Sorting out the

INTRODUCTION

Dementia is not a disease. It is a generic term that refers to the cognitive and behavioural disorder resulting from chronic brain disease or encephalopathy. Chronic encephalopathies may be non-progressive, occurring, for example, as a consequence of brain trauma or cerebral hypoxia, or progressive, arising as a result of an intrinsic, extrinsic or metabolic cerebral disorder. The primary focus of this article is the dementia syndromes that result from progressive degenerative disease. However, vascular disease will also briefly be addressed, because vascular dementia is relatively common and is an important cause of dementia.

The traditional view of dementia as a global loss of intellect is inaccurate. Cerebral diseases do not affect the brain uniformly, but preferentially affect certain brain regions and spare others. Moreover, psychological processes themselves are regionally organized in specific brain regions. Different cerebral diseases therefore are associated with distinctive and characteristic neuropsychological syndromes, whose identification can lead to a high degree of accuracy in clinical diagnosis. A useful empirical classification of progressive encephalopathies leading to dementia can be made on the basis of the predominant anatomical distribution of pathology within the brain: cortical, subcortical, cortico-subcortical and multifocal. These regional lesions lead to highly-distinct patterns of cognitive and behavioural change, neurological symptoms and signs, and findings on functional single-photon emission computed tomographic (SPECT) imaging, and electroencephalography (EEG). The process of syndrome analysis permits a differential diagnosis of the different forms of dementia.

CORTICAL ENCEPHALOPATHIES

Functional topography of the cerebral cortex

Psychological functions are regionally organized in the cerebral cortex (Fig. 1). The posterior hemispheres are critical for perceptual and spatial functions, that is, appreciation of the identity of visual percepts (e.g. objects in the environment) and of their spatial relationship with respect to each other and to the individual. Breakdown in visual perception leads to a failure to recognize objects (agnosia) and faces (prosopagnosia), whereas spatial impairment leads to inability to navigate external surroundings (spatial disorientation). Language is dependent on the areas around the Sylvian fissure, extend-

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Figure 1 Functional topography of the cerebral cortex and the various psychological syndromes that arise from breakdown of function in particular cortical areas.

ne dementias

ing from the frontal into the parietal and temporal lobes in the left hemisphere. Breakdown of language leads to an inability to express and comprehend spoken and written words (aphasia) and to communicate by gesture (gestural apraxia). Parietal lesions of the left hemisphere may be associated with an inability to calculate (acalculia). The superior parietal areas are important for the organization of skilled movements. Failure of executive motor functions leads to difficulties in the purposeful use of the limbs, face and mouth (apraxia). The medial portion of both hemispheres, designated the limbic system, which includes the hippocampus and amygdala, is essential for the acquisition and retention of information. Damage to limbic structures leads to a failure to learn new information and to recall past experience (amnesia). The anterior, or prefrontal, cortex is essential for the regulation of mental life, including strategic planning and monitoring, and evaluation of actions taking place over time. Breakdown in these regulatory or executive processes leads to aberrant personal and social behaviour, change

in personality, and inability to conceive of and successfully achieve behavioural goals. Cortical encephalopathies give rise to distinct dementia syndromes, reflecting the topographical distribution of pathological change within anterior, medial and posterior cortices (Fig. 2).

Alzheimer’s disease

Alzheimer’s disease is a cortical dementia, with predominant involvement of the medial temporal and temporoparietal cortex (Cummings & Benson 1992) (Table 1). Patients have difficulty learning new information and are forgetful of day-to-day events. Information from the recent past may appear more affected than from the distant past. Visuospatial impairment leads patients to have difficulty aligning cutlery when laying a table, and orienting clothing when dressing. They have problems negotiating stairs because of impaired judgement of spatial depth. They become lost in their surroundings and eventually disoriented even in their own home. Spatial problems typically outweigh problems in visual perception. Nevertheless, in the later stages patients fail to recognize faces, including their own face in the mirror, and may misidentify objects secondary to visuoperceptual disorder. Breakdown of skilled movements of the arms and legs may be secondary to spatial disorientation, which results in difficulty in copying drawings and designs (constructional apraxia) and in dressing (dressing apraxia). However, apraxia disproportionate to perceptuospatial impairment may occur, impairing the manual use of objects and walking.

