

The frontal dementias

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Abstract

The frontal variant of frontotemporal dementia (FTD) is an important cause of early-onset dementia. Yet, despite the publication of consensus criteria in 1998, the diagnosis is often delayed. In part, this seems to stem from a lack of appreciation of the variability in behavioural and neuropsychological features found in the FTD's, and in part from over-reliance on structural neuroimaging. This review sets out 11 principles to guide the general neurologist in the diagnosis of the FTD's: 1) "Frontal" impairments may arise from frontal connections beyond the anatomical confines of the frontal lobes, 2) The FTD's are uncommon, but they are over-represented in younger patients with dementia, 3) A range of different pathologies, with different genetic implications, underlies the FTD syndromes, 4) The clinical presentation of FTD in an individual patient primarily depends on the location of the pathology, not on its nature, 5) The recognised FTD syndromes represent polar ideals; mixed presentations and evolving clinical pictures are the norm, 6) A complete FTD diagnosis must be made on three axes: clinical syndrome, pathological/biochemical type, and (if possible) genetic basis, 7) Many neuro-psychological tests are insensitive to executive dysfunction, 8) Neuropsychological tests of executive function do not assess orbitofrontal dysfunction adequately, 9) Executive function can be fractionated, and not all FTD patients are impaired in every aspect of executive functioning, 10) Structural imaging changes lag behind behavioural changes, and may be absent in early FTD, while functional imaging is relatively more sensitive, but may also be normal, and 11) The neurologist's role extends beyond diagnosis to management, despite the lack of proven pharmacological disease-modifying therapies for FTD.

INTRODUCTION

Since the publication of consensus clinical criteria for the diagnosis of the frontotemporal dementias (FTD's)¹ and the discovery in that some familial FTD's are caused by mutations in the tau gene on chromosome 17², there has been an upsurge of interest in this group of disorders. However, the neurologist who encounters these disorders only occasionally may find the field somewhat confusing. This article sets out eleven practice points, or clinical aphorisms, in an attempt at clarification for the practising clinician.

1. "Frontal" impairments may arise from frontal connections beyond the anatomical confines of the frontal lobes.

Functional imaging studies have confirmed that complex behaviours are subserved by networks of interconnected brain regions rather than by discrete cortical areas.³ Examples include the dorsolateral prefrontal-dorsolateral caudate-thalamic-dorsolateral prefrontal loop, the

orbitofrontal-ventromedial caudate/ventral striatum thalamic-orbitofrontal loop, the anterior cingulate-limbic striatum-mediadorsal thalamic-anterior cingulate loop⁴, and the prefrontal-pontine-cerebello-thalamo-frontal loop.⁵ Interruption of such circuits outside the frontal cortex will reproduce many of the classical features of "frontal" dysfunction. For example, infarcts in the caudate head may disturb planning and sequencing, with disinhibition or apathy depending on which part of the caudate (and therefore which circuit) is disrupted^{6,7}, and discrete cerebellar lesions may also result in perseveration, disorders of planning, and behavioural dysregulation.⁸ Perhaps the most striking example is progressive supranuclear palsy, in which a recent meta-analysis of neuropsychological data has shown that the "frontal" deficits exceed those seen in the (cortical) frontotemporal degenerations, although the pathological burden is subcortical.⁹ The imaging counterpart of this finding is the typical prefrontal hypoperfusion/hypometabolism seen on SPECT scanning in

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progressive supranuclear palsy, in the absence of volume loss. The various other causes of “subcortical” cognitive impairment, such as small vessel ischaemic disease and multiple sclerosis, also produce typical “frontal” features such as cognitive slowing and concreteness with impairment of memory retrieval, presumably on the basis of disruption of frontal connections.¹⁰ It is therefore preferable to avoid inaccurate anatomical implications, by referring to these cognitive functions as “executive” rather than “frontal”.

