

Neuropathology autopsy practice: Post-mortem examination in dementia

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1 The role of the post-mortem examination

Dementia is variously defined as a progressive and irreversible disorder characterised by loss of cognitive function in more than one domain (e.g. memory, attention, executive function), leading to impairment in normal activities of daily living such that the patient becomes dependent on the care of others. Dementia syndromes are common and represent an important health burden, especially in older people. These syndromes are defined in terms of a combination of clinical features and underlying brain pathology. Clinical diagnosis does not always reliably predict the pathological cause of a dementia syndrome. In some causes of dementia, a specific complication may have a direct bearing on the cause of death.

In cases of death related to dementia, the post-mortem examination may provide:

- a detailed description of the pathology associated with dementia to facilitate accurate classification and diagnosis
- additional information relating to response to treatment or complications in cases where there has been use of a disease-modifying therapy
- audit information related to clinical and imaging diagnoses
- accurate national statistical information regarding the incidence of the various pathologies seen in dementia, including prion diseases
- support appropriately consented research into dementia.

A post-mortem examination in a patient who has had a clinical dementia syndrome may be performed with consent from the family or may be performed under a legal authority (Coroner or Procurator Fiscal). As such, and in many instances, the brain (and spinal cord) will be examined by a general and/or forensic pathologist. However, involving a neuropathologist in the brain examination will maximise information about the nature of the disease processes.

Certain special stains and techniques required for the diagnosis of dementia syndromes will typically only be available in a dedicated neuropathology laboratory. Many UK centres offering comprehensive diagnostic support for dementia diagnosis at autopsy are associated with the UK Medical Research Council (MRC) Brain Bank Network (www.mrc.ac.uk/Ourresearch/Resourceservices/UKBrainBanksnetwork).

An autopsy in a patient who has had dementia should be recommended as a full post-mortem examination because important information can be obtained that may bear upon the cause of dementia from an examination of the main organs. However, it is recognised that some families choose to consent to an examination limited to the central nervous system even when the benefits of a full examination have been explained. The disadvantages of a limited examination in being able to provide a full explanation of a death should be explained as part of obtaining consent..

2 Brain pathology encountered at the post-mortem examination

A range of pathologies may be seen in a patient with clinical dementia.

Alzheimer's disease is the most common causal pathology and, while it predominantly affects patients over the age of 75 years, it may affect younger patients when there is a higher probability of a genetic cause associated with a significant risk of heritability.

Dementia with Lewy bodies is related to Parkinson's disease and has been found to be relatively common. Involvement of certain brain areas can explain certain causes of death, for example aspiration pneumonia related to medullary involvement. Patients with this disease may die as a result of neuroleptic sensitivity if they have been exposed to this class of drugs.

Frontotemporal dementia syndromes have emerged in recent years as a common form of dementia, sometimes overlapping with the pathology seen in motor neuron disease. This group of disorders includes a range of molecular pathologies.

Vascular dementia syndromes are common, both in a pure form as well as contributing to neurodegenerative diseases as 'mixed dementia'. Rare forms are familial.

Multiple pathologies: Cognitive impairment usually occurs in elderly individuals recognised to have increased risk of multiple pathologies, for example, vascular pathology may exist with Alzheimer-type pathology. Changes seen in Parkinson's disease may also be seen in combination with the pathology of Alzheimer's disease. The relative contribution of different pathologies to the clinical picture should carefully be considered.

Prion diseases are rare, fatal, potentially transmissible, degenerative diseases with an incidence of about one per million population per year. They are not common causes of dementia but it is important for pathologists to know the clinical features that would suggest such a possibility, so that appropriate health and safety procedures can be implemented for the conduct of the autopsy examination and subsequent histopathological studies.

Rarer causes of dementia: a wide range of rare causes of dementia are described.

3 Clinical information relevant to the post-mortem examination

Most of the information will come from hospital clinical case notes. In some circumstances, this may be supplemented by access to GP records.

As with any post-mortem examination, knowledge of the medical history is important. It is useful to have details in relation to the following.