When temporoparietal areas around the perisylvian fissure are involved, language skills

Figure 2 Topographic distribution of impaired function in cortical dementias.

Table 1 Alzheimer’s disease: demographic features, clinical profile, pathology and genetics

AGE OF ONSET	ANY AGE FROM 30 YEARS ONWARD. MOST COMMON AFTER 65 YEARS OF AGE.
Sex ratio	Affects females more than males.
Duration	Variable, average 8 years, range 2–12 years.
Main clinical features	Memory loss, visuospatial disorientation, language disorder.
Gross pathological features	Generalized cortical atrophy with temporal lobe preference, ventricular dilatation.
Histopathology	Numerous deposits of amyloid A4 protein in the cerebral cortex, many with dystrophic neurites (neuritic plaques). Also amyloid A4 protein deposits in cerebellar cortex and basal ganglia. Numerous neurofibrillary tangles in cerebral cortex and hippocampus containing tau and ubiquitin. Amyloid angiopathy; A4 protein in vessel walls. Hirano bodies and granulovacuolar degeneration in hippocampus.
Genetics	Point mutations in codons 670/671 and codon 717 of gene for amyloid precursor protein, located on the long arm of chromosome 21. Other genetic loci on chromosome 14, 19 (apolipoprotein E), and 22 segregate with the disease. Can be autosomal dominant inheritance.

are affected. The patient's speech is halting, reflecting difficulty in finding words, and failure to maintain a line of thought. Repetition is impaired, and patients have a reduced digit span and make sound-based errors in repeating polysyllabic word sequences. Comprehension is impaired, particularly at the sentence level. Reading, writing and calculation may all be impaired. Alexia, agraphia and acalculia are compounded by spatial difficulties, because the patient has difficulty tracking along a line when reading, or organizing written words and numerals in space.

In contrast to the severe cognitive deficits, social graces are well preserved and patients present a normal social façade because the frontal cortex is preserved. Failure on conventional neuropsychological 'frontal lobe' tests can typically be accounted for by the heavy demands of such complex, executive tasks on instrumental abilities of language, perceptuospatial skills and memory and do not reflect a primary disorder of frontal lobe function.

Neurological signs in Alzheimer's disease consist of akinesia, rigidity, and myoclonus, which emerge with the gradual involvement of subcortical structures. Physical problems, however, are dwarfed by the momentous psychological disturbance and may be totally absent until the relatively late stages of disease.

The EEG shows progressive slowing of wave forms. Structural imaging reveals non-specific cerebral atrophy but functional imaging techniques, such as positron emission tomography

(PET) and SPECT, reveal characteristic abnormalities of the parietal regions. Abnormalities may be present in the anterior regions, but typically these emerge relatively late in the disease and invariably in the context of posterior hemisphere deficits.

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration is associated with circumscribed atrophy of the frontal and anterior temporal neocortex, with sparing of the posterior temporoparietal neocortex and the medial temporal limbic cortex ((Table 2) (Snowden *et al.* 1996; Neary *et al.* 1998). It encompasses distinct subsyndromes determined by the distribution of pathology within the anterior hemispheres (Fig. 3). Bilateral frontal and anterior temporal lobe involvement is characterized by the prominent behavioural disorder of frontotemporal dementia. Asymmetrical involvement predominantly of the left dominant anterior hemisphere leads to the syndrome of progressive non-fluent aphasia. Predominant involvement of both temporal lobes leads to a syndrome of fluent aphasia with associative visual agnosia (semantic dementia). These syndromes may be complicated by the development of the amyotrophic form of motor neurone disease.

