction is very severe.

The disease is equally notable for what it spares: patients regularly have no elementary motor or sensory deficits. It is as if all higher-ordered mental functions are singled out. The amnesic dementia of AD is the paradigm for the syndrome of primary dementia. Social graces are usually preserved for quite a while, giving way later to profound alteration in personality and sometimes psychosis, such as that manifested by Alzheimer's original case (Adams & Victor, 1989; Cummings & Benson, 1992).

The clinical research criteria for AD were formulated in 1984 by McKhann *et al.* These criteria, which are expected to be established by clinical examination and standardized brief mental status examination, and confirmed by neuropsychological tests, include: (a) deficits in two or more areas of cognition; (b) progressive worsening of memory and other cognitive function; (c) no disturbance of consciousness; (d) onset between ages 40 and 90; and (e) absence of other systemic or neurological disorders sufficient to account for the progressive cognitive defects. Note the similarity of these criteria to those of the ICD-10 for dementia, underscoring the fact that the prevailing definition of dementia is heavily influenced by the Alzheimer paradigm. Secondly, note the prominent exclusion criterion. These criteria do not permit a separation of AD from other degenerative dementias, notably FTLD

and DLB. Autopsy series have documented that the positive predictive value of the NINDS/ADRDA criteria is about 90%, although the negative predictive value is unclear.

Although an amnesic presentation applies to the majority of patients with AD, a substantial number have variant presentations. Some patients, for example, have early and prominent extrapyramidal signs or myoclonus; these patients tend to decline more rapidly (Mayeux *et al.*, 1985). Some patients have relatively greater language disturbance at the onset (Chui *et al.*, 1985). The pattern of pathology in these patients has yet to be discovered. On the other hand, a subset of patients presenting with prominent higher-order visual impairment have a distinctive pattern of pathology. This presentation and other 'focal' cognitive presentations will be considered later in this discussion.

Frontotemporal lobar degeneration

FTLD is the term applied to a group of conditions that also present with the syndrome of primary dementia. Investigation of FTLD is one of the most active areas of research in degenerative dementia, and the concepts are still evolving. In general, this cluster of diseases is characterized by disproportionate atrophy of the anterior frontal and temporal lobes. The cortex and white matter are both affected heavily, and the affected gyri may narrow to a 'knife-edged' configuration. The term FTLD encompasses the disorder formerly referred to as Pick's lobar atrophy, as well as frontal atrophy associated with motor neuron disease (Neary *et al.*, 1990; Peavy *et al.*, 1992); frontal atrophy without distinctive histopathology, also termed frontal lobe degeneration (FLD) (Brun & Passant, 1996); some cases of corticobasal degeneration and other rarer conditions. A striking gross pathological feature of these diseases is that the atrophy is often asymmetric, both with respect to the degree of involvement of the frontal and temporal lobes, and with respect to the degree of involvement of the right and left hemispheres. FTLD is usually manifested as a syndrome of frontotemporal dementia (FTD), in which the neuropsychological profile is dominated by defective executive function and social misconduct, rather than defects in memory and visuospatial function (Tissot *et al.*, 1985; Knopman *et al.*, 1989). The nomenclature is unfortunately confusing: FTLD is a general pathological term; FTD is a clinical term; and FLD is a term for a specific pathological subtype of FTLD. The clinical distinction of FTD from the dementia of AD can be difficult. As in AD, there is usually a paucity of non-cognitive neurological signs, and the disease progresses relentlessly over a 8–10-year period. Cases of FTD usually have prominent bilateral frontal involvement, though as mentioned above there is frequently left–right asymmetry. When the atrophy is lateralized to the left, dysfluent speech is usually present, and the syndrome might be termed progressive aphasic dementia.

