Clinical advances in degenerative dementias

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Until recently there was widespread nihilism in the clinical approach to the demented patient. Most physicians believed that there was little reason to spend money or effort diagnosing diseases with no known risk factors, preventive measures or treatments. However, a multi-disciplinary effort has transformed this field, leading to a better understanding of the clinical presentation, risk factors, pathogenesis and treatment of the three main degenerative dementias: Alzheimer's disease (AD), fronto-temporal dementia (FTD) and dementia with Lewy bodies (DLB). These advances have evolved so quickly that even the physician with a primary focus upon dementia may have difficulty keeping up with the changing terminology, new risk factors, better diagnostic strategies and emerging therapies.

Alongside the new discoveries related to the pathogenesis of various dementia syndromes, there have been steady advances in the clinical diagnosis of AD, FTD and DLB. The ability to diagnose and separate these different dementias accurately has advanced both basic and clinical research. Additionally, the diagnostic advances in dementia described below are beginning to transform the clinical approach to elderly patients with neurological or psychiatric impairment.

ALZHEIMER'S DISEASE

Almost 30 years ago, in this journal, Blessed *et al* (1968) provided the first definitive proof that amyloid plaques and neurofibrillary tangles correlated with dementia severity in the elderly. Their observations were based on the meticulous recording of mental status in elderly patients, upon whose death the brain concentration of amyloid plaques was determined. The authors found a strong correlation between dementia severity and brain amyloid. Six decades before, Alois Alzheimer had described similar pathological abnormalities in the brains of two pre-senile dementia patients. Suddenly, what had been called 'arteriosclerotic dementia' became Alzheimer's disease. Soon afterwards, a cholinergic deficit was discovered in association with AD (Bowen *et al*, 1976; Davies & Malony, 1976; Perry *et al*, 1977).

These studies represented a paradigm shift by showing that elderly subjects with cognitive impairment were demented as a result of specific neurochemical and pathological changes in the brain. Subsequently, formal research criteria were established for the diagnosis of AD, which required both the quantification of mental status (McKhann *et al*, 1984) and counting of amyloid plaques and neurofibrillary tangles. Emphasis upon quantifying mental status improved diagnostic accuracy for dementia. Simultaneously, AD research became directed toward determining the function, mechanisms of formation and neuronal toxicity of B-amyloid. The discovery of a cholinergic deficit eventually led to the development of cholinergic drugs with some efficacy against AD.

More recently, genetic research helped better to define the relationship between amyloid and AD. Chromosome 21 was found to be the site for the amyloid precursor protein gene (*APP*), and specific mutations adjacent to or involving *APP* were discovered in families with early-onset AD (Goate *et al*, 1991). Subsequently, apolipoprotein E4, which was encoded on chromosome 19, was found to be a strong risk factor for AD (Roses, 1994). Of the three haplotypes for the apolipoprotein E (E2, 3 and 4), E4 had the greatest avidity for amyloid, suggesting that abnormal processing of brain amyloid might explain the higher risk associated with E4. Although basic research into the relationship between apolipoprotein E and AD continues, apolipoprotein E4 lacks sensitivity and specificity as a screening tool for AD.

Other genes were found. Many early-onset AD cases were discovered to have an abnormality in the 'presenilin' protein encoded on chromosome 14 (Schellenberg, 1995). Also, chromosome 1 encodes a protein partially homologous with presenilin 1 (presenilin 2) linked to some familial cases of AD (Rogaev *et al*, 1995). The functions of these two proteins are under active study.

Unfortunately, many patients with non-AD degenerative dementias fulfil the current research criteria for AD. Not surprisingly, this has led to unacceptably high misdiagnosis rates for disorders such as FTD and Parkinsonian dementias. Mendez *et al* (1993) reported that 18 out of 21 patients with Pick's disease at autopsy were diagnosed as having AD during their life. Similarly, Parkinsonian dementia accounted for many of the patients misdiagnosed at AD diagnostic centres (Galasko *et al*, 1994). Recently, clinical pathological studies into FTD and Parkinson's disease led to the realisation that both disorders were clinically distinctive and could be separated from AD during life.

FRONTO-TEMPORAL DEMENTIA

Longitudinal studies from the research groups in Lund, Sweden and Manchester, England suggested that more than 15% of patients with degenerative dementia had a disorder which selectively attacked the anterior frontal and temporal cortex (Brun, 1987; Neary *et al*, 1988). The typical age of onset was the sixth decade and many FTD subjects had a history suggesting a late-life onset dominantly inherited disorder (Gustafson, 1993). Some patients developed motor neuron disease and others had relatives with a history of motor neuron disease (Mitsuyama, 1993). Accurate diagnosis of FTD required careful observation of behaviour because mental status testing alone was not sufficient (Gustafson, 1987; Neary *et al*, 1988). Functional imaging with single photon emission computed tomography (SPECT) showed selective fronto-temporal hypoperfusion and helped improve diagnostic accuracy for FTD (Read *et al*, 1995).