2. The FTD's are uncommon, but they are over-represented in younger patients with dementia.

The FTD's are typically disorders of late middle (mean 58.5 ± 8 years¹¹; range 21-75¹²), accounting for about 10% of dementias with an onset below age 65.¹³ This age distribution is quite unlike that of Alzheimer's disease, where the age-specific prevalence approximately doubles every five years up until at least age 90.¹⁴ Also unlike Alzheimer's disease, and no doubt due in part to the younger age of onset, there is no female predominance.¹² The FTD's may indeed occur very early: the youngest onset patient the author has assessed was grossly affected both clinically and radiologically in her early 20's. The natural history is quite variable; the median life expectancy from diagnosis is less than that of Alzheimer's disease at about 6-7.5 years^{11,13}, with a range from 2 to 20.¹²⁻¹⁵ The FTD's with motor neuron disease-like neuronal inclusions have a male predominance of 2:1 and run a more aggressive course¹², with a mean survival of 2-3 years^{11,12}, while those FTD's with tau pathology (see below) run a less aggressive course with a median survival after diagnosis of 9 years.¹¹ The poor outlook of motor neuron disease-FTD is not just accounted for by the development of anterior horn cell involvement, as the dementia runs a more aggressive course even before the typically associated bulbar palsy becomes evident during the first year or so.¹¹

3. A range of different pathologies, with different genetic implications, underlies the FTD syndromes.

Overall, about 40-50% of FTD cases are familial.^{16,17} The commonest pathological substrate for the FTD's is probably dementia lacking specific histology^{12,18}, although this has not been so in all series.¹⁹ This description means

that specific tau and/or ubiquitin-immunoreactive inclusions are lacking; the pathology is dramatic enough, with neuronal loss and microvacuolar change (unlike the spongiosis seen in the spongiform encephalopathies such as Creutzfeldt-Jakob disease), although gliosis is only mild. About a third to half of such patients have a positive family history, and a locus for one of these families has been reported on chromosome 3.²⁰

The term “Pick's disease” requires some clarification. In the English-speaking world, and more recently in Europe²¹, it is used to define an FTD pathology characterised by achromatic ballooned neurons (Pick cells) and agyrophilic, tau and ubiquitin-immunoreactive inclusions (Pick bodies), - that is, type A of Constantinidis - and is distinguished biochemically by a predominance of 3-repeat tau isoforms.²² As such, it is less common than dementia lacking specific histology, accounting for perhaps 20% of FTD cases¹⁸, although a more recent estimate was as high as 30%.¹⁹ This entity is typically sporadic²¹, although occasional instances of tau mutations with Pick bodies have been described.²³ In contrast, the term “Pick's disease” was often used in central Europe as a synonym for FTD: that is, to describe a clinical syndrome rather than specific pathological findings. As such, statements that about 50% of cases have a positive family history are reconcilable with the typically sporadic nature of pathologically defined Pick's disease. Kertesz and Munoz²⁴ have attempted to unify usage by proposing the term “Pick complex” to equate with FTD. The author's view is that this has not resolved the confusion.

Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) is also characterised by tau-positive inclusions. It only comprises about 5% of FTD's and about 10% of familial FTD's²⁵, but is disproportionately important, as it is always dominantly inherited and is the only FTD for which routine genetic testing is currently available. Furthermore, the demonstration that FTDP-17 is caused by any of at least 30 different mutations in the tau gene²⁶, whereas none cause Alzheimer's disease, finally laid to rest the idea that the primary pathogenic event in Alzheimer's disease is an abnormality of tau rather than of the A β peptide. The pathology of FTDP 17 is characterised by tau-immunoreactive inclusions in neurons and oligodendroglia, but it has recently become evident that Pick's disease, progressive supranuclear palsy and corticobasal degeneration

pathologies can on rare occasion be caused by *tau* mutations^{23,26}, although all three are typically sporadic rather than inherited. Perhaps linked to this pathological variability, different *tau* mutations result in different proportions of 3- and 4-repeat isoforms.²²

Corticobasal degeneration itself was originally described as an uncommon cause of an asymmetric rigid/ akinetic syndrome, with the additional features of apraxia and cortical sensory loss. However, it is now recognised that corticobasal degeneration pathology, characterised by ballooned achromatic neurons strongly immunoreactive for α B-crystallin and variably for tau and ubiquitin, can also present as an FTD.²⁷ As with progressive supranuclear palsy, which is characterised by tau-immunoreactive globose neuronal tangles, analysis of tau isoforms in corticobasal degeneration indicates a preponderance of the 4-repeat form.²⁸ Also as with progressive supranuclear palsy, corticobasal degeneration is typically sporadic, although occasional phenocopies are seen with FTDP-17.

