NEUROPATHOLOGICAL INVESTIGATION OF DEMENTIA: A GUIDE FOR NEUROLOGISTS

S Love

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Dementia is among the most common and disabling of diseases and places a huge burden on carers and families as well as on social and medical services. Its prevalence rises from about 1.4% of adults aged between 65–70 years to 23.6% of those over 85. The number of patients with dementia is predicted to increase steeply as the proportion of people surviving well in to old age continues to rise. The annual economic cost is estimated at £7 billion per annum in the UK and over \$100 billion in the USA.

Accurate diagnosis of most diseases that cause dementia depends on post-mortem neuropathological examination. In this review, I shall cover some of the practical issues involved in the post-mortem investigation of dementia and describe the principal abnormalities in the more common diseases that are responsible. This is not an exhaustive review of the neuropathology of dementia, which is well covered in many large reference books and is beyond the scope of the present text.

WHY BOTHER EXAMINING THE BRAIN POST MORTEM?

In most published series, the accuracy of clinical diagnosis of the different diseases that cause dementia is of the order of 70–80%. Establishing a precise diagnosis by post-mortem neuropathological examination will not, of course, benefit the individual patient but matters nonetheless, for several reasons:

- ▶ With rare exceptions, brain tissue from patients with dementia cannot be obtained for diagnosis except post mortem.
- ▶ The post-mortem examination yields accurate epidemiological data and is an important means of auditing and assuring the quality of clinical care.
- ▶ The findings help to educate clinicians, and the post-mortem diagnostic process to train pathologists.
- ▶ Many neurodegenerative diseases are inherited or are associated with specific genetic risk factors (table 1). Accurate diagnosis is important for assessing the risk to other members of the family.
- ▶ This is a field in which improvements in understanding of disease aetiology and pathogenesis are rapidly being translated into new approaches to diagnosis and treatment. However, reliance on clinical diagnosis without necropsy confirmation risks misinforming the studies on which these advances rely.
- ▶ Prion disease can mimic other dementias but, unlike these, may have public health implications, particularly if the patient has had a surgical procedure or donated tissue that carries a risk of transmission of disease.
- ▶ With rare exceptions, brain tissue from patients with dementia cannot be obtained for research except post mortem.

CONSENT

Since the Bristol Heart Inquiry and the Royal Liverpool Children's Inquiry into the retention of tissue at Alder Hey Hospital (the reports of both inquiries were published in 2001) it has, in the UK, become much more difficult to obtain consent from relatives for post-mortem examination. This is particularly so if the examination entails the retention of an entire organ (the brain) for several weeks. As will be evident from the advice below, the process of obtaining consent is now quite complicated and time consuming. On the plus side, the inquiries into organ retention have led to the formulation of clearer guidance as to how consent should be obtained, the provision of model consent forms (these can be downloaded from the Department of Health website: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Tissue/TissueGeneralInformation/TissueGeneralArticle/fs/en?CONTENT_ID=4002253&chk=pjRv4o) and, perhaps, improved public awareness of both the complexity and benefits of properly examining the brain post mortem. Written, informed consent from the next-of-kin is a prerequisite for post-mortem neuropathological examination of the brain to ascertain the cause of dementia; with few exceptions this is requirement applies even if the necropsy is performed on behalf of the coroner or procurator fiscal.

Several points merit emphasis during discussions with the next-of-kin before the necropsy:

Correspondence to:
Professor Seth Love,
Department of
Neuropathology, University of
Bristol Institute of Clinical
Neurosciences, Clinical
Science at North Bristol,
Frenchay Hospital, Bristol
BS16 1LE, UK; seth.love@bris.ac.uk

Table 1 Neurodegenerative and vascular diseases that present with or often cause dementia: patterns of inheritance and key neuropathological abnormalities