Pathologically distinct from AD, frontal and temporal cortex demonstrated marked gliosis and neuronal loss, but only a minority had Pick bodies (Brun, 1987). Unlike AD, FTD was not associated with a pre-synaptic cholinergic deficit, although severe pre- and post-synaptic serotonin losses were found (Sparks & Markesbery, 1991).

https://doi.org/10.1192/bjp.171.1.1 Published online by Cambridge University Press

The Lund and Manchester groups set research criteria for FTD, which consisted of 29 items divided into the catagories: behaviour, speech, affect, spatial orientation/praxis, physical signs, investigations and supportive findings (Brun *et al*, 1994). Some of these items strongly distinguish FTD from AD, including disinhibition, loss of personal awareness, hyper-orality, stereotyped and perseverative behaviour, progressive reduction of speech, and preserved spatial orientation (Miller *et al*, 1997). Neuropsychological tests distinguish FTD patients from healthy controls. However, they do not easily differentiate FTD patients from those with AD (Pahana *et al*, 1996).

FTD offers a fascinating model for understanding the clinical manifestations of selective anterior frontal or temporal dysfunction. Symptoms reflect the relative involvement of the left or right frontal or temporal lobes. Left-sided dysfunction causes loss of speech and language (Snowden *et al*, 1992), while selective right-sided degeneration commonly leads to behavioural disinhibition and altered expression of affect (Miller *et al*, 1993). Stereotyped compulsive behaviours and increased eating may be secondary to the serotonin deficit in FTD (Miller *et al*, 1995). Treatment with serotonin-boosting antidepressants has demonstrated promise of ameliorating some of the behaviours found in these patients, although they have shown no effect on the cognitive disturbance. Preventive measures seem unlikely until there is a better understanding of the molecular basis for this disorder. However, recent demonstration of linkage between familial cases of FTD and chromosome 17 suggests that the molecular mechanisms associated with FTD may soon be clarified (Wilhelmsen *et al*, 1994).

DEMENTIA WITH LEWY BODIES

This term was chosen at a recent international meeting which established research criteria for the group of patients who present with a mixture of dementia and Parkinsonism (McKeith *et al*, 1996). Whether these patients suffer from a variant of AD (Hansen *et al*, 1990) or have a distinct disorder (Perry *et al*, 1990*a*,*b*; Dickson *et al*, 1991) is still debated, but it is accepted that clinical and pathological findings are distinctive in DLB.

Studies from England (Byrne *et al*, 1989; Perry *et al*, 1990*b*) and Japan (Kosaka, 1990) were the first to emphasise the distinctive clinical features of DLB patients. In many, visual hallucinations occur (McKeith *et al*, 1996), often featuring complex scenes with animals, dwarves, children or supernatural creatures. Neurochemical studies documented a profound cholinergic deficit in DLB and suggested that the visual hallucinations and fluctuating mental status characteristic of this disorder might have a chemical basis (Perry *et al*, 1990*a*). Parkinsonian features, often different from classical Parkinson's disease, have been reported in most DLB patients and can precede or follow the onset of dementia (McKeith *et al*, 1996). Postural instability and bradykinesia are common, while tremor is rare. Neuropsychological and neuroimaging studies have not shown robust differences between DLB and AD subjects (Burns, 1996). DLB patients have Lewy bodies in the substantia nigra and cortex (Perry *et al*, 1990*b*) and show depletion of dopamine in the substantia nigra. Amyloid plaques are present in some but not all subjects.

Diagnosis of DLB has therapeutic implications; because of the dopaminergic deficiency, treatment with neuroleptics can be fatal, while anticholinergic medications often precipitate life-threatening delirium (McKeith *et al*, 1996). Also, DLB patients may be more likely to respond to anticholinesterases than those with classical AD (Kaufer & Cummings, 1996).

CONCLUSION

With the steady march of important discoveries in dementia, including the emergence of treatment options, recognition of the clinical features of the different degenerative dementias has become particularly important. Despite the many basic scientific advances related to AD, FTD and DLB, diagnosis still requires hands-on evaluation of the patient, which must include meticulous recording of the history, testing of mental status and observation and quantification of psychiatric behaviours. Rather than being pushed aside by molecular biology, clinical neuropsychiatry has become central to the diagnosis and treatment of the major degenerative disorders.

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(First received 31 January 1997, accepted 25 March 1997)

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https://doi.org/10.1192/bjp.171.1.1 Published online by Cambridge University Press