Motor neuron disease-FTD is an uncommon cause of FTD, being responsible for about 15-20% of the FTD's.^{11,29} The motor neuron disease-like inclusions are tau negative but ubiquitin positive. Similar inclusions can be found without clinical motor neuron disease in a small percentage of cases, sometimes called ubiquitin body dementia.³⁰ Conversely, a significant minority of patients presenting with motor neuron disease rather than cognitive impairment have or develop some features of executive and/or language dysfunction.³¹ Those with clinical motor neuron disease or ubiquitin-positive inclusions in anterior horn cells are sometimes separated nosologically from those with other ubiquitin-positive/tau negative pathology³², although it is still unclear whether this distinction is valid. About 20% of FTD's with motor neuron disease-like inclusions are dominantly inherited³³; a locus has been reported on chromosome 9q21-q22.³⁴

Lastly, it should be borne in mind that Alzheimer's disease can also present with predominant executive dysfunction³⁵, and that most patients with FTD also fulfil the standard NINCDS-ADRDA criteria for probable Alzheimer's disease.³⁶ The accompanying impairment of episodic memory encoding (rather than retrieval), together with visuoperceptual abnormalities, helps to separate Alzheimer's disease from the typical FTD's.³⁵

As indicated above, biochemical analysis has complemented the usual histo- and

immunopathological classification of those FTD's with tau-positive inclusions. Whereas the tau comprising the neurofibrillary tangles of Alzheimer's disease is a mixture of 3 and 4 microtubule binding domain repeat isoforms, corticobasal degeneration, progressive supranuclear palsy and most FTDP 17 mutations are characterised by an excess of four repeat tau, while Pick's disease is typified by an excess of three repeat isoforms (that is, with exon 10 spliced out).^{22,28}

It is apparent from the above discussion that the various pathologies causing FTD have different genetic implications. A clearly dominant pedigree speaks for itself, of course, and a clinically *affected* member should be tested for a tau mutation. However, dominant inheritance is not infrequently disguised for reasons such as death from other causes prior to manifestation in previous generations, or non-paternity. Accurate genetic counselling in ostensibly sporadic FTD therefore requires postmortem neuropathological examination, if at all possible.

4. The clinical presentation of FTD in an individual patient primarily depends on the location of the pathology, not on its nature.

It is a truism that an impaired or dead neuron is dysfunctional no matter what pathological process damages it, and also that patient's clinical features depend on the pattern of involvement and sparing of neural structures and networks. It is not surprising, therefore, that different pathologies may cause the same clinical syndrome, and the same pathology may result in different clinical syndromes. Sometimes a certain pathological process has a predilection for a brain area generally spared by others (for example, posterior cortical atrophy is usually attributable to Alzheimer's disease pathology³⁷, but this is usually not the case with the FTD's. Exceptions to this principle are the clinical syndrome of asymmetrical parkinsonism and apraxia, which is typically but not invariably associated with corticobasal degeneration pathology³⁸, the clinical syndrome of motor neuron disease with a frontotemporal dementia, which is always associated with the tau-negative, ubiquitin-positive inclusions of motor neuron disease, and perhaps the clinical syndrome of non-fluent primary progressive aphasia, which has recently been reported to be strongly predictive of Pick's disease pathology.¹⁹ Nevertheless, pathological corticobasal

degeneration, Pick's pathology and motor neuron disease-type pathology, as with any of the other pathologies underlying FTD, can produce any of the prototypic FTD-related clinical syndromes.^{11,24}

A number of clinical syndromes are widely recognised within the FTD's. The FTD's themselves are usually classified into the frontal dementias, semantic dementia and (non-fluent) primary progressive aphasia.¹ The frontal dementias, which are (relatively) common compared with semantic dementia and PPA¹¹, are not homogeneous, and several different presentations are recognised. These presentations correspond to three distinct functional areas of prefrontal cortex: orbitobasal, dorsolateral, and mesial.³⁹ Involvement of orbitobasal regions tends to produce impulsiveness and disturbed behaviour/social interactions (disinhibited or "pseudopsychopathic" subtype); impaired dorsolateral function typically results in poor planning and deficits in sequencing and set-shifting; and mesial frontal involvement tends to result in apathy or even abulia ("pseudodepressed" subtype).^{12,40} The Manchester group, who with the Lund group have contributed so much to the modern resurgence of interest in the FTD's, also recognise a syndrome dominated by stereotyped behaviour and correlated with basal ganglia as well as frontal cortical atrophy¹², but this concept has not been widely adopted.