- Family history: for many diseases of the nervous system there is an emerging recognition of a genetic component to disease. Knowing this will allow planning for archiving of fresh material for genetic analysis, if consented.
- Social and general medical history: systemic diseases may affect the nervous system and lead to a clinical syndrome of dementia.
- The possibility that trauma has contributed to the development of cognitive decline should be considered from the clinical history with reference to chronic traumatic encephalopathy.
- A diagnosis of dementia is difficult to establish in many cases during life, particularly if of recent onset, so that the evolution of the cognitive state has not been observed over time. A number of clinical syndromes, including delirium and depression, may mimic dementia. The security of a dementia diagnosis will therefore depend on the extent to which specialist services have been involved during the patient's life. Conversely, many older people with dementia are not formally diagnosed prior to their death.
- It is essential to have details of any neurological symptoms and signs for planning the examination and determining the need for tissue retention. This is especially important in making decisions about retention of the spinal cord, peripheral nerve and skeletal muscle (see Box 1).
- Planning the examination and subsequent tissue sampling is greatly aided by knowledge of any clinical imaging findings.
- Full details of treatment should be ascertained in cases where a disease-modifying therapy has been used. If a history of use of sedative drugs or neuroleptic drugs is

present, consideration should be given as to whether these may have contributed to the death and further investigation taken forward using toxicology.

- The final diagnostic category assigned may depend upon clinical information. For example, the distinction between entities such as Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB), once the underlying Lewy body pathology has been determined, is reliant on clinical information alone.

Box 1: Dementia syndromes linked to associated clinical features

Ataxia

Spinocerebellar ataxia (particularly types 2, 12, and 17), paraneoplastic diseases, prion diseases (particularly familial forms and variant Creutzfeldt-Jakob disease [CJD]), dentatorubral-pallidoluysian atrophy (DRPLA, common in Japanese), fragile x-associated tremor ataxia syndrome, familial British and Danish dementias, mitochondrial disorders, superficial siderosis, neuronal ceroid lipofuscinosis (Kuf's disease), Niemann-Pick disease type C, multiple system atrophy (dementia usually mild, if present), Alexander's disease, and multiple sclerosis.

Pyramidal signs

Multiple sclerosis, frontotemporal lobar degeneration with motor neuron disease, Alzheimer's disease (some presenilin mutations), spinocerebellar ataxias, phenylketonuria, familial British and Danish dementias, hereditary spastic paraparesis (*SPG4*), adrenoleukodystrophy, vanishing white matter disease, polyglucosan body disease, polycystic lipomembranous sclerosing leukoencephalopathy (Nasu-Hakola disease).

Dystonia/chorea

Huntington's disease (and Huntington's disease-like syndromes 1–3), Kuf's disease (characteristic facial dyskinesia), Wilson's disease, neuroacanthocytosis, pantothenate kinase-associated neurodegeneration (neurodegeneration with brain iron accumulation), Lesch-Nyhan syndrome, DRPLA, corticobasal degeneration, neuroferritinopathy, anti-NMDA receptor-mediated limbic encephalitis, variant CJD.

Bucco-lingual mutilation

Neuroacanthocytosis, Lesch-Nyhan syndrome.

Akinetic-rigid syndrome

Lewy body disease (dementia with Lewy bodies and Parkinson's disease dementia), progressive supranuclear palsy, multiple system atrophy (dementia usually mild, if present), Huntington's disease (particularly juvenile onset), corticobasal degeneration, dementia pugilistica, Wilson's disease, pantothenate kinase-associated neurodegeneration (neurodegeneration with brain iron accumulation), frontotemporal lobar degeneration with parkinsonism-17, Alzheimer's disease (usually advanced).

Peripheral neuropathy

Neuroacanthocytosis, cerebrotendinous xanthomatosis, HIV infection, giant axonal neuropathy, alcohol-related diseases, metachromatic leukodystrophy, porphyria, adrenoleukodystrophy, GM2 gangliosidosis, polyglucosan body disease, Krabbe's disease, sialidosis, Fabry's disease, mitochondrial disorders, spinocerebellar ataxias (particularly type 3).