Disease	Types of inheritance in familial forms/genetic associations	Distinctive neuropathological abnormalities
Alzheimer's disease (AD)	Autosomal dominant in a minority of cases, due to mutations of: APP (amyloid- β precursor protein gene) PSEN1 (presenilin-1 gene) PSEN2 (presenilin-2 gene) Also has strong association with $\epsilon 4$ allele of APOE gene, and particularly in late onset cases, there is an association between AD and an increase in the number of mtDNA polymorphisms or the presence of mutations in complex I mtDNA. Several other genetic associations have been reported (see http://www.alzforum.org/res/com/gen/alzgene/) but not confirmed	A β plaques—diffuse and neuritic Neurofibrillary tangles and neuropil threads A β amyloid angiopathy in >90% of patients
Dementia with Lewy bodies and Parkinson's disease dementia	Very rarely autosomal dominant, due to mutation (Park1) or triplication (Park4) of SNCA (α -synuclein gene) Also has associations with $\epsilon 4$ allele of APOE and 'B' allele of CYP2D6 gene (for debrisoquine 4-hydroxylase)	Lewy bodies, of both cortical and brain stem type Lewy neurites ~75% of patients also have AD-type neuropathological abnormalities
Frontotemporal lobar degenerations (FTLDs): a pathologically and pathogenetically heterogeneous group of diseases characterised by the restriction of cerebral cortical degeneration to frontal and/or temporal regions	Several forms of autosomal dominant FTLD (FTDP-17 and some cases of Pick's disease) are caused by mutations in MAPT, encoding the microtubule associated protein tau. Rarely FTLD-U or FTLD-MND/ALS is familial	Pick's disease: Pick bodies, swollen/achromatic neurons ('Pick cells'), predominance of 3-repeat tau Frontotemporal lobar degeneration and parkinsonism linked to chromosome 17 (FTDP-17): tau immunopositive cytoplasmic inclusions (usually numerous) in neurons, astrocytes, and oligodendroglia; relative proportions of 3- and 4-repeat tau depend on mutation FTLD-U: superficial cortical microvacuolation, ubiquitinated cytoplasmic and nuclear inclusions in small neurons in dentate gyrus and superficial cortex FTLD-MND/ALS: changes of FTLD-U combined with those of motor neuron disease/amyotrophic lateral sclerosis FTLD-NF: neurofilament immunopositive neuronal cytoplasmic inclusions FTD: FTLD lacking demonstrable tau, ubiquitinated or neurofilament inclusions
Corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and argyrophilic grain disease (AGD)	CBD and PSP are associated with H1 haplotype of MAPT	All are associated with abnormal neuronal and glial accumulation of 4-repeat tau CBD: nigral degeneration and superficial cortical microvacuolation, tau-immunopositive neuronal and glial inclusions in basal nuclei (especially nigra – 'corticobasal inclusions') and cortex and including cortical astrocytic plaques; swollen/achromatic cortical neurons PSP: usually predominantly nigral and other subcortical degeneration with tau-immunopositive neuronal and glial inclusions but can involve cortex AGD: grain-like tau immunopositive argyrophilic bodies in hippocampus, entorhinal cortex, and some subcortical nuclei; granular tau immunopositivity of neurons in these regions
Huntington's disease	Autosomal dominant inheritance with anticipation; risk related to extent of CAG expansion in <i>huntingtin</i> gene	Striatal degeneration (particularly of putamen); mild cerebral cortical atrophy; nuclear inclusions (predominantly neuronal) that label for ubiquitin, polyglutamine, and huntingtin
Prion disease	Autosomal dominant forms of disease due to mutations in PRNP (prion protein gene) account for a minority of cases	Neuronal loss, microvacuolation of affected grey matter (spongiform degeneration), severe astrocytosis, accumulation of protease resistant prion protein PrP ^{Sc} /PrP ^{Res} /PrP ^P
Cerebral amyloid angiopathy (CAA)	CAA is usually sporadic and often occurs in association with AD (either sporadic or familial—see above), but may be the predominant abnormality in several uncommon familial diseases including: hereditary cerebral haemorrhage with amyloidosis of Dutch type (HCHWA-D) due to mutation in APP; hereditary cerebral haemorrhage with amyloidosis of Icelandic type (HCHWA-I) due to mutation in cystatin C gene, CYST C; familial British and Danish dementias due to mutations in BRI2 gene	HCHWA-D: A β amyloid angiopathy mainly affecting cortical and overlying leptomeningeal blood vessels; diffuse A β plaques HCHWA-I: cystatin C amyloid angiopathy mainly affecting cortical and overlying leptomeningeal blood vessels Familial British and Danish dementias: severe, widespread CAA due to deposition of ABri or ADan, respectively; parenchymal ABri or ADan plaques, some associated with dystrophic neurites; tau-immunopositive neurofibrillary tangles and neuropil threads
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) and rarer inherited arteriopathies	CADASIL is caused by mutations in NOTCH3. Another autosomal dominant disease, hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS), is linked to 3p21.3-p21.1. Linkage has not yet been established for cerebral autosomal recessive arteriopathy with subcortical infarcts and leucoencephalopathy (CARASIL) in which patients also develop spinal disc disease and alopecia	CADASIL: predominantly subcortical infarcts and ischaemic damage; pronounced thickening of leptomeningeal and parenchymal arteries and arterioles with accumulation of deeply eosinophilic, highly electron dense granular material adjacent to smooth muscle cells in the tunica media