Involvement of the dominant perisylvian region may produce the syndrome of primary progressive aphasia, characterised by non-fluent spontaneous speech with at least one of agrammatism, phonemic paraphasias, and anomia.¹ If the dominant anterior temporal neocortex is affected, semantic dementia, a progressive fluent aphasic syndrome with loss of semantic* knowledge and semantic paraphasias¹, tends to develop. Semantic dementia usually occurs in association with a surface dyslexia/dysgraphia (impaired ability to read/spell irregularly spelt words) and often with visual agnosia.¹ Involvement of the non-dominant temporal neocortex occurs less often, or more likely is recognised less frequently, but may give rise to the syndrome of progressive prosopagnosia.⁴¹ Such involvement also tends to produce considerably more disturbed behaviour than does dominant temporal neocortex disease, with social awkwardness and loss of insight.⁴² It is worth noting that Mesulam^{43,44}, who revived interest in this area with his description of primary

progressive aphasia, uses this term in a different sense. He encompasses non-fluent primary progressive aphasia and some cases of semantic dementia within it, excluding by definition those cases of semantic dementia (the majority) with agnosia or other cognitive deficits in addition to the aphasia within the first 2 years. The use of the terms semantic dementia to refer to fluent aphasia with dissolution of semantic knowledge, with or without agnosia and/or other deficits, and of primary progressive aphasia for progressive non-fluent dysphasia, are now well-entrenched in the literature, however.

5. The recognised FTD syndromes represent polar ideals; mixed presentations and evolving clinical pictures are the norm.

Just as it is rare to encounter profound Broca's aphasia without at least some evidence of impaired comprehension⁴⁵, so it is unusual to encounter one of the above clinical syndromes in pure form. Rather, their descriptions serve as intellectual marker posts to define the boundaries of the domain of the FTD's; the features of one syndrome will typically predominate, but less prominent features of one or more others will usually be found. This is not surprising: there is no reason to suppose that any of the causative pathologies will strictly respect one anatomical region or network and completely spare the others. As the disease evolves, the pathology tends to spread to other frontotemporal areas, and the original clinical syndrome becomes less distinct.^{24,29} The evolution may occur in a more or less predictable fashion: for example, semantic dementia usually extends to the orbitobasal frontal cortex, resulting in disinhibition.¹² Mixed presentations also exist, and the author's view is that it is more important to recognise all the behavioural and cognitive aspects of a particular patient's illness than it is to try to force them to fit a particular defined syndrome exactly.

6. A complete FTD diagnosis must be made on three axes: clinical syndrome, pathological/biochemical type, and (if possible) genetic basis.

It will be apparent from the above discussion that a complete diagnosis of an FTD syndrome must be made on three independent axes: predominant clinical syndrome, pathological/biochemical type,

* Knowledge devoid of a particular temporal and personal context - e.g., the meanings of words, the fact that Paris is the capital of France, etc.

and (if possible) genetic basis. Identification of the predominant clinical syndrome will guide the clinician to search for frequently associated features (e.g., surface dysgraphia and dyslexia in semantic dementia; orobuccal apraxia in primary progressive aphasia), and will enable correlation with neuropsychological and neuroimaging findings. Identification of the pathological type is rarely possible (or justifiable) antemortem (although it can be confidently assumed in patients with clinical features of motor neuron disease), but in the absence of a demonstrable tau gene mutation, pathological classification is currently the best available information on which to base genetic counselling in those situations (the majority) where clearly dominant inheritance is not apparent. This situation is likely to change in the near future, as further FTD causative genes are discovered.

7. Many neuropsychological tests are insensitive to executive dysfunction.

Intact executive functioning enables individuals to be motivated, and to determine goals, formulate hypotheses and plans, carry them out efficiently and productively, monitor their execution, switch between objectives or strategies, and disregard irrelevant stimuli or information. Most neuropsychological tests, on the other hand, are designed such that the subject is given an unambiguous single goal, and are carried out in a distraction-free environment. It is not surprising, therefore, that many neuropsychological instruments are incapable of detecting even gross executive dysfunction; the test's constraints substitute for the patient's defective executive system.⁴⁶ The mini-mental state examination (MMSE) is a case in point: FTD patients typically score in the normal range, and sometimes even ^{30/30}, while failing dismally in life.⁴⁷ An experienced neuropsychologist will pay particular attention to the *way* in which a test is performed, as well as to the result; qualitative features of perseveration, distractibility and poor planning, while not necessarily altering the final score, can be very revealing (Figure 1).