When the atrophy is markedly lateralized to the left, there is a primary progressive aphasia, in which language disturbances dominate the clinical presentation, often for years, before more widespread deficits ensue. Two forms of progressive aphasia are now recognized: progressive non-fluent aphasia (PNFA), and semantic dementia. PNFA conforms more or less to a progressive aphasia of Broca type, with effortful, dysfluent, agrammatic speech, and is accompanied by left perisylvian (i.e. left inferior frontal and superior temporal) atrophy. Semantic dementia occurs in FTLD cases in which the atrophy is temporal-predominant, and left-lateralized. The earliest manifestation is frequently anomia, progressing to fluent, empty speech, impaired verbal comprehension, visual agnosia and general semantic loss.

Corticobasal degeneration (CBD), though usually thought of as being associated with parietal lobar atrophy, serves well to illustrate the difficulties encountered in clinical diagnosis in FTLD. The problem cuts two ways: variability of phenotype and variability of regional pathology. Boeve *et al.* (1999) evaluated a series of 13 cases of clinically diagnosed CBD. The pathological diagnosis was CBD in only 7, the other cases being AD, PSP, Pick's disease, non-specific histology, and CJD. Grimes *et al.* evaluated another series of 13 cases of pathologically confirmed cases of CBD. The clinical diagnosis was CBD in only four cases. A majority of the cases had dementia, which preceded the movement disorder. Speech difficulty, memory loss and dysexecutive presentations were common, and most of the patients did not have prominent apraxia at presentation. Surprisingly, the most consistently atrophied region was the frontal lobe (Grimes *et al.*, 1999).

Dementias with parkinsonism

Dementia presenting in association with parkinsonism is often not due to AD and raises a differential diagnosis of idiopathic Parkinson's disease (IPD), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). The most common presentation is dementia with levodopa-responsive parkinsonism, which may be due either to idiopathic Parkinson's disease (or combined AD and IPD) or dementia with Lewy bodies. Approximately 20 to 40% of patients with IDP eventually exhibit some degree of dementia, but in such cases dementia is not the presenting symptom, and the profile is usually one of 'subcortical' dementia, characterized by slowed cognition, impaired problem solving, and memory retrieval difficulty (with relative sparing of

recognition memory). In most such cases, concurrent AD is not present and cortical Lewy bodies, while they may be present in small numbers, are not prominent. In DLB, in contrast to IPD, cognitive symptoms are often the presenting complaint, and parkinsonism is often mild enough that treatment with levodopa is not recommended initially. In addition to the extrapyramidal signs, patients with DLB have a similar pattern of cognitive impairment to AD, but may have prominent and sustained fluctuations in performance (Ballard *et al.*, 2001), and salient hallucinations. In addition, patients may have more prominent visuospatial impairment than is the norm in AD. The current consensus criteria (McKeith *et al.*, 1996) for probable DLB are the presence of dementia and two of the three cardinal mentioned features (fluctuating sensorium/cognition, parkinsonism and visual hallucinations). Delusions, frequent falls and a REM sleep behaviour disorder are often present. Because of difficulty ascertaining the presence of fluctuation, the criteria appear insensitive in retrospective analyses, but perform better in prospective use (McKeith *et al.*, 2000).

Dementia with levodopa-unresponsive parkinsonism is usually due to either CBD or to PSP. In CBD, parkinsonism is usually markedly asymmetric and associated with signs of parietal lobe dysfunction, including apraxia and cortical sensory loss. Limb dystonia may be a presenting feature, and in some cases the alien limb phenomenon is prominent. Asymmetric, circumscribed parietal atrophy is often a feature, and tau-positive inclusions are found in neurons in basal ganglia. These features indicate that CBD is closely related to the frontotemporal lobar atrophies. Further underscoring the close relationship to FTLD, it is noteworthy that many cases which are classified as CBD at autopsy presented with dementia and frontal lobe atrophy (Grimes *et al.*, 1999).

PSP is usually characterized by parkinsonism, imbalance and vertical gaze abnormalities. The parkinsonism usually features axial rigidity. Supranuclear paresis of downgaze is particularly characteristic. Autopsy series have shown that a substantial number of cases of PSP present with dementia. The associated dementia was the paradigm for subcortical dementia (Albert *et al.*, 1974). Dementia may precede the eye movement abnormalities by a year or more.