Myoclonus or early seizures

Prion disease, Alzheimer's disease, Lewy body disease, DRPLA, mitochondrial disorders, Gaucher's disease, GM2 gangliosidosis, neuroserpinopathy, polycystic lipomembranous sclerosing leukoencephalopathy, subacute sclerosing panencephalitis, progressive myoclonic epilepsy syndromes, Kuf's disease, Lafora body disease, sialidosis.

Gaze palsy

Niemann Pick disease type C (vertical supranuclear; early downgaze loss), Gaucher's disease (horizontal supranuclear), progressive supranuclear palsy (vertical supranuclear), mitochondrial disorders, spinocerebellar ataxias (particularly type 2), paraneoplastic disorders, Whipple's disease.

Deafness

Superficial siderosis, mitochondrial disorders, familial Danish dementia, alpha mannosidosis, sialidosis.

Dysautonomia

Lewy body disease, multiple system atrophy, prion disease (fatal familial insomnia), porphyria, adrenoleukodystrophy, anti-NMDA receptor-mediated limbic encephalitis.

This list is not comprehensive. Note that vascular disease, structural disorders, and (para) neoplastic disease can be associated with a wide range of presentations.

Adapted from: Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. *Lancet Neurol* 2010;9:793–806.²

3.1 When to suspect a prion disease

A prion disease will usually have been clinically diagnosed, or at least suspected, in life. The main clinical diagnoses include Creutzfeldt-Jakob Disease (CJD), variant Creutzfeldt-Jakob Disease (vCJD), the Gerstmann–Straussler–Scheinker Syndrome, and fatal familial insomnia. Some patients should be regarded as being 'at risk' of having a prion disease.

These include:

- those in receipt of a blood transfusion from someone subsequently diagnosed with CJD or vCJD
- those in receipt of pituitary-derived human growth or sex hormones, or dural grafts
- patients who have had positive prion gene testing and those with a family history of disease
- any person who has undergone an intradural neurosurgical procedure or operation on the spinal cord prior to August 1992.

When reading medical records prior to the post-mortem examination, the main features suggesting the possibility of CJD are rapidly progressive dementia, with a duration of less than two years, associated with two of the following features:

- myoclonus
- visual or cerebellar signs
- pyramidal or extrapyramidal movement disorder
- akinetic mutism.

Pathologists in the UK should seek advice from the National CJD Surveillance Unit (www.cjd.ed.ac.uk).

4 Autopsy procedure

A post-mortem examination in a patient with dementia should be performed in the standard way, with removal of the brain and spinal cord when indicated.¹ After sampling and freezing fresh tissue, if indicated, the brain should be fixed in formalin for later dissection.

For a suspected prion disease (e.g. CJD), guidance on risks and laboratory handling has been published by the ACDP TSE Working Group in 2003 (see www.dh.gov.uk/ab/ACDP/TSEguidance/DH_098253) and regular updates are available online. Autopsies on cases of suspected prion disease may be safely undertaken in general mortuary facilities if published guidelines are followed.²⁻⁵ After sampling and freezing fresh tissue, the brain is fixed in formalin for later dissection under appropriate containment. Disposable instruments should be used wherever possible and surface contamination avoided by using disposable surface coverings. Tissue blocks should be placed in 96 per cent formic acid for one hour (which substantially reduces infectivity), before being returned to formalin for tissue processing to paraffin wax blocks.³⁻⁵

External examination of the body

In dementia, there may be non-specific abnormalities that are commonly found. Patients have typically lost weight and show cachexia. Immobility may have predisposed to pressure sores. The full external examination of the body should include looking for features that may raise suspicion of inflicted injury or sub-optimal care, which should be discussed with an appropriate authority if present.

A photograph may be useful for future reference.

Internal examination of the body

In a full post-mortem examination, there should be a standard macroscopic description of each organ system including measurement of the organ weights. Morbid anatomical causes of death that are visible at the time of post mortem should be sought and where necessary supported by histological confirmation. For example, a common mode of death in dementia is the development of a bronchopneumonia.

5 Specific significant organ systems

5.1 Head and neck

The scalp and skull should be carefully examined for sign of bruises which may have been associated with falls. When reflecting the dura, note the presence of any old or recent haematoma. Chronic subdural haematoma in particular may be a cause of progressive cognitive decline and loss of activities of daily living.