Frontotemporal dementia

Frontotemporal dementia (FTD) accounts for approximately 20% of cases of primary cerebral

Table 2 Frontotemporal lobar degeneration: demographic features, clinical profile, pathology and genetics

Age of onset	Usually 45–65 years, range 21–75.
Sex ratio	Equal males and females.
Duration	Variable, median 8 years, range 2–20.
Main clinical features	Behavioural change or circumscribed cognitive disorder.
Gross pathological features	Atrophy particularly affecting the frontal and/or temporal lobes. Bilateral frontal lobe and anterior temporal atrophy (frontotemporal dementia). Asymmetrical atrophy of left hemisphere, particularly involving frontal and temporal regions (progressive non-fluent aphasia). Bilateral atrophy of temporal lobes (semantic dementia).
Histopathology	Affected areas of cortex show loss of pyramidal cells, microvacuolation of outer cortical laminae, and mild astrocytosis. No inclusion bodies or swollen neurones. or: Affected cortex shows severe loss of pyramidal cells with severe astrocytosis, sometimes with inclusion (Pick) bodies and swollen (Pick) neurones
Genetics	Up to 50% of patients have a positive family history of dementia and autosomal dominant inheritance is demonstrable in the majority. Some familial cases with Parkinsonian features show mutations in the <i>tau</i> gene on chromosome 17. Cases of frontotemporal dementia with motor neurone disease have shown linkage to chromosome 9.

Figure 3 The clinical syndromes of frontotemporal lobar degeneration.

atrophy occurring in the presenium (Gustafson 1987; Neary *et al.* 1988). The striking characteristics are of changes in personality and social and personal behaviour. Patients rapidly become incapable of managing their own affairs and lose their jobs through irresponsibility and impaired judgement. They may appear apathetic, lacking in motivation and emotionally blunted, or overactive, disinhibited and fatuous. Insight is lost and, in contrast to those with Alzheimer's disease, patients show no distress or concern when confronted with task failures. Patients show reduced capacity to demonstrate both primary emotions, such as happiness, fear and surprise, and social emotions such as sympathy, empathy and embarrassment. Stereotyped and perseverative behaviours may occur, ranging from simple repetitive actions such as hand rubbing to complex rituals surrounding activities of daily living. Gluttony, food fads and a preference for sweet foods are common. The diagnostic importance of these behavioural characteristics is exemplified by the finding that changes in emotion and insight, combined with the presence of behavioural stereotypies and altered dietary habits, and an absence of any spatial localization problem, distinguishes FTD from Alzheimer's disease with an accuracy of 95% (Bathgate *et al.* 2001).

Speech in FTD is economical and concrete, and verbatim copying of what is said by others (echolalia) and repetition of their own responses (perseveration) may occur, particularly in more apathetic patients. Patients eventually become mute. Severe difficulties in abstraction, mental set shifting, organizational and strategic skills are elicited on psychological tests sensitive

to frontal lobe dysfunction, and responses are concrete and perseverative. Despite the severity of their behavioural disorder, patients are not clinically amnesic and remain orientated in their environment. Inefficiencies on formal memory tests are secondary to inattention and impairments in strategic and organization skills. Patients show no visuospatial abnormalities until the terminal stages of the disorder, due to sparing of the posterior cortices, and even when patients are mute and formally untestable they may spatially align objects and negotiate their environment without difficulty. Neurological signs are minimal and consist of primitive reflexes in the early stages. Akinesia and rigidity do occur, but typically very late in the disease. Myoclonus, seen in Alzheimer's disease, does not occur.

The routine EEG is normal. CT confirms cerebral atrophy, which may be more evident in the frontal regions. Preferential involvement of frontal and anterior temporal lobes is typically demonstrable on magnetic resonance (MR) imaging. SPECT confirms selective abnormalities in the frontal and temporal lobes.

Progressive non-fluent aphasia

In this syndrome, progressive decline in language production occurs in the relative absence of other psychological deficits (Mesulam 1982). Speech is non-fluent, effortful and lacking in prosody. Repetition, series speech (reciting well-rehearsed verbal series, such as the days of the week) and reading aloud are also impaired, with effortful production and phonemic paraphasic errors (e.g. 'tig' for 'big'). Anomia is prominent. Writing and oral spelling are impaired. Comprehension is relatively preserved.

