■Special Lecture

Neuropsychological Correlates of Fronto-temporal Cerebral Atrophy

David Neary*

Introduction

The clinical pathological correlates in three clinical syndromes arising from fronto-temporal cerebral atrophy and based on work from Manchester, UK are reviewed and comprise dementia of frontal lobe type (DFT), DFT and motor neurone disease (MND), and progressive aphasia (PA).

Dementia of Frontal Lobe Type

Clinical Syndrome

DFT appears usually in the presenium and there is a family history of a simlar disorder in half of the cases. The presentation is of a disorder of conduct and personality and in the late stages mutism supervenes. There are few neurological signs initially, but with progression striatal signs of akinesia and rigidity emerge. Survival of up to 10-15 years is not uncommon. The EEG remains normal late into the disease and SPET imaging displays abnormalities in the anterior cerebral hemispheres.

Dramatic changes in personal and social conduct occur and individuals lose insight. Two polarised clinical profiles emerge : an apathetic inert state contrasts with disinhibition, restlessness and inappropriate affect. Speech becomes increasingly brief, echolalic and stereotypic until mutism supervenes. Spatial and executive abilities are well preserved. In addition to motor perseverations of an elementary type, stereotypic and ritualistic behaviour comes in acts of daily living. Individuals over-eat, develop food fads and hyperoral activity. Repetitive rituals of dressing, toileting, hoarding and wandering occur.

Anatomical Correlates and Histology

The topographical distribution of the gross histological and immunohistochemical pathologies and their severity indicate that the clinical syndrome is pathologically heterogeneous and appears to compromise three distinctive sub-groups.

The first subgroup (type A) (5 brains) is characterised by a fronto-temporal atrophy defined histologically by a loss of large cortical nerve cells (chiefly from layers III and V), and a spongiform degeneration of the superficial neuropil (layer II) ; gliosis is minimal and restricted to subpial regions ; layers III and V shows no gliosis. No distinctive changes (swelling or inclusions) within remaining nerve cells are seen. The limbic system and the striatum are affected but to a much lesser extent.

The second subgroup (type B) (5 brains) is also characterised by a fronto-temporal atrophy but which is defined by a loss of

*Department of Neurology, Manchester Royal Infirmary, Manchester, UK

large cortical nerve cells with widespread and abundant gliosis but minimal or no spongiform change. Swollen neurones or inclusions that are both tau and ubiquitin positive are sometimes typically present in some patients, and the limbic system and striatum are more seriously damaged.

Type A and type B subgroups shared a common clinical syndrome and familial incidence.

In the third subgroup (type C) (3 brains), the brunt of the pathology is borne by the striatum with (usually) severe limbic involvement but variable cortical and nigral involvement. Immunochemistry reveals no significant changes.

The patients in type C subgroup are characterised by stereotypic and ritualistic behaviour as the predominant symptomatology and they develop striatal neurological signs early in the course of the illness.

Dementia of Frontal Lobe Type and Motor Neurone Disease

Clinical Syndrome

Here typical DFT is followed by the amyotrophic form of MND with wide-spread fasciculations, muscular weakness, wasting and bulbar palsy. Death takes place within 3 years. Electrophysiology demonstrates muscular denervation, electroencephalogram remains normal and SPET imaging reveals defects in the anterior hemispheres. In the Manchester series no patients developed extrapyramidal neurological signs.

Anatomical and Histological Changes

The structural changes are similar to type A subgroup of DFT. Atrophy is less marked and is mostly frontal with less temporal involvement. Ubiquitinated but not tau-immunoreactive inclusions are present within the frontal cortex and hippocampus (dentate gyrus). In the brainstem, the hypoglossus nucleus shows atrophy and loss of neurones. Within the anterior horn cells there is gross loss of neurones at all levels, and many of the surviving anterior horn cells contain large pale ubiquitinated inclusions within the cytoplasm. No lewy or Pick-type inclusions are observed in any cortical or subcortical neurones.

Progressive Aphasia

Clinical Syndrome A

A non-fluent aphasia with anomia, impaired repetition, phonemic errors with relative preservaton of comprehension occurs and behavioural changes akin to DFT occur late in the disease. However, the brother of one patient developed such behavioural change shortly after the onset of his linguistic presentation. Neurological signs are usually absent. SPET images reveal reduced tracer uptake in the left cerebral hemisphere exclusively.