5.2 Cardiovascular system

Vascular dementia may be associated with cardioembolic pathology and atheromatous disease, especially in the carotid arteries.

5.3 Respiratory system

Bronchopneumonia is a common cause of death in patients with dementia. Aspiration pneumonia is predisposed in patients with involvement of motor nuclei (dementia with Lewy bodies or frontotemporal dementia).

5.4 Alimentary system

Patients with swallowing problems may have been treated with a PEG feeding tube.

6 Organ retention

In all cases of dementia, it is necessary to retain the brain for prolonged fixation in formalin, prior to examination, to achieve a pathological diagnosis. The person in a qualifying relationship giving consent or the Coroner (or Procurator Fiscal), and through their office the deceased's family, should be informed that a completed neuropathological examination will be provided within a period of three months from the time of death.

The following compromises may be discussed in situations where there is no consent, or coronial authorisation, for retention of the brain for prolonged fixation.

1. Macroscopic examination only. There are no situations where the macroscopic pathology alone is sufficiently informative to allow a confident statement to be made on the cause of dementia. The limitations of this should be explained to those requesting or authorising the procedure, and should be documented in the final report.
2. The brain may be retained in formalin fixation for a period of 24-48 hours and then sectioned in the standard way. Samples taken for histological analysis can then be selected and placed into cassettes so that they can be fully fixed. This provides sufficient fixation such that sectioning of the brain is significantly easier than in the fresh state. The brain can be photographed, histologically sampled (see protocol below) and the remainder returned to the body for burial or cremation. The limitations of this approach and risk that a final diagnosis may not be established in all cases should be explained to those requesting or authorising the procedure.
3. Retention of strategic samples of brain in the fresh state (Appendix 1) may be undertaken. In this scenario, the brain is examined and sectioned in the fresh state. It should be explained to those requesting or authorising the procedure that all tissue retained will be processed for histological examination and that no tissues will be retained outwith paraffin blocks.
 - Coronal slice 1 cm thick taken at the level of the cerebral peduncles to include the hippocampus at the level of the lateral geniculate body.
 - Frontal cortical slice 1 cm thick.
 - Cerebellar hemisphere slice 1 cm thick.
 - Midbrain including substantia nigra.

The limitations of this approach and risk that a final diagnosis may not be established in all cases should be explained to those requesting or authorising the procedure.

In any method, it is preferable that the brain is photographed. The photographs should be labelled and stored with the case file for future reference.

7 Histological examination

Histological examination of brain tissue, including molecular pathology (immunocytochemistry) is essential in the diagnosis of dementia syndromes. The following is suggested for a minimum approach to the investigation of dementia.

7.1 General histology

Representative histology should be taken as appropriate, and determined by the findings at the post-mortem examination. For example, lung may be taken if there has been a suspected bronchopneumonia.

7.2 Neuropathology

7.2.1 Focal pathology

Any focal pathology identified in the brain should be examined microscopically. Subdural haemorrhages should be sampled in the form of a dural roll. This requires a section of dura to be rolled up and cut to a thickness of no more than 1 cm before being placed into a histology cassette. Sampling of these lesions may allow a rough estimation of the duration of the lesion if the clinical history is incomplete. Other examples of focal pathology include areas of severe atrophy, areas of cerebral softening, areas of apparent demyelination and areas suspicious of tumour.

7.2.2 Regional sampling

The following minimal block set is recommended as part of the assessment of dementia. The blocks should represent both the right and left cerebral hemispheres (see block sheet, Appendix 1). Multiple small blocks may be taken or alternatively a smaller number of large blocks may incorporate several specified regions.

Block 1	Middle frontal gyrus
Block 2	Superior and middle temporal gyri
Block 3	Basal ganglia
Block 4	Cingulate gyrus
Block 5	Anterior hippocampus and/or amygdala at the level of uncus
Block 6	Posterior hippocampus at level of lateral geniculate body
Block 7	Inferior parietal lobule
Block 8	Occipital cortex to include calcarine cortex the calcarine fissure, primary visual cortex with band of Gennari and para-/peristriate areas
Block 9	Midbrain to include substantia nigra
Block 10	Pons
Block 11	Medulla oblongata to include hypoglossal nucleus
Block 12	Cerebellar hemisphere (including the dentate nucleus)
Block 13	Samples of any macroscopically visible lesions
Block 14	Spinal cord in suspected frontotemporal dementia.