- ▶ An accurate diagnosis cannot be made without the retention and histological examination of tissue from the brain.
- ▶ The likelihood of establishing the diagnosis will depend on how much tissue is retained.
- ▶ The likelihood of establishing the diagnosis will also depend on the time constraints under which the examination has to be performed.

Optimum preservation of the brain for macroscopic and microscopic examination is achieved by suspending and fixing it intact for 2–3 weeks in formalin. Accurate neuropathological assessment requires comprehensive sampling, a relatively long processing schedule for embedding the samples of brain tissue in blocks of paraffin wax, and the use of a range of tinctorial and immunohistochemical stains on the sections that are cut from those blocks. Retention of frozen tissue is sometimes needed for western blotting or molecular genetic studies. While diagnoses can sometimes be made by examining limited samples of brain tissue after only relatively brief fixation, this approach increases the risk of missed diagnosis or misdiagnosis. There is a compromise to be struck between accuracy and speed of diagnosis. With these considerations in mind, it is important to establish and document, before the necropsy, what level of assessment is wanted by the next-of-kin in a given case, and to explain the associated advantages or limitations:

- ▶ The family may wish the brain to be retained in its entirety for comprehensive assessment, and not returned to the body before burial or cremation.
- ▶ The family may allow the brain to be retained briefly and comprehensively sampled, provided that any remaining tissue is returned to the body within a few days.
- ▶ The family may consent to only limited post-mortem sampling of brain tissue and indicate that the rest of the brain should be returned to the body at the time of the necropsy.
- ▶ The family may, of course, refuse to allow *any* retention of brain tissue, in which case there is little likelihood that an accurate diagnosis can be made.
- ▶ Except in the event of refusal to allow any tissue retention, the family should be asked whether fresh brain tissue might be frozen and stored for possible protein or molecular genetic analysis.

Protocols have been proposed to optimise the diagnostic value of the tissue even if consent is limited to the retention of only a few samples of brain for histology (fig 1).

In addition to establishing what level of assessment is wanted, the clinician responsible for obtaining consent should find out and document (1) whether the next-of-kin wish the tissue to be used only for diagnosis, or also for audit, teaching, or research that has the approval of a research ethics committee, and (2) whether tissue remaining after a diagnosis has been made should be kept, disposed of respectfully by the hospital trust, or released for cremation or burial. This information should be sought irrespective of whether or not the patient is to have a hospital necropsy or one performed on behalf of the coroner or, in Scotland, the procurator fiscal. In the case of necropsies performed on behalf of the coroner (but not the procurator fiscal), it has, since the implementation of The Coroners (Amendment) Rules 2005 on 1 June 2005 (<http://www.legislation.hmso.gov.uk/si/si2005/20050420.htm>), become necessary to obtain consent from the next-of-kin for retention beyond the inquest not only of remaining wet or frozen tissue but also of any tissue in paraffin blocks or in sections on glass slides.

