Brain Pathology 8: 403-406(1998)

Establishing a Pathological Diagnosis in Degenerative Dementias

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While clinicopathological studies have confirmed that Alzheimer's disease (AD) is the most common neurodegenerative cause of dementia, these same studies have also revealed that other degenerative pathologies account for a significant proportion of patients with cognitive decline. Because pathological assessment of non-Alzheimer neurodegenerative diseases now demands routine use of a costly panel of immunohistochemical techniques a scheme for staged examination of brain tissue has been developed. This scheme is weighted to initially screen out cases of Alzheimer's disease, dementia with Lewy bodies and vascular dementia using conventional staining methods and established diagnostic protocols, bringing in immunochemical techniques to discriminate between non-Alzheimer degenerative dementias. Diagnosis of pathologies causing the clinical syndrome of frontotemporal dementia can be ascertained using conventional staining supplemented by immunochemical detection of ubiquitin, tau protein and α B crystallin. The diagnosis of prion disease is reliably confirmed by immunohistochemical detection of prion protein. This morphological assessment complements emerging genetic insights into many of these neurodegenerative diseases.

Introduction

Most pathologists involved in the routine pathological diagnosis of dementias will feel torn between the demands of doing a thorough job to the highest standards and keeping the workload in the laboratory down to a reasonable level. There are several pressures:

- A new range of non-Alzheimer degenerative diseases have been recently highlighted, especially in the differential diagnosis of frontoremporal dementias. Many of these diseases have been discussed in other parts of this edition of Brain Pathology.
- Inreased reliance is now being placed on immunohistochemical investigations to establish certain diagnoses and reagents are expensive.
- Most laboratories operate under circumstances of limited manpower and financial resources. Performing a comprehensive battery of staining procedures on a large number of blocks from every case is difficult to justify.

In response to these pressures a scheme for the staged examination of autopsy brain has been developed that facilitates diagnosis of recently described primary degenerative disorders, presented here as a flowchart (Fig 1). This chart was originally presented at the Wye Neuropathology Meeting UK July 1997, developed further and presented at the XIII Congress of Neuropathology sponsored by the British Neuropathological Society in Perth September 1997 (15). It is presented here with modifications resulting from informal discussions with several colleagues both during and after the meeting. The chart covers the main causes of degenerative dementia and is intended for routine diagnostic practice - rare neurodegenerative disorders that have been reported in small numbers or in geographically limited distribution are not covered.

In any pathological diagnostic assessment, many important causes of dementia need to be considered, and while most are included briefly in this chart, they are not the main focus of this discussion which concentrates on primary neurodegenerative diseases. These include:

- Head injury
- Mass lesions (1)
- Dementia caused by infective diseases
- Dementia as part of a more defined neurodegenerative process such as Huntington's disease.
- Hydrocephalus.
- Inherited or acquired disease of white matter.
- Dementia associated with degenerative disorders normally presenting in childhood (5).
- Dementia caused by toxins, nutritional, or metabolic disease.