Additional sampling should be considered according to clinical judgment, for example the mammillary bodies and hypothalamus in suspected Korsakoff psychosis.

7.2.3 Spinal cord

The most common reason that the spinal cord is examined in dementia is in the setting of an associated movement disorder (usually motor neuron disease) or where there is suspected frontotemporal dementia.

7.3 Staining

7.3.1 General stains

The blocks should be stained with H&E, and usually a myelin stain for general morphological assessment.

7.3.2 Specific stains

A scheme for the staged examination of the brain in dementia using immunohistochemical methods and/or silver staining methods should be followed. Examples have been proposed.^{7,8} A suggested system is illustrated (Appendix 3).

Laboratories handling such cases require access to a range of specialised immunohistochemical techniques including antibodies to A β protein, PrP, phospho-tau, alpha synuclein, TDP-43, FUS, p62, ubiquitin, GFAP, neurofilament protein.

7.3.3 If relevant, the dura and any extra/subdural haematoma should be stained with H&E, Perl's and CD68, which are useful stains to age the haematoma.

8 Other samples required

Fresh tissue should be preserved in the context of consent to perform genetic testing.

In cases of suspected prion disease, it is recommended that samples of frontal lobe and cerebellum (as a minimum) should be frozen and stored at -70°C to enable biochemical characterisation of the pathological protein. In suspected cases of vCJD, where peripheral lymphoid tissues are known to contain abnormal prion protein, fresh samples of appendix, tonsil, gut and lymph node should be preserved.

9 The clinicopathological summary

The clinicopathological summary needs to be clear and concise. Statements of fact should be provided. The pathologist should clearly outline the macroscopic and microscopic observations. This should be considered in light of the clinical history provided. An overall summary should be made to correlate the pathological findings with the clinical history provided and in particular to highlight any consistencies or inconsistencies between the two.

Summary of post-mortem examination in case of dementia

Macroscopic brain examination

1. Atrophy:
 - distribution (diffuse or localised)
 - if local, specify regions or structures affected.
2. Haematoma:
 - site: deep or lobar, temporal, frontal, other site
 - measurement.
3. Brain herniation (\uparrow ICP):
 - uncal herniation (remove brainstem and cerebellum for better assessment), bilateral or unilateral
 - tonsillar herniation, usually associated with haemorrhage and necrosis rather than only bulging

- supracallosal (or sub-falcine) herniation
 - mid-line brain shift – corpus callosum and lateral ventricle.
4. Brain swelling – flattening of gyri, bilateral or one cerebral hemisphere
 5. Infarction and ischaemia:
 - site
 - arterial territory.
 6. White matter softening or gliosis:
 - site
 - size.
 7. Cerebral vessels:
 - anatomy
 - atheroma – specify degree of occlusion
 - thrombosis.

Microscopic brain examination

Criteria for the pathological diagnosis of diseases causing dementia should be applied according to published references.⁹⁻¹⁷ The BrainNet Europe website maintains a list of relevant references to diagnostic areas relevant to dementia at www.brainnet-europe.org/index.php?option=com_content&view=article&id=98&Itemid=98

The main causes of dementia ascertained by histopathological examination include the following.

Alzheimer's disease

Sporadic

Familial

Parkinson's disease dementia and dementia with Lewy bodies

Vascular dementia

Sporadic

Familial

Cerebra autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (cadasil)

Hereditary vascular amyloidosis (multiple types)

Mixed dementia

Frontotemporal lobar degeneration (FTLD) (sporadic or familial)

FTLD-tau

Pick's disease

Progressive supranuclear palsy

Corticobasal degeneration

Argyrophilic grain disease

Tangle predominant dementia

FTLD-TDP
FTLD-FUS
 FTLD-UPS
 FTLD-ni

Normal pressure hydrocephalus

Alcohol and dementia

Hippocampal sclerosis

Rarer neurodegenerative disorders

Thalamic dementia
Familial dementia associated with neuroserpin mutations
Heredodegenerative and metabolic causes of early onset dementia

Other diseases

Infective disorders
Neoplasia
Autoimmune disease
Prion disease.