Much of the stress and unpleasantness of dealing with all of these issues can be avoided if the possibility of brain donation is considered and discussed before death. A great deal of support and advice is available from organisations such as the Alzheimer's Society (<http://www.alzheimers.org.uk>) and the Parkinson's Disease Society (<http://www.parkinsons.org.uk>). The Alzheimer's Society website includes a list of brain banks that accept donations from patients with dementia (http://www.alzheimers.org.uk/After_diagnosis/Helping_with_research/info_braindonations.htm). Most brain banks are very experienced in dealing with families and providing information about the necropsy and examination of the brain. Donation to a brain bank ensures that the diagnostic workup is performed to a consistent, high standard and that good use will be made of the tissue once the diagnosis has been established.

CLINICOPATHOLOGICAL CORRELATION

The neuropathological approach to diagnosis should be informed by the clinical history. The approach to post-mortem investigation of, for example, frontotemporal dementia or Alzheimer's disease is very different from that to the investigation of cerebrovascular dementia or prion disease. It is important that the neuropathologist be provided with a full clinical history that includes information as to the sequence, tempo, and age at onset of clinical abnormalities, the neuroradiological and electrophysiological findings at different stages of the disease, the possible involvement of other organ systems (for example liver, bone marrow), and any relevant family history.

MAIN TYPES OF DEMENTIA

In the great majority of cases, neuropathological examination reveals one of three types of neurodegenerative disease or combinations of these:

- ▶ Alzheimer's disease
- ▶ Dementia with Lewy bodies or Parkinson's disease dementia
- ▶ Cerebrovascular disease.

ALZHEIMER'S DISEASE (AD)

Gross examination usually shows cerebral atrophy, which may be pronounced (fig 2). In most cases the atrophy affects all lobes but the occipital lobe may be relatively spared and the medial part of the temporal lobe (particularly the hippocampus) is generally more severely atrophic than are other parts of the brain. Occasionally the atrophy is predominantly frontal and temporal, and the appearance mimics that of the frontotemporal dementias.

On microscopic examination, AD is characterised by a combination of abnormalities:

- ▶ Plaques—proteinaceous extracellular deposits that consist largely of a peptide known as amyloid- β or A β . A β is cleaved from a larger transmembrane protein—amyloid- β precursor protein—by the action of β - and γ -secretases, and its formation is prevented by the action of α -secretase (fig 3). These deposits measure up to several hundred micrometres in diameter and are widely distributed throughout the cerebral cortex (fig 4). Plaques vary in appearance, and two main subtypes are recognised. Diffuse plaques consist largely of non-fibrillar extracellular A β . Neuritic plaques contain A β that is mostly in the form of amyloid fibrils, among which are irregularly swollen dystrophic neurites. The neurites are well visualised with silver stains. Microglia and astrocyte processes are present towards the periphery of neuritic plaques.

Figure 1 Diagram illustrating the minimum set of small blocks (red rectangles) of brain needed to establish the diagnosis in most cases of dementia. 1 = middle frontal gyrus; 2 = cingulate gyrus; 3 = superior and middle temporal gyri; 4 = hippocampus and parahippocampal gyrus; 5 = inferior parietal lobule; 6 = putamen and globus pallidus; 7 = midbrain; 8 = pons; 9 = caudate nucleus; 10 = cerebellar vermis; 11 = hemisphere (including the dentate nucleus); 12 = medulla. The illustrated blocks should be supplemented by samples of any macroscopically visible lesions that are noted when the brain is sliced. Adapted with permission from: Love S. Post mortem sampling of the brain and other tissues in neurodegenerative disease. *Histopathology* 2004;**44**:309–17.

v11

Figure 2 Brain atrophy in Alzheimer's disease. The narrowing of gyri and widening of sulci involves all of the lobes of the cerebrum. The cerebellum is macroscopically normal.

Figure 3 Cleavage of amyloid- β precursor protein. This diagram illustrates that cleavage of transmembrane amyloid- β precursor protein by β - and γ -secretases leads to the formation of A β . This is prevented by the action of α -secretase.

Figure 4 A β plaques in Alzheimer's disease. The plaques have been immunolabelled with antibody to A β and appear as brown structures. Many of the plaques have a dense central core.