Vascular dementia

Vascular dementia is commonly considered as the second most common cause of dementia in the United States. The diagnosis of vascular dementia depends on both clinical assessment and neuroimaging. Hachinski developed a clinical scoring system for distinguishing between AD and other degenerative and vascular dementia (Hachinski *et al.*, 1975). The score embodies features such as a stroke-like course of illness (abrupt onset, stepwise deterioration, fluctuating course), the presence of atherosclerotic vascular disease risk factors (hypertension, history of strokes, evidence of atherosclerosis) and signs of focal brain damage. A meta-analysis reported that the Hachinski score correctly classified 76% of AD cases, 84% of vascular dementia and 12% of mixed dementia (Moroney *et al.*, 1997). Present criteria go beyond the Hachinski ischaemic score, mainly by incorporating neuroimaging, which was not available routinely when the Hachinski scale was devised. Although this approach is useful in establishing an important role for vascular factors, it cannot distinguish between pure vascular dementia *per se* and mixed vascular and Alzheimer dementia. It is likely that many patients with vascular dementia have a component of AD (Hulette *et al.*, 1997; Snowdon *et al.*, 1997). Another set of diagnostic criteria for vascular dementia was drafted by an NINDS/AIREN task force. These research criteria diagnose probable vascular dementia on the basis of (a) dementia; (b) cerebrovascular disease evidenced by neurological signs and imaging; and (c) a relationship between (a) and (b) defined as the onset of dementia within 3 months of a recognized stroke or with abrupt onset and/or fluctuating stepwise progression. These criteria are relatively insensitive but very specific, and are meant to facilitate research rather than to be applied routinely clinically.

The form of dementia associated with small vessel ischaemic disease does not conform well to the progressive amnesic paradigm (i.e. Alzheimer-type dementia). The more common clinical correlate of ischaemic vascular dementia is one of general slowing and inefficiency of thought, impaired memory retrieval, poor problem solving, and apathy (i.e. the profile which has been termed 'subcortical dementia'). The cognitive defects are demonstrated most effectively with tests of executive function and of speeded information processing, neither of which is presented on the usual cognitive screening instruments such as the Mini-Mental State Examination. This is one reason why the prevalence of vascular dementia in the population has been difficult to ascertain.

Normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) is defined by the presence of ventricular enlargement, normal CSF pressure at the time of lumbar puncture, and a clinical picture of gait disorder, cognitive impairment and urinary incontinence. Many cases of NPH arise as a result of events leading to chronic impairment of CSF reabsorption, namely

subarachnoid hemorrhage, head injury, prior surgery or meningitis. The fully developed gait disorder is characterized by short slow steps, a failure to lift the feet from the floor, a wide base, and variable stepping force ('vertical ataxia'). It is frequently the first component of the triad to appear and often the most prominent. Early, prominent gait impairment is a predictor of successful shunting. The cognitive impairment usually conforms to the subcortical profile, though it can be confused with Alzheimer's disease or superimposed on it. Marked cognitive impairment is a predictor of unsuccessful shunting.

Creutzfeldt–Jakob disease

Prion diseases, though relatively uncommon, are another important cause of degenerative dementia. Creutzfeldt–Jacob disease (CJD) is the prototypical prion disease of humans. In the classic, myoclonic form of CJD dementia evolves rapidly after an insidious onset. The course usually includes a characteristic stage in which myoclonic jerks and startle responses are prominent. Highly characteristic periodic sharp waves are usually seen on the EEG at some phase of the illness. CJD is fundamentally a fulminant disorder in which the dissolution of cognition occurs in a few short weeks. Death follows in less than 6 months after onset. The profile of cognitive impairment varies from case to case. The Heidenhain variant of CJD presents as a rapid impairment of vision, even cortical blindness, due to spongiform changes beginning in the visual cortex. There is also a substantial variability in the pace of the disease. The variability relates in part to genetic factors, primarily to polymorphism at codon 129. Methionine homozygosity at codon 129 is characteristic of patients who develop the classic myoclonic form of CJD, whereas valine homozygosity or valine–methionine heterozygosity is associated with ataxic presentations, longer course, and less reliable diagnosis with EEG or 14-3-3 antigen assay.