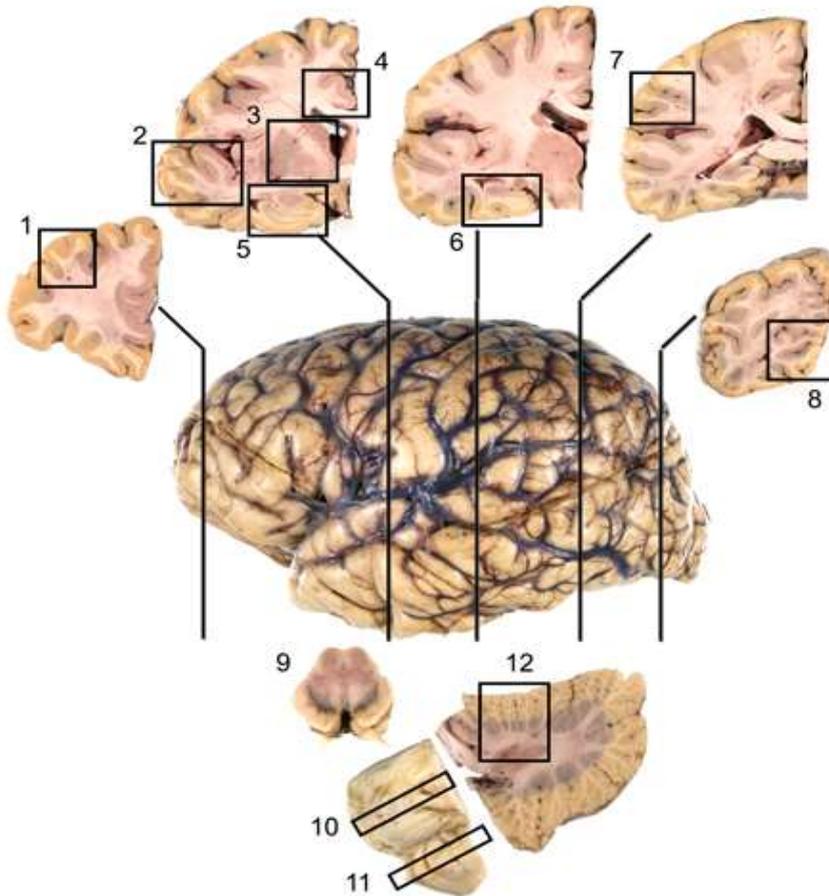
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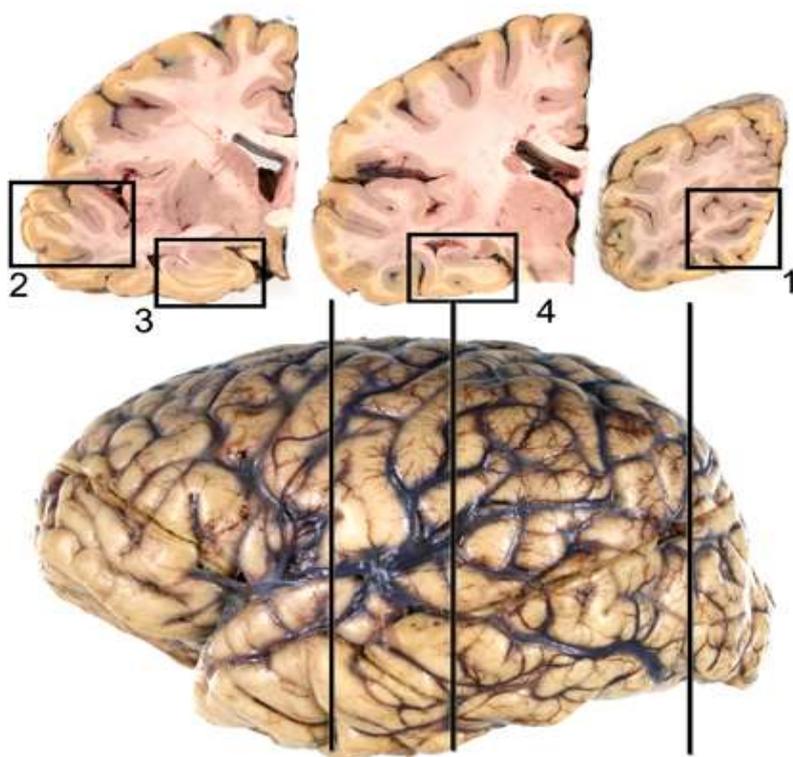
Appendix 1 Recommended blocks to sample in suspected dementia