Clinical Syndrome B

A fluent aphasia with preserved repetition, verbal paraphasias, profound problems in comprehension occurs but with relatively preserved reading aloud and writing to dictation. A proportion of these patients go on to develop a visual agnosia (semantic dementia) (Snowden et al, 1989). Behavioural changes akin to DFT are sometimes observed. None have significant neurological signs. SPET images reveal bilateral defects in the anterior hemispheres.

Anatomical and Histological Findings

In profile A patients, the brains showed markedly asymmetrical atrophy being slight and generalised on the right side but gross on the left side, particularly affecting fronto-temporal, fronto-parietal and lateral parietal/occipital regions. The left anterior

temporal cortex showed "knife edge" atrophy. The pattern of atrophy involved the hippocampus, amygdala, the caudate, putamen, globus pallidus and thalamus on the left side alone. Histologically frontal, fronto-parietal and anterior temporal cortices on the left side were severely affected and showed changes similar to those of DFT type A.

The brother of a patient with profile A, with an identical linguistic breakdown developed the rapid changes of DFT. His brain revealed asymmetrical and severe atrophy of the fronto-temporal lobes, more marked on the right than the left side. The histological changes were identical to those of his brother.

The brain of a single patient with fluent aphasia and associative agnosia (profile B) revealed a fixed brain which was grossly normal with only slight enlargement of the lateral ventricles and no obvious asymmetries of brain slices. The pathological changes were identical to those of patients with clinical syndrome A and particularly affected the middle and inferior temporal gyri with preservation of the superior temporal gyrus and parietal and occipital cortices.

Clinico-Anatomical Correlations

The clinical syndrome emerging from patients with fronto-temporal cerebral atrophy appear to reflect the topographical distribution of the pathology rather than the specific histological change. When the frontal lobes are bilaterally, symmetrically and predominantly affected, the syndrome of DFT emerges. When the left cerebral hemisphere is predominantly affected, the syndrome of non-fluent PA occurs. However, when the process is distributed asymmetrically, the behavioural disturbances of DFT are seen in association with linguistic disturbance, as in the more behaviourally disturbed brother with progressive non-fluent aphasia. Predominant involvement of the temporal lobes bilaterally leads to progressive fluent aphasia and associative visual agnosia. In this series of patients, MND has been associated with DFT but not with PA.

Clinico-Histological Correlations

If a distinction is made between the spongiform appearances and the gliotic change, with and without Pick bodies, then DFT can be associated with both histologies in roughly equal proportions and with a similar familial incidence. In DFT and MND the histology is that of spongiosus change. This is also the case with PA. However, the subgroup of patients with DFT who have stereotypic traits and early striatal neurological signs had a mixed histological picture sharing features of both types of change.

It apears more likely that the two histologies represent a spectrum of change and this is reinforced by the literature which indicates an association between the three clinical syndromes of DFT, DFT/MND and PA, the occurence of the two pathologies in each syndrome and the observation of familial examples of all three syndromes.

Gustafson (1987), Brun (1987) and Risberg (1987) described 20 cases of fronto-temporal dementia from Lund. The term "frontal lobe degeneration" (FLD) referred to the histology of neuronal cell loss and spongiform appearances, in the absence of 'inflated cells and inclusions'. The latter were held to define Pick's disease. There were only small and non systematic clini-

cal differences between……FLD and Pick's cases'. Thus the same clinical syndrome shares the two pathologies.

Tissot et al (1985) in reviewing Pick's disease describe a clinical syndrome consonant with DFT. They described three categories of histological change : gliosis ; gliosis with neuronal swellings (NS) and gliosis with NS and argyrophilic inclusions (AI). In both Lund and Manchester there was a high familial incidence, as in 'familial dementia of adult onset' described by Kim et al (1981) in 4 of 10 siblings of an Italian family.

Gustafson (1987) noted that one FLD patient 'showed evidence of motor neurone disease'. Mitsuyama (1984) described 'presenile dementia with motor neurone disease in Japan'. In reviewing the extensive Japanese literature, Morita et al (1987) noted 'dementia……is the frontal temporal type, or "anterior dementia"'.