A diagnosis of CJD can be made when periodic sharp waves are found on EEG in a patient with subacute dementia, normal standard MRI and normal CSF. Brain biopsy may be avoided. In the setting of subacute dementia and normal imaging, CSF assay for the 14-3-3 protein is highly sensitive and specific, but CSF 14-3-3 may be elevated in other settings that lead to widespread neuronal loss, including HSV encephalitis, recent ischaemic stroke, hypoxic–ischaemic encephalopathy, and Hashimoto thyroiditis. In some cases, brain biopsy may still be the only way to establish the diagnosis and exclude potentially treatable conditions, such as primary angiitis of the nervous system and other inflammatory conditions (see Chapter 5 for safety considerations).

In 1996 a new form of prion disease was identified among young British and French patients with a novel clinical phenotype characterized by ataxia, sensory loss, and psychiatric symptoms. These patients are methionine homozygous at codon 129, have no periodic sharp waves on EEG, and no prion protein mutations. The pathological changes differ from classical CJD, and include extensive prion protein plaques surrounded by intense spongiform degeneration. These cases are thought to be due to bovine spongiform encephalopathy, which has crossed the species barrier.

Differential diagnosis

The leading aetiology of dementia, accounting for at least half and possibly two-thirds of cases, is AD. Primary dementia with no other reasonable explanation is usually presumed to be AD. In AD, the anterograde amnesia may be moderate to severe before there is obvious impairment of other cognitive domains. The dementia of Alzheimer type, amnesic primary dementia, is the modal form of dementia, and departures from this profile (i.e. 'disproportionate' impairments in some other domain of cognition) raise the possibility of another diagnosis. In terms of prevalence, the second tier of dementing disorders is occupied by vascular dementia, FTLD, and DLB, all of which have been claimed to be the second most common cause of dementia. Vascular dementia is usually suggested by a history of stroke or significant cardiovascular disease, and compatible findings on imaging studies. FTLD may be suggested by a dysexecutive profile, but is probably most commonly recognized on the basis of the characteristic lobar atrophy on imaging studies. DLB is suggested by prominent psychiatric symptoms and parkinsonism, but may be difficult to distinguish from AD and IPD. All other causes of dementia are quite uncommon. Among the uncommon causes, hydrocephalic dementia (associated with gait difficulty and urinary incontinence), CBD (with asymmetric dopa-unresponsive parkinsonism, and apraxia), and CJD (associated with subacute course and often myoclonus) have the most distinctive presentations. Reversible secondary dementia is quite uncommon, probably accounting for about 1–2% of all cases of dementia.

Diagnostic challenges

While diagnosis of dementia has certainly improved substantially, it is still not as accurate as one could wish. Clinical diagnoses of dementia rely on recognizing patterns of neurological and cognitive impairment, rather than

on specific biomarkers or other laboratory approaches. Diagnostic problems arise because the neurological findings are usually non-specific, and the cognitive profiles may overlap. For example, both AD and FTLD manifest defects in executive function and memory. By the time FTLD presents to a neurologist, the disease may be quite advanced, as suggested by the discovery of pronounced lobar atrophy, and at that stage the associated amnesia may be comparable in severity to that of AD. Problems also arise because the processes that cause dementia are not mutually exclusive, and multiple factors may coexist in any given patient. Given the high base rate of AD, the most common overlaps are of AD and small vessel cerebrovascular disease; AD and cortical Lewy bodies; AD and metabolic disorders; and AD and IPD. Superimposed diseases present challenges for both diagnosis and management. Degenerative, vascular, and metabolic factors must all be considered for their relative contribution(s) to the patient's presentation as potential components of a dementing illness. In addition, depression may complicate AD, FTLD, parkinsonian syndromes or vascular dementia. Finally, in order to realize the potential benefit of therapies that slow down the natural history of dementia, the problem of early diagnosis will have to be tackled. Amnesic MCI which is an inaugural manifestation of AD will have to be distinguished from amnesic MCI with a benign prognosis. Additional challenges may lie ahead in detecting MCI at the inaugural stages in other degenerative diseases, such as FTLD and DLB.