Neuritic plaques may contain a dense central core of amyloid. The most widely used (CERAD) criteria for a diagnosis of AD require that neuritic plaques be present in densities exceeding certain illustrated standards, after adjusting for the age of the patient (with age some plaques may occur in people who are cognitively normal).

- ▶ Neurofibrillary tangles—looped or twisted, skein-like aggregates of filamentous material, largely composed of hyperphosphorylated tau proteins (fig 5). Most tangles are faintly basophilic. They can be impregnated with silver or immunostained for tau to facilitate their light microscopic detection. Tangles are formed within the neuronal cell body and most remain intraneuronal. However, when neurons degenerate, the tangles persist extracellularly, although they lose their basophilia and some of their affinity for silver salts. The swollen neurites that are present in neuritic plaques contain tangle-like material, and this also accumulates in numerous fine nerve cell processes (known as neuropil threads (fig 5)) in the vicinity of the tangle bearing neurons. The involvement of different parts of the brain by tangles and neuropil threads follows a stereotyped progression that correlates well with the evolution of clinical disease. The earliest pattern of involvement is usually not associated with clinical disease: tangles and neuropil threads are restricted to parts of the entorhinal cortex and the CA1 field of the hippocampus. As dementia develops, tangles and neuropil threads accumulate in increasing density in other parts of the hippocampus and medial temporal neocortex, and then in other cortical regions and in subcortical grey matter structures such as the hypothalamus and thalamus. A staging scheme devised by Braak and Braak (1995) is widely used to describe the extent of tangle related abnormalities in AD and correlates well with the severity of dementia.
- ▶ Cerebral amyloid angiopathy (CAA)—the accumulation of A β in the walls of blood vessels (particularly arteries and arterioles) in the cerebral cortex and overlying leptomeninges. This affects about 30% of normal elderly people but over 90% of patients with AD, in whom the angiopathy tends also to be much more severe. CAA is an important cause of strokes in the elderly. Most of these are haemorrhagic, although CAA does also increase the risk of ischaemic strokes and can, if very severe, cause diffuse ischaemic damage to the white matter. As CAA is confined to superficial cerebral blood vessels, rupture of

Figure 5 Neurofibrillary tangles and neuropil threads. The section has been immunolabelled with antibody to hyperphosphorylated tau protein. The tangles appear as densely labelled flame shaped structures within several of the nerve cells (arrows). The neuropil threads are present as a fine meshwork throughout the cortex in this figure but form denser aggregates within the neuritic plaques (arrowheads to some).

the amyloid laden blood vessels usually causes relatively superficial, lobar haemorrhages that may extend into the subarachnoid space.

- ▶ Other abnormalities:
 - reduction in the density of synaptic proteins in the cerebral cortex
 - neuronal loss
 - astrocytic gliosis
 - microglial activation.

DEMENTIA WITH LEWY BODIES (DLB) AND PARKINSON'S DISEASE DEMENTIA (PDD)

This term encompasses several disorders in which dementia is associated with the presence of Lewy bodies in the cerebral cortex. Clinical features in addition to dementia typically include parkinsonian extrapyramidal signs (although rarely tremor), fluctuating course and recurrent visual hallucinations.

Figure 6 Lewy bodies in substantia nigra. In this case of dementia with Lewy bodies, several remaining nigral neurons contain Lewy bodies (arrows): homogeneously stained deeply eosinophilic cytoplasmic inclusions that are surrounded by a paler "halo". Note the clusters of pigment laden macrophages (arrowheads), reflecting previous neuronal degeneration.

DLB is differentiated clinically from PDD on the basis that patients with DLB have had less than one year of parkinsonism preceding their dementia, but it is not possible to distinguish the findings in the two groups neuropathologically. There is also considerable overlap between the neuropathological findings in DLB and those in patients whose Parkinson's disease is not complicated by dementia.