Structural brain imaging with CT and MRI reveals atrophy of the left cerebral hemisphere. Left hemisphere abnormalities are also apparent on SPECT imaging. The EEG may be normal or show slow waves over the dominant cerebral hemisphere.

The presence of a highly selective disorder of language in progressive aphasia contrasts with the *range* of cognitive deficits typical of Alzheimer's disease. Nevertheless, Alzheimer's disease may sometimes present with a language disorder so that the two can be confused in the early stages. Typically, however, in Alzheimer's disease other deficits emerge with progression of disease, particularly visuospatial impairments.

Semantic dementia

Patients with semantic dementia lose the meaning of words, and of face and object identity (Snowden *et al.* 1989, 1996; Hodges *et al.* 1992). Spontaneous speech is fluent, effortless and grammatically correct, but empty of content and there are semantic paraphasias (e.g. 'dog' for 'pig'). There is profound anomia and impaired comprehension of spoken and written words. Patients can repeat what is said to them, albeit without understanding. They can also read aloud and write to dictation, provided that words have regular pronunciations and spellings. They fail to recognize objects and to identify faces, despite preserved ability to copy accurately and match objects and faces (associative agnosia).

Visuospatial skills and day-to-day memorizing are well preserved, contrasting with the striking loss of semantic knowledge. However, patients perform poorly on traditional formal memory tests, which typically employ words or pictures that the patient may not understand. Behavioural alterations are common, but less severe than in frontotemporal dementia, and have a more compulsive quality.

Brain CT reveals either non-specific cerebral atrophy or widening of the Sylvian fissures, suggesting temporal atrophy. Prominent temporal lobe atrophy is invariably detected by MRI. This is bilateral, but often asymmetrical. In patients with a left temporal emphasis, the initial presenting symptoms are in the realm of language, whereas in patients with right temporal emphasis the earliest deficit is in face recognition. SPECT shows reduced uptake of tracer in the anterior regions, which may be asymmetrical. The EEG is normal.

Semantic dementia is most commonly confused with Alzheimer's disease, not least because patients and their relatives tend to frame the patient's deficits in terms of memory (e.g. 'I can't remember things'). However, what the patient cannot remember is the meaning of words, the identity of faces and the significance of objects (semantic memory). Memory for day-to-day, autobiographical events that is so characteristically impaired in Alzheimer's disease is notably spared in semantic dementia. The presence of profound anomia or prosopagnosia in the presence of preserved orientation and autobiographical memorizing ought to alert the physician to the presence of semantic dementia.

Frontotemporal lobar degeneration and motor neurone disease

Frontotemporal lobar degeneration, in particular the syndrome of frontotemporal dementia can be complicated by the development of motor neurone disease (Neary *et al.* 1990). This is of the amyotrophic form with bulbar palsy, weakness, wasting, and fasciculations of the limb muscles, in the absence of significant spasticity of the muscles. Typically the neurological symptoms and signs appear after the development of the dementia and lead to death within 3 years from respiratory complications. In longer-surviving patients, extrapyramidal signs seen in the late stages of frontotemporal dementia can make an appearance. Electrophysiologic studies demonstrate widespread denervation of muscles.

SUBCORTICAL ENCEPHALOPATHIES

Several diseases predominantly affect subcortical structures with relative sparing of the cerebral cortex. These include degenerative disorders such as Parkinson's disease, Huntington's disease, progressive supranuclear palsy and rare late onset leucodystrophies in young people. Subcortical structures and their projections to the cerebral cortex exert a quantitative and regulatory effect on the pace and organization of psychological functions (Cummings 1990). Patients with subcortical disorders show slowness and rigidity of thinking (bradyphrenia) with inflexibility and difficulty in switching responses (perseveration). Although forgetful they do not have a severe amnesia. Rather they have difficulties in planning and sequencing mental events and may fail on tests sensitive to frontal lobe dysfunction, thus showing similarities to patients with frontal cortical disease. They do not, however, show the specific abnormalities of language, visual perception and spatial functioning seen in cortical disorders. Nor do they typically show the gross behavioural disorder of frontal cortical disease. The exception to this is Huntington's disease in which personality change and bizarre behaviour are not uncommon (Harper 1996). Progressive supranuclear palsy represents the prototypical subcortical dementia (Albert *et al.* 1974).