The neuroanatomical basis of dementia

We have asserted that the degenerative disorders manifesting as dementia are not diffuse processes, in pathological terms. We have also reviewed the major aetiologies of dementia, which may present different cognitive profiles. The question arises as to whether the selective distribution of pathological changes explains the pattern of cognitive impairments in dementia. Is there a correspondence between the profile of cognitive deficits and the degenerating neural systems for given conditions or cases? Such a correspondence is not obligatory. For example, the pathological hallmarks of a disease could conceivably cause little dysfunction in the tissue, and the dysfunction could arise instead from an associated process that does not alter macroscopic structure (e.g. a neurotransmitter deficiency.) We were drawn to attempt a structural explanation of the dementias because the early manifestations of AD resemble, in some instances, some of the focal cognitive syndromes that have been observed in subjects with focal and stable brain lesions.

Normal functional neuroanatomy

Cognition and behaviour emerge from the dynamic activity within and between the nodes of distributed neural systems, particularly among association, limbic, and paralimbic regions, and their supporting subcortical structures and motor cortices. Regions tend to be relatively specialized for one or more functional aspects. In other words, the distributed neural systems underlying different aspects of cognitive function are regionalized (Damasio & Damasio, 1989), and cognition is susceptible to dissociation by focal brain damage. A wealth of information has been obtained concerning the nature of the mapping of cognitive function onto brain structure, principally from the lesion method, and more recently also from functional neuroimaging. Though a systematic discussion of the basic findings is beyond the scope of this chapter, some general principles of functional anatomy are important.

An overarching principle is that the posterior cortical regions (parietal, occipital, temporal lobes) are mainly concerned with perception and integration of sensory stimuli and with encoding knowledge, while anterior regions (frontal lobe) are mainly concerned with functions of an executive character, such as elementary and complex motor function, planning, manipulation of mental images, and strategic and complex allocation of processing resources. Another overarching principle of functional anatomy is hemispheric dominance. More than 90% of right-handers and at least 60% of left handers are left hemisphere-dominant for language, based on incidences of aphasia in stroke, as well as studies conducted with Wada tests. The right hemisphere plays a dominant role with respect to complex perceptual processing (for example, recognizing faces), emotion, the representation of body state and the spatial distribution of attention.

The functional correlates of a given cortical region depend in part on the functional type of cortex (primary, unimodal association, heteromodal association (higher order), or paralimbic/limbic), and in part on its location relative to the sensory and motor portal regions.

Unimodal sensory association regions have to do with perception in their proper sensory channel and are located near their primary regions. Thus the areas surrounding the primary visual cortex in the occipital lobe are concerned with higher aspects of vision, and when damaged lead to deficits that are confined to visually dependent tasks. Within these unimodal association regions there is substantial segregation of the sensory processing streams

representing the features and properties of individual entities, which are located in ventral occipital and temporal regions and those representing their location in space, which are located in lateral and dorsal occipital regions. Areas adjacent to the primary sensory cortex, in the parietal operculum or superior parietal lobule, are concerned with higher aspects of somatic sensation, and their damage leads to deficits confined to somatosensory tasks. The premotor and supplementary motor regions, just anterior to the primary motor cortex, are related to higher aspects of motor function, including motor preparation and planning and when damaged lead to motor disorders (e.g. akinesia).