8. Neuropsychological tests of executive function do not assess orbitofrontal dysfunction adequately.

There are, of course, a number of quantitative neuropsychological instruments that examine various aspects of executive functioning, such as planning (e.g., Tower of London, Zoo Map test of

the BADS), sequencing and alternation (e.g., Trail Making Test), cognitive inhibition (e.g., Stroop), flexibility and productivity (e.g., F,A,S test) and hypothesis generation and self-monitoring (e.g., Wisconsin Card Sorting test). The interested reader will find excellent discussions of these instruments in recent editions of standard texts.^{48,49} However, such tests are predominantly sensitive to dorsolateral prefrontal dysfunction.⁵⁰ Individuals with orbitofrontal dysfunction, despite all the massive interpersonal and social disruption that may occur in this syndrome, may perform satisfactorily on these sorts of tasks.⁴⁷ One research approach to this difficulty has been to devise tests sensitive to disruption of social perception (e.g., the Faux Pas test)⁵¹ or judgement (e.g., the gambling game)⁵², although such promising instruments have not yet entered routine clinical practice. Another approach has been to devise questionnaires, answered by an informant such as a relative, seeking to score behavioural abnormalities in a semi-quantitative fashion. Three such questionnaires are the Neuropsychiatric Inventory (NPI)⁵³, the Frontal Behavioural Inventory⁵⁴, and the (unnamed) questionnaire devised by the Cambridge group.⁵⁵ These have all been shown to discriminate FTD from Alzheimer's disease⁵⁴⁻⁵⁶, although the distinctions were more finely drawn in the more specialised Frontal Behavioural Inventory than in the NPI. When taking an informant history, it is important to bear in mind the wide range of normal human personality and behaviour - what is inappropriate for a neurologist may be quite acceptable in a used car salesman - and to concentrate on reports of behavioural *change*. The neurologist should also pay due attention to important behavioural observations, such as blinkered unconcern, reduced speed output, impersistence, distractibility, impulsivity, stereotyped motor behaviours, and flattened (rather than depressed) affect. Such observations are signs every bit as valid as reflex or gait abnormalities.

9. Executive function can be fractionated, and not all FTD patients are impaired in every aspect of executive functioning.

Given that the human frontal cortex comprises almost a third of the cerebral cortex⁵⁷, and encompasses several architectonic areas, it is not surprising that its functions may be fractionated to some extent. At a very broad level this has been referred to in section 4 above, where the