The development of bulbar palsy is likely to dictate the early death of patients who may have insufficient time to manifest extrapyramidal signs, as in the Manchester series. This is supported by the occurrence of the latter in cases of longer duration (Morita et al, 1987). Moreover of patients with striatal signs 88% had significant degeneration of the substantia nigra. This subgroup of patients with extrapyramidal signs is commented on by Salazar et al (1983) in their studies of the syndrome "ALS and dementia".

Knopman et al (1990) in assessing forms of non-Alzheimer's disease dementia from a brain bank referred to 'dementia lacking distinctive histological features (DLDH)' to describe the non-specific large neuronal cell loss and spongiform appearances. Three fifths of patients with DLDH pathology also had that of MND. Again there was a familial incidence, half the cases having a family history of dementia, and one a family history of MND. In the Manchester series, one patient with DFT/MND had a mother with dementia, but not MND. The importance of genetic factors is again highlighted in this syndrome by Constantinidis' (1987) report of 4 members of 2 generations who developed characteristic DFT and later MND. In 2 autopsied cases, there was predominant fronto-temporal atrophy, asymmetrically favouring the left hemisphere. The histological findings were not of spongiosus, but of gliosis, neuronal cell loss and ballooned neurones, in the absence of inclusion bodies. Brion et al (1980) have also noted sporadic cases of DFT/MND with gliotic rather than spongiform histology. Thus the latter in DFT/MND is not an invariable finding.

Case descriptions have proliferated of PA but there have been few clinico-pathological studies. Pick's original clinical description of a case of lobar atrophy (Pick, 1892) was of progressive linguistic impairment. Interestingly, the first modern case of 'pre-senile dementia presenting as aphasia' described by Wechsler (1977), subsequently came to autopsy (Wechsler et al, 1982) and proved to have fronto-temporal atrophy, principally left sided with a histology of Pick's disease as strictly defined. A subsequent case with very similar clinical and pathological findings has been described (Graff-Radford et al, 1990).

The familial nature of progressive aphasia has been attested to by Morris et al (1984) who use the term 'hereditary dysphasic dementia'. The majority of cases of PA display, histologically, the spongiform appearances rather than Pick's disease and

in one of two cases (Kirshner et al, 1987) there was also wasting and fasciculations of the upper and lower limbs as well as a similar disease in the patient's mother. Thus the link between PA and MND is further established.

Conclusion

The distinctive clinical syndromes of lobar atrophy are dictated by the anatomy of pathology within the frontal and temporal lobes. The syndrome does not predict the precise histology. The latter appears to represent a spectrum of pathological change, rather than demarcated entities, especially since familial cases exist for each syndrome and for each histological type……

It is clear from the foregoing that clinical terms cannot be used interchangeably with pathological designations. DFT, DFT/MND and PA refer to clinical syndromes whereas FLD, DLDH and Pick's disease denote particular histologies. There is, as yet, no accepted definition of the pathological criteria for Pick's disease. It was Alzheimer (1911) not Pick who referred to 'ballooned cells', argentophilic globes' and 'spongi cortico wasting'. Some authors simply accept circumscribed fronto-temporal atrophy without characteristic histology (Malamud et al, 1940 ; Constantinidis et al, 1987). More recently it has been proposed (Kim et al, 1981 ; Verity et al, 1987) that a combination of progressive dementia, lobar atrophy and neuronal argentophilic inclusion (Pick) bodies be diagnostic of Pick's disease. Since fronto-temporal degeneration is heterogenous and can occur in a minority of cases of Alzheimer disease and Creutzfeldt-Jacob disease (Brun, 1987), and since ballooned neurones occur in a variety of neurodegenerative conditions (Lowe et al, 1992 ; Kato et al, 1992), it might be suggested that the presence of Pick inclusion bodies represents the conclusive histology since they are rarely found in other conditions (Clark et al, 1986).