All figures in appendices are published in: Burton JL, Ratty G. *The Hospital Autopsy: A manual of fundamental autopsy practice (3rd edition)*. ISBN 978 0 34096 514 6. Hodder Education, now CRC Press, Taylor and Francis Group, 2010)



- Block 1 Middle frontal gyrus
- Block 2 Superior and middle temporal gyri
- Block 3 Basal ganglia
- Block 4 Cingulate gyrus
- Block 5 Anterior hippocampus and/or amygdala at the level of uncus
- Block 6 Posterior hippocampus at level of lateral geniculate body
- Block 7 Inferior parietal lobule
- Block 8 Occipital cortex to include calcarine cortex the calcarine fissure, primary visual cortex with band of Gennari and para-/peristriate areas
- Block 9 Midbrain to include substantia nigra
- Block 10 Pons
- Block 11 Medulla oblongata to include hypoglossal nucleus
- Block 12 Cerebellar hemisphere (including the dentate nucleus)
- Block 13 Samples of any macroscopically visible lesions
- Block 14 Spinal cord in suspected frontotemporal dementia

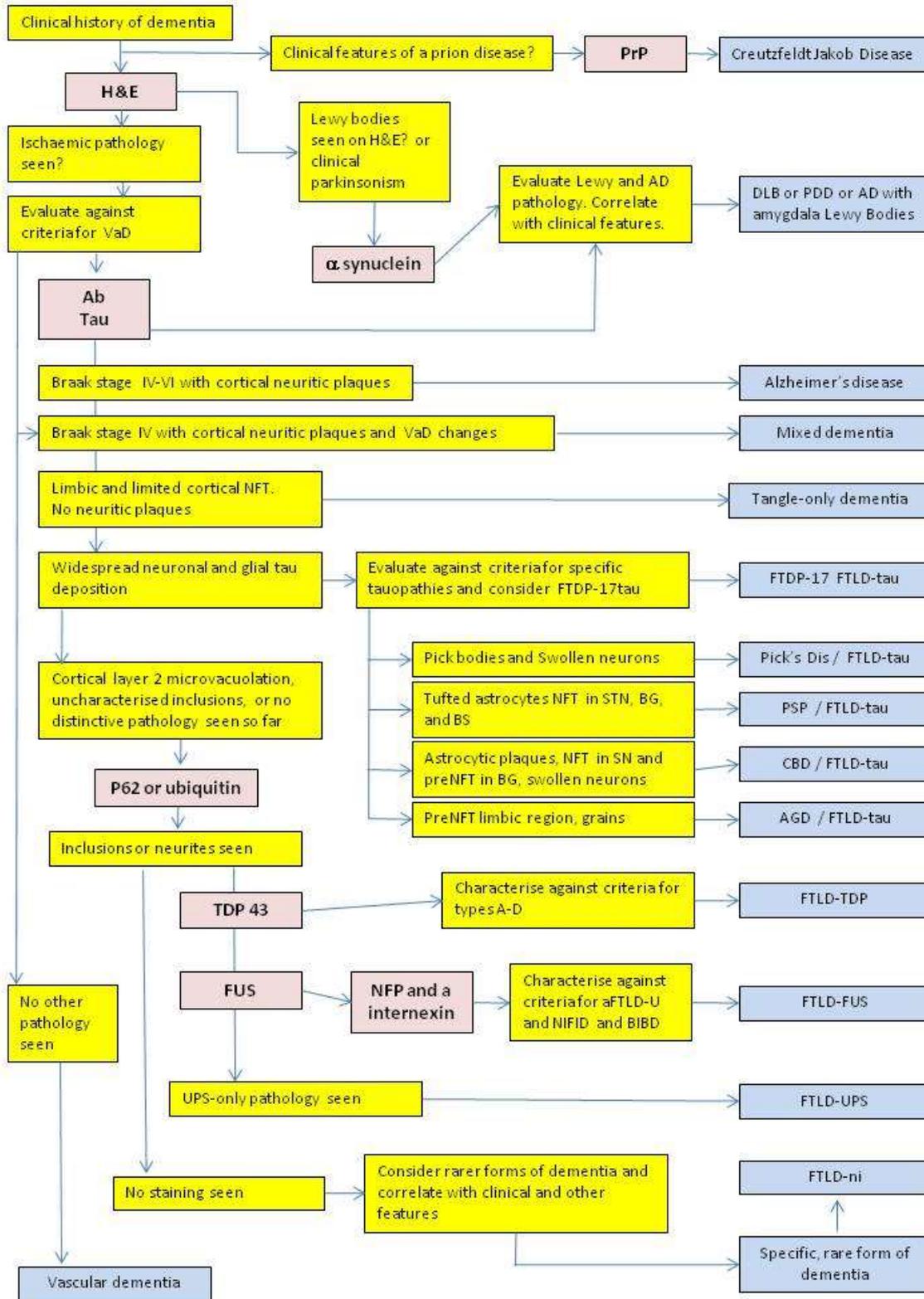
Appendix 2 Recommended blocks used in staging of suspected Alzheimer's disease with BrainNet Europe criteria¹³