In subcortical disorders the neuropsychological deficits are overshadowed by profound and characteristic neurological symptoms and signs: akinesia, rigidity and tremor in

Parkinson's disease; involuntary and purposeless movements in Huntington's disease; and paralysis of eye movements in progressive supranuclear palsy.

The EEG may be normal or show slight slowing of wave forms but is of no diagnostic significance. Brain CT and MRI may both be normal or show just non-specific cerebral atrophy. In progressive supranuclear palsy, PET and SPECT reveal abnormalities in frontal cortex similar to those of frontotemporal dementia.

Vascular dementia

Recurrent completed strokes lead to an accumulated neurological and psychological deficit. Their sudden onset, together with evidence of multiple infarctions or haemorrhages on brain imaging, is not likely to lead to diagnostic confusion. But, when vascular lesions predominantly affect the subcortical white matter, a characteristic subcortical syndrome (subcortical arteriosclerotic dementia) emerges that is progressive without stroke-like clinical events (Table 3). This syndrome requires differentiation from subcortical neurodegenerative diseases and from communicating hydrocephalus.

Neurological symptoms and signs reflect subcortical white matter lesions with dysarthria, dysphagia, pyramidal weakness, rigidity, ataxia and gait disorder (*marche à petits pas*). Subcortical lesions in the cerebrum are predominantly anterior and periventricular so that behavioural changes together with failure on psychological tests of frontal executive function can lead to diagnostic confusion with frontotemporal dementia.

Structural and functional brain imaging reveals asymmetrically distributed focal lesions in the white matter of the cerebral hemispheres.

CORTICO-SUBCORTICAL ENCEPHALOPATHY

Two degenerative disorders show features of both cortical and subcortical syndromes because of the spread of pathology to both structures. In Lewy body disease the distribution of pathology is relatively symmetrical whereas in corticobasal degeneration it is highly asymmetrical.

Cortical Lewy body disease

Lewy body disease – or dementia with Lewy bodies – is a disorder of the elderly that is usually sporadic (Table 4) (McKeith *et al.* 1996). Mental changes develop before or after parkinsonian symptoms and signs of akinesia, rigidity and tremor, which are responsive to the administration of L-dopa. Changes in the cerebral cortex may give rise to cortical symptoms of aphasia, agnosia and apraxia akin to those seen in Alzheimer's disease. However, the dominant feature of the illness is a fluctuating mental state with visual illusions and hallucinations leading to secondary delusions. Such fluctuations, which are presumably due to simultaneous disorder of cortex and subcortex, are highly diagnostic, because they are not characteristic of the cortical or subcortical encephalopathies. Dementia with Lewy bodies can also be distinguished qualitatively from Alzheimer's disease by the presence of distractibility, incoherence in line of thought, confabulatory responses, perseverations and intrusions (Doubleday *et al.* 2002).

Table 3 Vascular dementia: demographic factors, clinical profile, pathology, and genetics

Age of onset	Usually after 40 years. Most common in elderly
Sex ratio	Males affected more often than females
Duration	Variable, up to 12 years
Main clinical features	Physical and mental change
Gross pathological features	Multiple infarcts in cerebral cortical and subcortical grey matter and internal capsule or: White matter demyelination, often with lacunes, usually in frontal and temporal lobes. Incomplete infarction.
Histopathology	Completed infarcts, many cases with histopathology of Alzheimer's disease or: Fibrous and hyaline degeneration of small artery walls. Microcystic degeneration around blood vessels, sometimes confluent leading to incomplete infarction of white matter. Reactive astrocytosis.
Genetics	No associations except with atherosclerosis of extracerebral arteries, or hypertension and cigarette smoking