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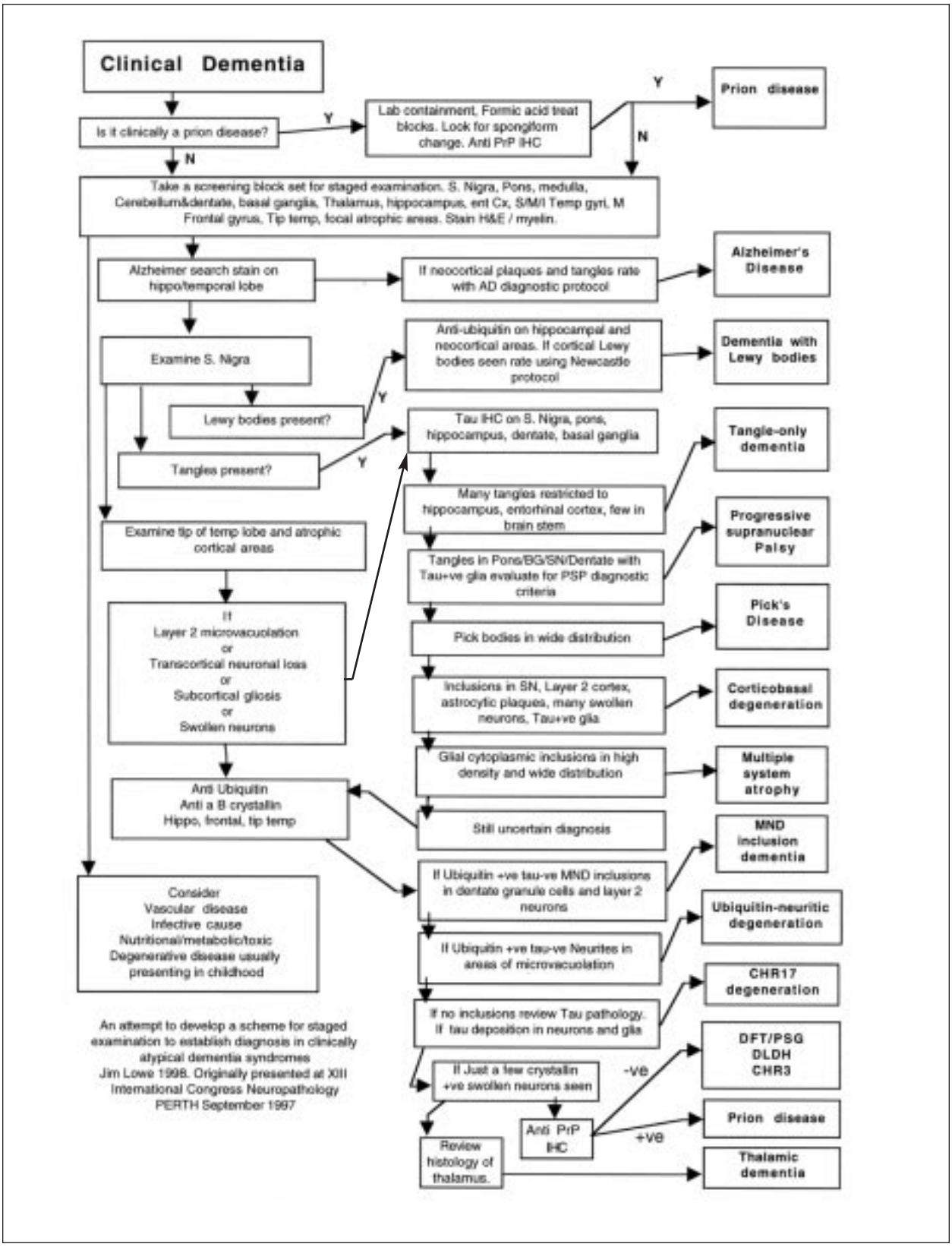
Clinical Dementia
Is it clinically a prion disease?
Y
N
Lab containment, Formic acid treat blocks. Look for spongiform change. Anti PrP IHC
Y
N
Prion disease
Take a screening block set for staged examination. S. Nigra, Pons, medulla, Cerebellum&dentate, basal ganglia, Thalamus, hippocampus, ent Cx, S/M/I Temp gyri, M Frontal gyrus, Tip temp, focal atrophic areas. Stain H&E / myelin.
Alzheimer search stain on hippo/temporal lobe
If neocortical plaques and tangles rate with AD diagnostic protocol
Alzheimer's Disease
Examine S. Nigra
Anti-ubiquitin on hippocampal and neocortical areas. If cortical Lewy bodies seen rate using Newcastle protocol
Dementia with Lewy bodies
Lewy bodies present?
Y
Tangles present?
Y
Tau IHC on S. Nigra, pons, hippocampus, dentate, basal ganglia
Tangle-only dementia
Many tangles restricted to hippocampus, entorhinal cortex, few in brain stem
Progressive supranuclear Palsy
Examine tip of temp lobe and atrophic cortical areas
Tangles in Pons/BG/SN/Dentate with Tau+ve glia evaluate for PSP diagnostic criteria
Pick's Disease
If
Layer 2 microvacuolation
or
Transcortical neuronal loss
or
Subcortical gliosis
or
Swollen neurons
Pick bodies in wide distribution
Inclusions in SN, Layer 2 cortex, astrocytic plaques, many swollen neurons, Tau+ve glia
Corticobasal degeneration
Glial cytoplasmic inclusions in high density and wide distribution
Multiple system atrophy
Anti Ubiquitin
Anti a B crystallin
Hippo, frontal, tip temp
Still uncertain diagnosis
MND inclusion dementia
If Ubiquitin +ve tau-ve MND inclusions in dentate granule cells and layer 2 neurons
Ubiquitin-neuritic degeneration
If Ubiquitin +ve tau-ve Neurites in areas of microvacuolation
CHR17 degeneration
If no inclusions review Tau pathology. If tau deposition in neurons and glia
DFT/PSG DLDH CHR3
If Just a few crystallin +ve swollen neurons seen
-Ve
Anti PrP IHC
+Ve
Prion disease
Review histology of thalamus.
Thalamic dementia
Consider
Vascular disease
Infective cause
Nutritional/metabolic/toxic
Degenerative disease usually presenting in childhood
An attempt to develop a scheme for staged examination to establish diagnosis in clinically atypical dementia syndromes
Jim Lowe 1998. Originally presented at XIII International Congress Neuropathology PERTH September 1997

It is intended that these areas will be incorporated more fully into the diagnostic scheme at a later date.