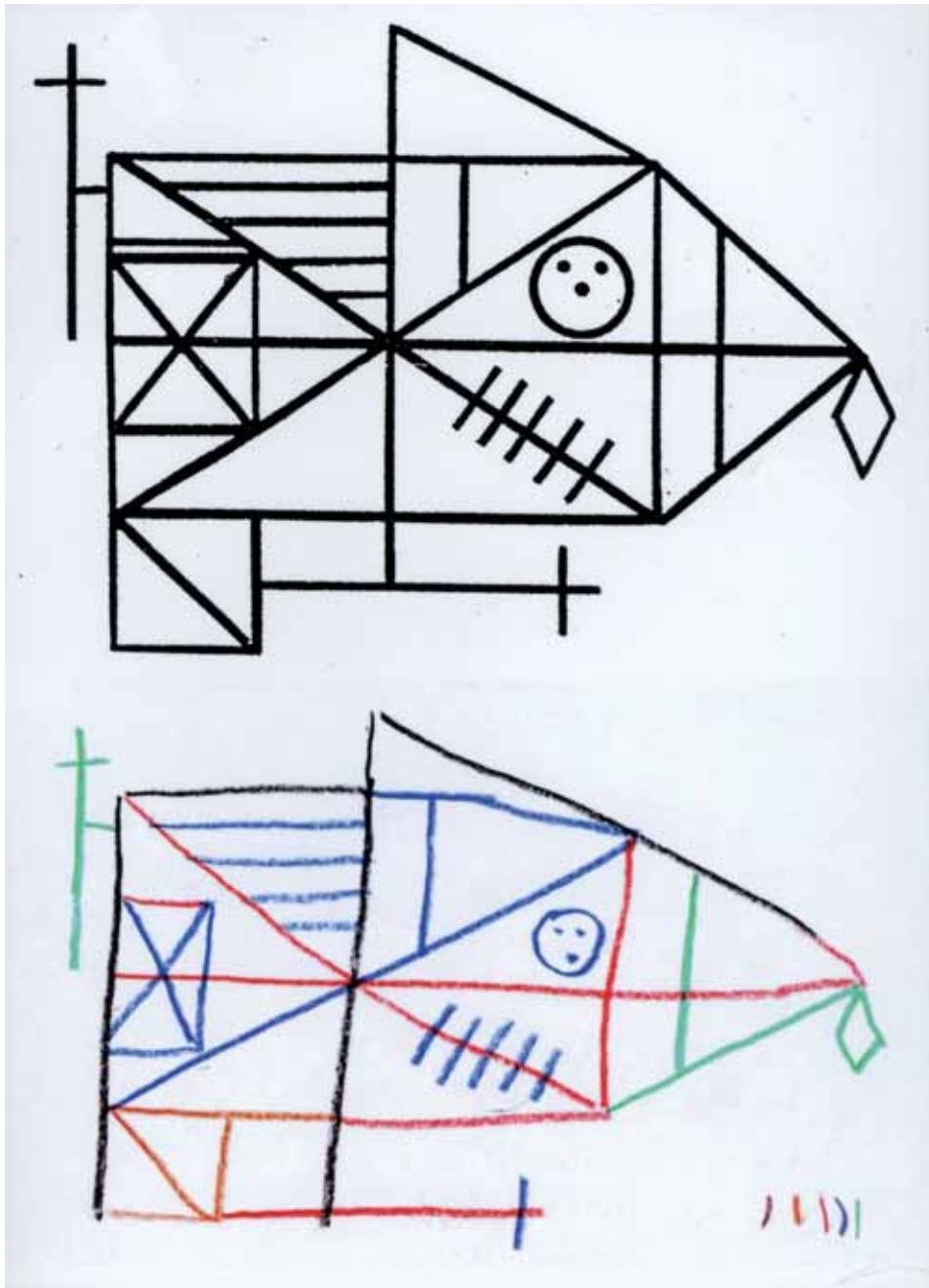


Figure 1: The way in which an FTD patient performs a test is often more revealing than the test score itself.

Above: Rey Complex Figure, to be copied accurately by the patient.

Below: Copy of the Rey Complex Figure by a tertiary-educated man in his early 40's with an early FTD syndrome. The colours (black, then brown, then red, then blue, then green) mark the order in which he copied the Figure. Note that while the final copy is reasonably accurate, the *sequence* of copying is poorly planned. For example, the main rectangle was completed in four separate stages.

clinical differences between the dorsolateral, orbitofrontal and mesial prefrontal syndromes were summarised. However, finer-grained differences in the pattern of executive deficits also exist between patients with FTD's. This may deter clinicians who expect to see the full panoply of executive dysfunction in FTD patients before making the diagnosis, whereas relative preservation of some functions is more the rule than the exception. The arguments in favour of multiple rather than single process theories of executive function, underlining the possibility of fractionation of the syndrome, have been skilfully summarised by Burgess and Robertson.⁵⁸

Delineation of the various networks underlying different aspects of executive functioning is a relatively recent field of study, but it is clear that right/left, latero-medial and supero-inferior differences exist that can result in different patterns of failure on standard neuropsychological tests assessing aspects of executive functioning, such as the Stroop test (inhibition), Trails B (alternation and sequencing), etc.⁵⁹, as well as on such classically lateralised tests as verbal fluency by initial letter (F,A,S test or COWAT)⁴⁹ sensitive to left dorsolateral dysfunction, and design fluency, that has been proposed as its right hemisphere equivalent.⁴⁹ * Similarly, as already mentioned in section 4, the neuropsychiatric consequences of prefrontal damage will also vary with the location of the pathology. Waiting for the "full hand" of frontal features, as exemplified by the famous case of Phineas Gage⁶⁰, before diagnosing an FTD is somewhat akin to waiting for complete quadriplegia before diagnosing a cervical cord lesion!

10. Structural imaging changes lag behind behavioural changes, and may be absent in early FTD; while functional imaging is relatively more sensitive, but may also be normal.