In order to clarify these nosological issues the groups in Lund, Sweden and Manchester, UK have produced a "Consensus on Clinical and Neuropathological Criteria for Fronto-temporal Dementia" (Brun et al, 1993). For the clinical syndrome the term 'fronto-temporal dementia' or FTD has been adopted and is therefore synonymous with DFT. Provisionally 3 histological types have been designated. Fronto-lobe degeneration (FLD) type refers to the predominantly spongiform histology, whereas Pick's type refers to the pathology of severe gliosis with the presence of inclusion bodies and ballooned neurones. Provisionally it would seem judicious to include those brains with severe gliotic change, in the absence of inclusion bodies and ballooned neurones, in the Pick type group. Further studies will presumably justify or refute such a basis for classification. The Motor Neurone Disease (MND) type refers to a mild FLD change in the cerebral hemispheres and severe anterior horn cell death in the spinal cord.

The tasks for the future are to determine the nature of the differing pathological changes underlying lobar atrophy and, given the high familial incidence, to search for a molecular biological basis which might explain them.

References

1) Allen IV, Dermott E, Connolly JH et al : A study of a patient with the amyotrophic form of Creutzfeldt-Jakob disease. Brain

94 ; 715-724, 1971
2) Alzheimer A : Über eigenartige Krankheitsfälle des späteren Alters. Z Gesamte Neurol Psychiatr 4 ; 356-385, 1911
3) Brion S, Psimaras A, Chevalier JF et al : L'association maladie de Pick et sclérose latérale amyotrophique. Etude d'un cas anatomo-clinigue et revue de la littérature. Encéphale 6 ; 250-286, 1980
4) Brun A : Frontal lobe degeneration of non-Alzheimer's type : Neuropathology. Arch Gerontol Geriatr 6 ; 193-208, 1987
5) Brun A, Mann DMA, Englund B et al : Concensus on clinical and neuropathological criteria for fronto-temporal dementia. J Neurol Neurosurg Psychiatry (in press)
6) Clark AW, Manz HJ, White C et al : Cortical degeneration with swollen chromatolytic neurons : Its relationship to Pick's disease. J Neuropathol Exp Neurol 45 ; 268-284, 1986
7) Constantinidis J : Syndrome familial : association de maladie de Pick et sclérose latérale amyotrophique. Encéphale 13 ; 285-293, 1987
8) Constantinidis J, Richard J, Tissot R : Pick's disease : Histological and clinical correlations. Eur Neurol 11 ; 208-217, 1987
9) Goulding PJ, Northen B, Snowden JS et al : Progressive aphasia with right-sided extrapyramidal signs : Another manifestation of localised cerebral atrophy. J Neurol Neurosurg Psychiatry 52 ; 128-130, 1989
10) Graff-Radford NR, Damasio AR, Damasio H et al : Progressive aphasia in a patient with Pick's disease. Neurology 40 ; 620-626, 1990
11) Gustafson L : Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. Arch Gerontol Geriatr 6 ; 193-208, 1987
12) Kato S, Hirani A, Umahara T et al : Comparative immunohistochemical study on the expression of crystallin ubiquitin and stress-response protein 27 in ballooned neurons in various disorders. Neuropathol Appl Neurobiol 18 ; 335-340, 1992
13) Kim RC, Collins GH, Paris JE : Familial dementia of adult onset with pathological findings on a 'non-specific' nature. Brain 104 ; 61-78, 1981
14) Kirshner H, Ogurz T, Lawrence T et al : Progressive aphasia without dementia. Two cases with focal spongiform degeneration. Ann Neurol 22 ; 527-532, 1987
15) Knopman DA, Mastri AR, Frey WH et al : Dementia lacking distinctive histological features : A common non-Alzheimer degenerative dementia. Neurology 40 ; 251-256, 1990
16) Lindgren AKH : The patho-anatomical classification of morbus Alzheimer and morbus Pick. Acta Psychiatr Neurol Scand 81 (suppl); 118-152, 1952
17) Lowe J, Errington DR, Lennox G et al : Ballooned neurons in several neurodegener ative diseases and stroke contain d crystallin. Neuropathol Appl Neurobiol 18 ; 341-350, 1992
18) Malamud N, Boyd DA : Pick's disease with atrophy of the temporal lobes : A clinicopathological study. Arch Neurol Psychiatry 43 ; 210-222, 1940
19) Mann DMA, South PW, Snowden JS et al : Dementia of frontal lobe type : Neuropathology and immunohistochemistry. J Neurol Neurosurg Psychiatry 56 ; 605-614, 1993
20) Mesulam MM : Slowly progressive aphasia without generalised dementia. Ann Neurol 11 ; 592-598, 1982
21) Mitsuyama Y : Presenile dementia with motor neuron disease in Japan : Clinicopathological review of 26 cases. J Neurol Neurosurg Psychiatry 47 ; 953-959, 1984
22) Morita K, Kaiya H, Ikeda T et al : Presenile dementia combined with amyotrophy : A review of 34 Japanese cases. Arch Gerontol Geriatr 6 ; 263-277, 1987
23) Morris JC, Munroe C, Barker BQ et al : Hereditary dysphasic dementia and the Pick-Alzheimer spectrum. Ann Neurol 16 ;