Table 4 Dementia with Lewy bodies: demographic features, clinical profile, pathology and genetics

Age of onset	Usually over 40 years. Most common in elderly
Sex ratio	Affects males at least as or more often than females
Duration	Variable, range 1–12 years. Often more rapid course than Alzheimer's disease.
Main clinical features	Hallucinations, fluctuating mental state, extrapyramidal signs
Gross pathological features	Mild generalized cortical atrophy, depigmentation of substantia nigra
Histopathology	Lewy inclusion bodies in cerebral cortical neurones, usually layers V and VI mostly in cingulate and entorhinal cortex. Ubiquitin protein. Lewy bodies in substantia nigra. Numerous cortical deposits of amyloid A ₄ protein in 40% of patients. A few tangles present, more in the hippocampus and entorhinal cortex, and such patients have an amyloid angiopathy
Genetics	Usually sporadic

The EEG characteristically reveals severe slowing of wave forms and sometimes periodic wave complexes. Brain CT reveals cerebral atrophy. SPECT shows reduced uptake in the cerebral cortex especially in the posterior hemispheres.

Corticobasal degeneration

Corticobasal degeneration is a rare condition in which a cortical neuropsychological syndrome (apraxia) is superimposed on a subcortical dementia and neurological signs of basal ganglia disorder (Rinne *et al.* 1994). There is significant left-right asymmetry in the severity of neurological signs and extent of apraxia, reflecting an asymmetrical distribution of pathology within cortical and subcortical sites.

Asymmetrical akinesia and rigidity affect predominantly the upper limbs, which are also the site of tremor, dystonic movements and myoclonus. Psychologically there is slowing, inflexibility and perseveration consistent with a subcortical syndrome. The cortical syndrome is characterised by a profound, asymmetrical apraxia, typically most marked in the upper limbs, but gradually involving buccofacial, lower limb and whole body movements. The limbs progressively lose all executive functions and may develop autonomous movements (alien limb). Additional features of parietal lobe disease, namely visuospatial deficits, may also emerge.

Brain CT reveals cerebral atrophy. Functional imaging (PET and SPECT) reveals asymmetrical abnormalities of the basal ganglia and associated frontoparietal cortex. EEG changes are of non-specific asymmetrical slow waves.

MULTIFOCAL ENCEPHALOPATHY

Subacute spongiform encephalopathies (prion

diseases), such as Creutzfeldt–Jakob disease, are rapidly progressive disorders with a low familial risk, and are often terminal within about six months (Matthews 1985; Kretschmar *et al.* 1996). Longer survival may occur in familial disease forms such as the Gerstmann–Strausler–Scheinker syndrome and in the new variant form of Creutzfeldt–Jakob disease in young people (Will *et al.* 2000).

The aggressive disease process seems not to respect anatomical boundaries or functional systems so that a wide variety of psychological and neurological deficits rapidly emerge (Fig. 4). Some patients present with neurological symptoms such as a cerebellar syndrome, cortical blindness, sensory motor deficits, myoclonus and epileptic seizures. Focal psychological syndromes such as aphasia may herald the onset of the disease. When thalamic structures are preferentially involved the pre-

Figure 4 Neurological and cognitive disorders associated with multifocal encephalopathy. The diagram illustrates the widespread cerebral involvement, including cerebellum and brain stem as well as cortical and subcortical areas, resulting in ataxia (unsteadiness) and paresis (paralysis).

dominant picture may be one of progressive somnolence. In contrast to cortical encephalopathies, in Creutzfeldt–Jakob disease psychological impairment occurs together with the rapid march of neurological disorder and in an unpredictable manner. However, in the new variant form of Creutzfeldt–Jakob disease, linked to the epidemic of bovine spongiform encephalopathy, a ‘psychiatric’ presentation with depression, withdrawal, apathy or psychosis may precede the onset of ataxia, rigidity and myoclonus for prolonged periods, making early diagnosis difficult (Lowman *et al.* 2001). In the final stages of Creutzfeldt–Jakob disease, episodes of unresponsiveness increase in frequency and duration until akinetic mutism supervenes.