The heteromodal (higher order) areas are found primarily in the prefrontal regions, the inferior parietal lobules, the mesial parietal regions, and the inferotemporal regions. The proximity of heteromodal association regions to particular unimodal association regions also provides a useful heuristic for understanding their functions. The association cortex of the occipito-parietal junction, which is interposed between visual and sensory unimodal regions, is associated with visuospatial integration; damage to this region produces disorders such as optic ataxia and simultanagnosia. The association cortex of the occipito-temporal region is interposed between the visual and auditory unimodal regions and the mesial temporal limbic regions. Damage to these areas leads to impaired object recognition (agnosia), impaired naming (anomia), and semantic memory loss. The association cortex of the superior parietal lobule, near the primary somatosensory cortex, is associated with representing and orienting personal and extrapersonal space; damage to it causes spatial neglect and impairment in spatial orientation. The association cortex rostral to the premotor region is concerned with the manipulation of internally generated images, referred to as working memory, among other processes.

Limbic regions, by virtue of their connections to homeostatic and autonomic systems, and the convergence/divergence pattern of cortical connectivity linking them to the association regions, are implicated in arousal, emotion, motivation, prioritization of attention and memory. Damage to these regions usually causes deficits of memory, emotion and decision making.

The convergence zone framework

A theoretical neural systems account of the basis of certain aspects of cognition in the interaction of early association, limbic, and higher order association regions has been proposed by Damasio and colleagues (Damasio, 1989a,b, 1999; Damasio *et al.*, 1990a; Damasio & Damasio, 1994).

Briefly, this framework distinguishes between images, i.e. explicit, on-line mental patterns of any sensory type (e.g. visual, auditory, somatosensory), some of which constitute the manifest mental contents of conscious experience; and dispositions, i.e. latent, nonconscious, knowledge that directs operations on images, e.g. the construction of images in the process of recall, the manipulation of images in thought, the generation of action, and the regulation of body processes. The principal neural substrates for images are the explicit, topographical, neural patterns (or maps) formed in areas of cerebral cortex located in and around the points of entry of sensory signals in the cerebral cortex (the early sensory cortices). These neural patterns continuously change under the influence of external and internal inputs involved, for example, in perception or recall. All knowledge, that which was accumulated in evolution and is innately available, and that which has been acquired through learning, exists in dispositional form (implicitly, covertly, non-consciously), with the potential to become an explicit image or action.

The neural substrates for dispositions are distributed in higher-order (association) cortices, parts of the limbic cortices, and numerous subcortical nuclei (e.g. basal ganglia, amygdala). The framework posits that dispositions are held in neuron ensembles called convergence zones. Convergence zones are made of microcircuits and cannot be resolved individually by current neuroimaging techniques, although it is presumed that aggregates of many activated convergence zones constitute anatomically macroscopic sets that can be visualized by imaging techniques or selectively affected by neurologic disease. The process of anatomical selection of convergence zones, both during learning and during subsequent operation is probability driven, flexible, and individualized, but because of the constraints of the brain's anatomical design, convergence zones involved in certain classes of tasks are likely to be found, in most individuals, in the same large-scale convergence region of the brain, e.g. temporal pole; anterior inferotemporal cortex; frontal operculum.

One important set of constraints is the pattern of connectivity among cortical regions. For example, one consistent relationship in posterior cortices is that feedforward projections arising from the pyramids in layer III of a cortical region project to layer IV of the next higher-order region. Feedback projections arise from layer VI of the latter and project to layer II of the former. Feedforward/feedback architecture is a general property of the posterior sensory regions, tying together early and higher-order regions as large scale systems (Rockland & Pandya 1979, 1981). The entorhinal cortex is an important node of convergence/divergence among the pathways emanating from unimodal regions

proper to each sensory modality. Thus, in this framework, the entorhinal cortex is a convergence region, whose convergence zones 'hold' dispositions pertaining to patterns of activity across early sensory regions. The process of making these memories explicit in recall involves a role for these convergence zones in directing activity in the early regions.