; 455-466, 1984
24) Neary D : Non-Alzheimer's disease forms of cerebral atrophy. J Neurol Neurosurg Psychiatry 53 ; 929-931, 1990
25) Neary D, Snowden JS, Bowen DM et al : Neuropsychological syndromes in presenile dementia due to cerebral atrophy. J Neurol Neurosurg Psychiatry 49 ; 163-174, 1986
26) Neary D, Snowden JS, Mann DMA et al : Frontal lobe dementia and motor neuron disease. J Neurol Neurosurg Psychiatry 52 ; 23-32, 1990
27) Neary D, Snowden JS, Northen B et al : Dementia of frontal lobe type. J Neurol Neurosurg Psychiatry 51 ; 353-361, 1988
28) Neary D, Snowden JS, Shields RA et al : Single photon emission tomography using ^{99m}Tc-HM-PAO in the investigation of dementia. J Neurol Neurosurg Psychiatry 50 ; 1101-1109, 1987
29) Northen B, Hopcutt B, Griffiths H : Progressive aphasia without generalised dementia. Aphasiology 4 ; 55-65, 1990
30) Pick A : Über die Beziehungen der senilen Hirnatrophie zur Aphasie. Prager med Wochenschr 17 ; 165-167, 1892
31) Risberg J : Frontal lobe degeneration of non-Alzheimer type. III. Regional cerebral blood flow. Arch Gerontol Geriatr 6 ; 225-233, 1987
32) Salazar AM, Masters CL, Gajdusek C et al : Syndromes of ALS and dementia : Relation to Creutzfeldt-Jakob disease. Ann Neurol 14 ; 17-26, 1983
33) Snowden JS, Goulding PJ, Neary D : Semantic dementia : A form of circumscribed cerebral atrophy. Behav Neurol 2 ; 167-182, 1989
34) Snowden JS, Neary D, Mann DMA et al : Progressive language disorder due to lobar atrophy. Ann Neurol 31 ; 174-183, 1992
35) Tissot R, Constantinidis J, Richard J et al (ed): Pick's Disease. Handbook of Clinical Neurology. Amsterdam, Elsevier Science Publishers, 1985, vol 2 (46), Chapt 132, pp. 233-246
36) Verity MA, Wechsler AF : Progressive subcortical gliosis of Neumann : A clinicopathological study of 2 cases with review. Arch Gerontol Geriatr 6 ; 245-261, 1987
37) Wechsler AF : Presenile dementia presenting as aphasia. J Neurol neurosurg Psychiatry 40 ; 303-305, 1977
38) Wechsler AF, Verity MA : Pick's disease. A clinical computed tomographic and histological study with Golgi impregnation observations. Arch Neurol 39 ; 287-290, 1982

Abstract

Three clinical syndromes associated with fronto-temporal cerebral atrophy, studied in one centre are discussed : dementia of frontal lobe type (DFT), DFT and motor neurone disease (MND) and progressive aphasia (PA). The pathological findings in DFT, DFT and MND and PA permit a number of clinical pathological groupings. The nosological status of fronto-temporal atrophy is discussed with reference to the literature and it is suggested that a common underlying pathology, including Pick's disease as strictly defined by the presence of inclusion bodies, underlies the clinical syndromes, each being determined by the anatomical distribution of the pathology.