The severe neurological and psychological disorder is reflected in the grossly disturbed EEG in which there is profound slowing of wave forms, and characteristic periodic triphasic wave complexes emerge. Brain CT is either normal or reveals non-specific cerebral atrophy. SPECT imaging reveals a patchy reduction of uptake of tracer in the cerebral cortex.

DIAGNOSTIC CONSIDERATIONS

Cortical, subcortical, cortico-subcortical and multifocal dementias differ with respect to the relative prominence of the associated mental and physical changes during the evolution of disease (Table 5), providing an important framework for differential diagnosis of these disorders. Cortical dementias are characterised by profound mental changes and the relative absence of early neurological signs, whereas subcortical dementias are associated with striking physical signs while mental changes may be of relatively lesser significance and tend to emerge later in the disease. In cortico-subcortical and multifocal dementias, physical symptoms and signs emerge along with the psychological disturbance.

In the case of cortical dementias, the dearth of neurological signs means that differentiation is more crucially dependent on cognitive and behavioural characteristics elicited from the history and neuropsychological evaluation. Differential characteristics of the two prototypical cortical dementias, Alzheimer’s disease and frontotemporal dementia, are shown in Table 6. Comparisons with subcortical vascular dementia, also shown in the table, demonstrate that frontotemporal dementia shares affinities with subcortical vascular dementia. The principle distinctions lie in the greater preponderance of physical symptoms and signs in vascular dementia but with less personality and behavioural change.

Examination of the cerebrospinal fluid is unhelpful, except in sporadic Creutzfeldt–Jakob disease when there may be high levels of 14.3.3 proteinase inhibitor proteins, released from damaged neurones.

The EEG can be of diagnostic significance. In Alzheimer’s disease, the standard EEG often shows mild slowing of wave forms in the moderately advanced stages of the disease. Frontotemporal dementia is unique in that a normal record is preserved until the latest stages of the disease. Gross slowing of wave forms and periodic complexes are characteristic of the subacute spongiform encephalopathies (with the exception of new variant Creutzfeldt–Jakob disease) and also of cortical Lewy body disease.

Whereas brain CT is useful in delineating structural changes such as the presence of infarcts or hydrocephalus, it is less useful in differential diagnosis in neurodegenerative disorders because scans may be normal or reveal just non-specific cerebral atrophy. However, high-resolution brain MRI may be useful in highlighting prominent areas of atrophy, complementing the clinical and SPECT findings.

SPECT imaging demonstrates functional change in the brain, which is of high diagnostic value in the neurodegenerative disorder.

Table 5 Nature and relative severity of psychological, neurological and electroencephalographic (EEG) changes associated with various forms of dementia

	COGNITIVE DISORDER	NEUROLOGICAL DISORDER	EEG
Cortical	Severe, specific	Mild, specific	Slow (AD), normal
Subcortical	Mild, specific	Severe, specific	Non-specific
Cortico-subcortical	Severe, specific	Severe, specific	Periodic complexes
Multifocal	Severe, non-specific	Severe, non-specific	Periodic complexes

AD, Alzheimer’s disease.

Table 6 Comparative clinical diagnostic features: Alzheimer's disease, frontotemporal dementia and (subcortical) vascular dementia