Histological assessment of clinical dementia syndrome

At the outset, any clinical features that suggest a possibility of a transmissible spongiform encephalopathy (prion disease) should be ascertained from case notes prior to undertaking any diagnostic procedures, so that appropriate Health and Safety precautions can be taken (4). Immunostaining protocols which reliably detect abnormal accumulations of prion protein have been developed (2).

Histological sections are cut from representative brain areas based on those of the CERAD diagnostic protocol (18, 19). In addition to routine staining, the temporal lobe and hippocampal region are initially screened using techniques sensitive to the presence of senile plaques and tangles. Initial screening of these brain areas will enable diagnosis of the main types of dementia and will point the way for further special staining and additional sampling as required.

- Assessment made for Alzheimer's disease (18-20). Rare cases of dementia pugilistica will also be revealed on analysis of sections stained to detect plaques and tangles.
- Assessment made for Lewy bodies in brain stem and, if present, in cortex to establish a diagnosis of dementia with Lewy bodies (10, 17).
- Assessment made for vascular dementia and hippocampal sclerosis (7, 9, 22)
- Assessment made for tangles in the substantia nigra or for spongiform change in outer cortex of frontal and temporal lobes. If present, additional immunostaining is performed to determine the sub-type of disease (6, 12). Personal experience suggests that a block from the tip of the temporal lobe is very useful in detecting abnormalities that point to one of the frontotemporal dementias.

1. tau immunostaining is performed to define specific types of disease as presently characterised by regional patterns of abnormal tau deposition including senile dementia with tangles, progressive supranuclear palsy, Pick's disease, corticobasal degeneration, chromosome 17-linked neurodegeneration, argyrophilic grain dementia and multiple system atrophy (3, 8, 13, 14, 21, 23). There are a variety of antibodies that detect tau pathology, a personal preference being for tau-2 (Sigma) for routine work.

2. Ubiquitin immunostaining defines diseases with inclusions related to motor neuron disease as well as dementia characterised by distinctive neurites (11, 16, 24). Person experience has suggested that certain monocolonal antibodies to ubiquitin are not very sensitive for pathological changes in brain as they detect free ubiquitin rather than ubiquitin-protein conjugates.

3. An antibody that detects swollen neurons is helpful, but not essential in looking for swollen neurons. Certain antisera that detect phosphorylated neurofilaments can be used but a personal preference is to use an antiserum against α B crystallin. While immunostaining is useful in defining the presence of swollen neurons , their presence is not specific for any type of neurodegenerative process.

Cases which show no inclusions, with variable numbers of swollen neurons, in the presence of cortical microvacuolation can be considered as having dementia of frontal type, or progressive subcortical gliosis. If familial, the possibility of chromosome-3 linked disease should be considered (16).

Careful examination of the thalamus is warranted to define cases of thalamic dementia with inflammatory, vascular, neoplastic and degenerative aetiologies. It should be reinforced that some cases with dominant thalamic degeneration are prion diseases where immunohistochemistry may not detect abnormal prion protein accumulations.

Uncommon multi-system atrophies involving neuronal loss and astrocytic gliosis of subcortical nuclei can usually be related to one of the above disease groups using this immunostaining strategy. Personal experience suggests that many such cases have ubiquitin inclusions resembling those seen in extramotor areas in motor neuron disease.

Summary

This scheme for the staged pathological examination of cases of clinical dementia has been tried out by a number of pathologists and found to be helpful in covering the majority of cases encountered in routine practice. It is acknowledged that there are always going to be cases which present unusual pathological features, overlap cases, cases with dual pathology, and cases with apparently unique pathological findings that cannot fit into a simplistic framework. The scheme would benefit from further refinement, and suggestions and comments are welcome from any colleagues who try it out.

Acknowledgements

The financial support of The British Neuropathological Society is acknowledged for the opportunity to present this material at the XIII Congress of Neuropathology. I would like to thank the many colleagues who made helpful comments in refining earlier versions of this staged diagnostic scheme.

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