Gross examination of the brain may show little in the way of abnormalities apart from poor pigmentation of the substantia nigra in the midbrain and loci cerulei in the pons. On microscopic examination, DLB and PDD are characterised by:

- ▶ **Lewy bodies**—eosinophilic neuronal cytoplasmic inclusions, the principal component of which is α -synuclein. Lewy bodies are almost invariably present in the substantia nigra and loci cerulei, which also show neuronal loss and gliosis, and may also be found in the dorsal motor nucleus of the vagus. In these brain stem nuclei, Lewy bodies are usually roughly spherical, with an eosinophilic core surrounded by a paler "halo" (fig 6). Within the cerebrum, Lewy bodies are usually present in the amygdaloid nuclei, parahippocampal and cingulate gyri, and insula, but may also be found in other parts of the neocortex. The cholinergic nucleus basalis of Meynert is generally affected. Cortical Lewy bodies appear as regions of homogeneous eosinophilic staining in the neuronal cytoplasm, usually associated with eccentric displacement of the nucleus. The Lewy bodies are best visualised immunohistochemically, with antibody to α -synuclein (fig 7).
- ▶ **Lewy neurites**—these are nerve cell processes that contain aggregates of α -synuclein (fig 6). These abnormal structures can occur in both DLB/PDD and idiopathic Parkinson's disease and are most numerous in the CA2/3 region of the hippocampus and in the substantia nigra.
- ▶ **Other abnormalities:**
 - A high proportion of patients with DLB/PDD (about three quarters) also have AD-type neuropathological abnormalities. Although diffuse plaques may be abundant, in many cases there are too few neuritic plaques or neurofibrillary tangles to fulfil CERAD or other diagnostic criteria (for example, those of the NIA and Reagan Institute) for a diagnosis of definite AD or high probability of AD. However, in a significant proportion

Figure 7 Lewy bodies in the cerebral cortex. These Lewy bodies in the cingulated gyrus have been immunostained for α -synuclein. Note the scattered fine Lewy neurites in the surrounding neuropil that are also immunopositive for α -synuclein.

of cases a diagnosis of combined AD and DLB/PDD is appropriate.

- Some patients with DLB show microvacuolation of the cerebral cortex, predominantly in the medial temporal regions. This can lead to misdiagnosis of prion disease.

DEMENTIA CAUSED BY CEREBROVASCULAR DISEASE

The development of dementia as a result of ischaemic cerebrovascular disease is relatively common. However, while the pathological features in dementia caused by severe cerebrovascular disease are well recognised, they form a continuum with abnormalities that can occur in the absence of dementia. There are no objective neuropathological criteria to indicate the "threshold" for making this diagnosis. Ischaemic abnormalities of mild to moderate severity are often found in conjunction with changes of AD or DLB and may contribute to the dementia in many patients with those diseases.

Gross examination of the brain typically reveals mild to moderate, often asymmetrical, dilatation of the lateral ventricles. The basal arteries are often atheromatous but this may be quite mild, with the bulk of the pathology related to small vessel disease (see below). The white matter usually appears irregularly pitted or granular and contains ill defined foci of yellow or grey discoloration. Scattered lacunar infarcts are almost always present. In some cases the brain contains one or more larger infarcts; these may occur in the watershed regions between the perfusion territories of the major cerebral arteries. In a few patients, the dementia is caused by hippocampal sclerosis, and the hippocampi may appear greyish brown, shrunken, and granular. Rarely bilateral infarcts involving the hippocampus or thalamus are the cause of dementia. Microscopically, cerebrovascular dementia is associated with:

- ▶ Degenerative change of small blood vessels, especially in the deep cerebral white matter and basal ganglia. Small arteries and arterioles have thickened, hyaline walls with replacement of smooth muscle by collagen. There is often enlargement of perivascular spaces.
- ▶ Rarefaction of white matter, due to a combination of nerve fibre degeneration, gliosis, and patchy demyelination. Small foci of cavitation, and lipid laden macrophages are usually present.
- ▶ Microinfarcts in the cerebral cortex. Sparsely scattered microinfarcts are a common finding in cerebrovascular dementia. Occasionally the cortical microinfarcts are quite numerous.
- ▶ Other abnormalities:
 - These can include foci of old haemorrhage (with clusters of haemosiderin laden macrophages), cerebral amyloid angiopathy (sometimes severe), and hippocampal sclerosis.