	ALZHEIMER'S DISEASE	FRONTOTEMPORAL DEMENTIA	VASCULAR DEMENTIA (SUBCORTICAL TYPE)
History	Memory loss, spatial	Personality and	
behavioural change	Mental and physical decline		
	disorientation, language disorder		
Neurology	Akinesia, rigidity, myoclonus	Early primitive reflexes, late akinesia and rigidity	Early pseudobulbar palsy, corticospinal weakness and ataxia
Language	Aphasia, logoclonia*, loses train of thought	Speech economy, echolalia, perseverations, verbal stereotypies, mutism	Dysarthria, slowed word retrieval
Visuo-spatial skills	Impaired	Preserved	Preserved
Memory	Consistent and pervasive.	Patchy, inefficient	Patchy, inefficient
'Frontal' executive skills	Impaired secondary to other cognitive deficits	Impaired abstraction, planning and set shifting	Impaired abstraction, planning and set shifting
Motor skills	Impaired spatial configuration	Poor generation, perseveration	Poor generation, perseveration
Conduct	Socially appropriate, concerned. High mental effort.	Impaired temporal sequencing	Impaired temporal sequencing
		Socially inappropriate, unconcerned, cursory.	Usually appropriate, concerned, slowed.
		Low mental effort.	
Routine EEG	Slow waves	Normal	Slow waves
SPECT	Posterior hemisphere abnormality	Anterior hemisphere abnormality	Anterior deficits multifocal deficits, patchy

*logoclonia is the repeated production of a single sound or word, reminiscent of stuttering.

Table 7 SPECT abnormalities in dementia

SYNDROME	DISEASE	ABNORMALITY
Anterior cortical	Frontotemporal dementia	Anterior deficit
Posterior cortical	Alzheimer's disease	
Posterior deficit		
Subcortical	Progressive supranuclear palsy	Anterior subcortical deficits
Cortico-subcortical	Corticobasal degeneration	Asymmetrical frontoparietal deficits
Multifocal	Subacute spongiform encephalopathy	Diffuse and focal deficits

ders, because the abnormalities on imaging closely reflect the topographical distribution of pathology within the cerebrum (Table 7). In frontotemporal dementia the characteristic abnormality in the frontotemporal lobes contrasts strikingly with the bilateral parietal defects seen in Alzheimer's disease (Fig. 5). An asymmetrical dominant hemisphere defect characterises progressive non-fluent aphasia (Fig. 5), whereas predominantly bitemporal defects underlie the 'semantic' dementia of fluent aphasia and associative agnosia. Subcortical disorders, such as progressive supranuclear palsy, have an anterior cerebral defect that is less severe than in lobar atrophy. An asymmetrical frontoparietal defect is seen in corticobasal degeneration, whereas

multifocal lesions are demonstrated in subacute spongiform encephalopathy.

Advances in neurogenetics have permitted the diagnosis from blood samples of specific genetic mutations, accounting for Huntington's disease (huntingtin gene, chromosome 4) and familial Creutzfeldt-Jakob disease (prion gene, chromosome 20). However, mutations in the presenilin genes in presenile Alzheimer's disease, and in the tau gene on chromosome 17 in frontotemporal dementia, account for only small numbers of affected families and so cannot be the basis, as yet, of diagnostic tests. Moreover, the detection of risk factors for late onset Alzheimer's disease, such as the apolipoprotein e4 genotype, cannot be used diagnostically.

MRI coronal

**SPECT
coronal**

sagittal

Alzheimer's disease

(a)

MRI coronals

**SPECT
coronal**

sagittal

Frontotemporal dementia

(b)

CONCLUSIONS

Dementia is a generic term embracing a number of neuropsychological syndromes characteristic of different brain diseases that affect different parts of the brain. Dementia is not a non-specific end-stage intellectual failure, nor is it a synonym for brain disease. Hierarchical descriptions at the levels of neurological and psychological behaviour, taken together with the results of brain imaging and electrophysiology, permit a rational classification of disorders leading to the various forms of dementia.

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(c)

Figure 5 a) Structural and functional neuroimaging in a patient with Alzheimer's disease. The coronal MR scan shows temporoparietal atrophy. The SPECT scan shows low uptake of tracer in the posterior cerebral hemispheres. (b) Structural and functional neuroimaging in a patient with frontotemporal dementia. The MR scan shows frontotemporal atrophy. The SPECT scan shows anterior low uptake of tracer in the cerebral hemispheres. (c) SPECT scan of patient with progressive non-fluent aphasia, showing severe reduction of tracer uptake in the left cerebral hemisphere.

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