The anatomic basis of dementia

In the past, dementia was considered to be a 'global' encephalopathy. The idea that the pathology was vascular, or that ageing itself was in some way responsible for the disease, fostered the concept of truly diffuse degenerative pathology. But neither the cognitive impairment nor the pathology is usually diffuse. Diffuse neural degeneration would be incompatible with the phenomenon of primary dementia, in which patients may have advanced cognitive impairment, including virtually complete anterograde amnesia, yet no impairment of motor function, and indeed even have a preserved capacity for motor learning. Further, primary dementia is not a unitary entity – AD and FTLD both present this way, yet with different cognitive profiles. The typical patient with AD will present with anterograde amnesia and visuospatial disorientation, while the patient with FTLD will present with an insidious behaviour disorder and defective social decision-making, and demonstrate relatively good anterograde memory and visuospatial orientation on formal testing. Within the spectrum of FTLD, one patient presents with an apathetic, dependent, perseverative state; another with anomia, impaired speech comprehension and visual agnosia. In other subdisciplines of neurology, especially cerebrovascular disease, dissociations such as these are encountered commonly, and are explained by the anatomic properties of the nervous system damage. We now turn to discussing the anatomic basis of the dementias.

The anatomic basis of cognitive impairment in Alzheimer's disease

The cholinergic hypothesis

The disproportionate impairment of memory in AD was clearly perceived from the beginning, but it came to be explained by a subcortical abnormality under the 'cholinergic hypothesis' (Bartus *et al.*, 1982). The backdrop that set the stage for the acceptance of this account included the following observations: (a) there was a cholinergic deficiency in the brain tissue of affected patients (Perry *et al.*, 1977; White *et al.*, 1977; Davies *et al.*, 1988); (b) presynaptic cholinergic markers were severely depleted in the hippocampus and cerebral cortex; (c) the predominant source of cortical cholinergic afferents, the basal nucleus of Meynert, undergoes marked changes in Alzheimer's disease; and (d) neuritic plaques were known to be rich in cholinesterase activity, suggesting that the degenerating nerve terminals are the projections of cholinergic neurons (Perry *et al.*, 1981). Because anticholinergic pharmaceuticals, such as scopolamine, cause significant memory impairment, it was reasoned that a deficiency of cholinergic neural transmission in the cortex, resulting from cholinergic deafferentation, might underlie the amnesia of AD. The cholinergic hypothesis appealed to the clinical sense of many investigators, who realized that cholinergic drugs were available for the treatment of Alzheimer's disease. Twenty years after the proposal, there is now a consensus that cholinergic augmentation is modestly effective in improving attention, memory, concentration and psychiatric symptoms in AD.

Although the relationship between regional differences in the severity of neural degeneration and regional differences in cholinergic fibre loss (Geula *et al.*, 1998) has yet to be clearly worked out, it has become clear that memory impairment in AD is not primarily due to cholinergic deafferentation. In fact, recent autopsy studies of patients with mild cognitive impairment showed that there were elevated levels of choline acetyl transferase (a presynaptic marker) in the hippocampus and frontal cortex of patients with MCI, all of whom had histological AD. Up-regulation of cholinergic systems in MCI would seem to be incompatible with the cholinergic hypothesis of memory dysfunction (DeKosky *et al.*, 2002).

Not until a careful accounting of the distribution of the pathological hallmarks of Alzheimer's disease was made did a well-founded alternative to the cholinergic hypothesis become available. This account focused on mesial temporal limbic structures, as attention had been directed there by a new paradigm for amnesia: the bilateral hippocampal formation lesion. Before considering this evidence in detail, we must review the major neuropathological features of AD.

The pathological hallmarks of Alzheimer's disease

The pathology of AD is characterized by the accumulation of insoluble fibrous material in intracellular and extracellular locations. The intracellular pathology consists of tau-positive neurofibrillary pathology (neurofibrillary tangles, neuropil threads, and dystrophic neuritis), granulovacuolar change, and Hirano bodies. The extracellular deposits are diffuse and senile amyloid plaques (SPs).

Both SPs and neurofibrillary tangles (NFTs) are widespread in the brain in AD, and are felt to be directly related to the pathophysiology of the disease. How exactly they relate to this pathophysiology and to each other