Key	
1	Calcarine fissure to include the primary visual cortex with band of Gennari (involved in stage VI) and para-/peristriate areas (Brodmann area 18/19, (involved in stage V)
2	Middle and superior temporal gyrus (involved in stage IV)
3	Anterior hippocampus and/or amygdala at the level of uncus (involved in stage I-III)
4	Posterior hippocampus at level of lateral geniculate body (Involved in stage II and III)

Stage VI	Occipital cortex NTs (++ or +++) in layer V of the striate area.
Stage V	Occipital cortex NTs (++ or +++) in the superficial and deep layers of the peristriate area. No staining in the striate area
Stage IV	Middle temporal gyrus (++ or +++) in the superficial and/or deep layers. No staining in the peristriate area
Stage III	In section of posterior hippocampus at the level of the lateral geniculate body, NTs (++ or +++) in the outer and inner layers of remnants of the entorhinal region, continuing into the adjacent occipito-temporal gyrus. No staining in the middle temporal gyrus
Stage II	In section of posterior hippocampus at the level of the lateral geniculate body, NTs (++ or +++) in the outer layers of the entorhinal region and (+ or ++ or +++) in the inner layers of the entorhinal region. In section of anterior hippocampus at the level of uncus NTs (++ or +++) in the outer layers of the entorhinal region and (+ or ++ or +++) in the inner layers of the entorhinal region. No staining in the occipito-temporal gyrus
Stage I	In section of anterior hippocampus at level of uncus NTs (+ or ++ or +++) limited to the transentorhinal region.
Stage +	Tangles or pre-tangles or NTs in any region with a pattern that does not fit with a defined tauopathy, including a defined AD stage (above)
Stage 0	Sampling sections all IHC tau negative

Appendix 3 Staged approach to pathological diagnosis of dementia



AGD	argyrophilic grain disease	FTLD-UPS	frontotemporal lobar degeneration-ubiquitin proteasome system
CBD	corticobasal degeneration	FTLD-ni	frontotemporal lobar degeneration no inclusions
DLB	dementia with Lewy bodies	PrP	prion protein
FTDP-17tau	frontotemporal degeneration and parkinsonism linked to chromosome 17 tau	NFT	neurofibrillary tangle
FTLD-tau	frontotemporal lobar degeneration-tau	NFP	neurofilament protein
FTDP-FUS	frontotemporal lobar degeneration FUS	Aβ	a beta peptide
FTLD-TDP	frontotemporal lobar degeneration TDP	H&E	haematoxylin and eosin