NORMAL PRESSURE HYDROCEPHALUS

The classical clinical triad comprises early disturbance of gait, urinary incontinence, and impaired cognition, the last of these usually manifesting later than the other features. Features of frontal lobe dysfunction are common.

Gross examination of the brain reveals dilatation of the lateral and third ventricles. The leptomeninges may show fibrous thickening. On microscopy, there are multiple large gaps in the ependymal lining, the periventricular region is gliotic, and the deep white matter often contains ischaemic lesions.

PRION DISEASES

These diseases, of which the most common form is sporadic Creutzfeldt-Jakob disease (CJD), are relatively rare causes of dementia. They are caused by the accumulation within the brain of a normal cellular protein, prion protein (PrP), in an abnormal, protease resistant conformation, PrP^{Res}. Through a poorly understood mechanism, conversion of abnormal to normal prion protein is facilitated by the presence of the abnormal form of the protein and is therefore self-perpetuating. Variant CJD is a prion disease that probably resulted from the transmission of PrP^{Res} to humans, via food, from cattle with bovine spongiform encephalopathy. Iatrogenic CJD is the term given to prion disease which results from inadvertent transmission of CJD from human to human during medical or surgical procedures. A minority of prion diseases is caused by mutation in the prion protein gene, *PRNP*.

The importance of this group of diseases is due largely to the transmissibility of the disease and the hardness of PrP^{Res}, which is resistant to conventional disinfectants and sterilisation procedures. Transmission may result from the use, for invasive surgical procedures, of instruments that have previously been in contact with tissue containing PrP^{Res}, or from the donation of blood (at least in the case of variant CJD) or tissue from patients with clinical or preclinical prion disease.

The initial clinical presentation of sporadic CJD is very variable and can include visual disturbances and ataxia, but rapidly progressive dementia soon becomes the dominant clinical abnormality. This is generally accompanied by myoclonus, and periodic sharp wave complexes in electroencephalogram (EEG) traces. Death occurs within six months of disease onset. Whereas sporadic CJD is usually a disease of the middle aged or elderly, variant CJD typically affects young adults—psychiatric and sensory symptoms are common early manifestations, the duration is usually in excess of 12 months, and myoclonus and periodic sharp wave complexes are often lacking.

On gross examination, the brain in CJD may appear entirely normal. Less often it shows obvious atrophy. Microscopy reveals accumulation of PrP^{Res} within affected parts of the cortical and subcortical grey matter, and spongiform change—fine vacuolation of the neuropil, associated with neuronal loss and astrogliosis. Microglial activation is usually pronounced but lymphocytic inflammation minimal. The precise distribution and pattern of accumulation of PrP^{Res} varies according to the type of prion disease, the strain of prion agent, and the sequence of the two *PRNP* alleles—in particular, whether either or both of the codons at position 129 encodes methionine or valine. Further information about the pathogenesis and pathology of prion diseases is included in the references at the end of this review.

OTHER NEURODEGENERATIVE AND CEREbroVASCULAR CAUSES OF DEMENTIA

Table 1 lists some of the other neurodegenerative and cerebrovascular diseases that can cause dementia and summarises the key neuropathological abnormalities. A wide range of other degenerative diseases, infections, metabolic diseases and tumours can also cause dementia. For more detailed descriptions of these diseases and their clinical and

pathological features, the reader should consult the major reviews and reference texts cited in the bibliography.

APPROACH TO NEUROPATHOLOGICAL DIAGNOSIS

Neuropathological diagnosis must be guided by the clinical information, including the family history, age of onset of disease, tempo and sequence of manifestations, and the neuroradiological and electrophysiological findings. For example, the approach to diagnosis of rapidly progressive dementia in an elderly person with periodic sharp waves on electroencephalography is very different from that to a middle aged patient with a family history of strokes and dementia. There are published guidelines on the post-mortem sampling of brains for histology in dementia, and protocols for the diagnosis and staging of the diseases responsible. Neuropathological assessment is best performed in a centre with neuropathological expertise. Difficulties in diagnosis are most often caused by inappropriate initial handling and sampling of the tissue, inadequate fixation, and poor processing and embedding due to the use of routine histology protocols rather than the longer cycles required for brain tissue.

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