It is intuitively obvious that atrophy in the FTD's reflects cell death on a considerable scale, whereas clinical features arise as a result of neuronal dysfunction. It should not be surprising, therefore,

to discover that frontotemporal atrophy may not be apparent in patients with early FTD⁴⁷, yet the author's experience is that some clinicians are deterred from a diagnosis of early FTD by the absence of such atrophy. Its presence is most readily apparent on coronal T₁-weighted MRI images.⁶¹ Functional neuroimaging may be useful in early FTD⁶², and has the advantage of demonstrating frontal *system* dysfunction (as in progressive supranuclear palsy) as well as frontal cortical pathology.^{63,64} Other workers have reported that the presence of frontal hypoperfusion on SPECT scanning has high accuracy (~90%) in FTD⁶⁴⁻⁶⁷, although this sensitivity may be inflated in some reports in which such hypoperfusion was required to confirm the diagnosis⁴⁷: a potentially circular argument. Certainly, SPECT scanning, too, may initially be normal in FTD.⁴⁷ One disadvantage of functional imaging is that depression (often confused with the apathy of mesial prefrontal dysfunction), and schizophrenia may also reduce frontal metabolism.^{67,68}

11. The neurologist's role extends beyond diagnosis to management, despite the lack of proven pharmacological disease-modifying therapies for FTD.

The neurologist's responsibilities to the FTD patient and their family extend beyond accurate diagnosis and appropriate genetic counselling to education about the disease and its legal consequences, advocacy with relevant authorities, and advice on the management of difficult behaviours. Family members, particularly, require explanation of the neuropsychiatric features of the FTD's, to the effect that the changes in personality and difficult behaviours such as apathy or disinhibition are due to physical brain disease, and are not either under the patient's voluntary control or due to a psychological disturbance. In the author's experience, families may attribute apathy to depression consequent on, for example, losing employment or a failing relationship, rather than seeing these negative life events as resulting from the FTD itself. FTD's, particularly the frontal varieties, by their nature affect the patient's ability

* The reader may wonder why these and other tests are not discussed in greater detail. The reason is that many of them have inherent cultural and/or linguistic biases that necessitate great caution in their adaption into other societies. Obvious examples of qualitative bedside tests unsuitable for adaption elsewhere without re-standardisation include the cognitive estimation task of Shallice and Evans, or word similarities and differences. Even the Trail Making Test requires automatic knowledge of the English alphabet. Readers are advised to discuss potential tests with experienced local neuropsychologists.

to function effectively as an autonomous adult in a complex society, and such patients may well require protection from themselves and from others. In this regard, enduring legal/financial and medical powers of attorney (decision-making) should be established as soon as possible, if the patient is still capable of giving informed consent to such legal instruments. (It should be noted that competence to consent is situation-specific, and not all or none, at least in common-law jurisdictions such as Australia.) In some jurisdictions, at least, lack of competency to establish such legal instruments will require formal establishment of a guardianship or administration order, if the immediate situation warrants it. Testamentary capacity may also be affected even early in the illness. Patients without an up-to-date Will should therefore be advised to remedy this as soon as possible, with care being taken by the legal practitioner involved that testamentary capacity is preserved. At least in common-law jurisdictions, such capacity is a legal rather than a medical construct, and cannot be established merely on the basis of neuropsychological testing.

Driving restrictions cause the greatest problems in Western countries with car-dependent cultures, such as Australia, where a driving licence is widely regarded as a badge of adulthood. Unfortunately, the lack of judgement and the impulsivity of many patients with frontal dementias is typically complemented by lack of insight. The systems for driver disqualification vary in different jurisdictions, but failure in an on-road Occupational Therapy driving test (in a dual-control car!) is generally regarded as the gold standard, and has the advantage of face validity. Other legal infractions (e.g., impulsive shoplifting) may also require the neurologist to act as patient advocate in certifying diminished responsibility.

Behavioural issues are usually best managed with behavioural and environmental manipulation. As a general rule, frontal dementia patients respond best to an externally guided regular routine, and cope poorly with spur-of-the-moment activities. They are easily overwhelmed by multiple inputs (e.g., a large group with several simultaneous conversations), and do best one-on-one, with simple, unambiguous interactions. Burgess and Robertson⁵⁸ provide a useful overview of the links between theories of executive dysfunction and potential behavioural modification strategies. Pharmacological control of symptoms does have a place, however, with selective serotonin reuptake inhibitors (SSRI's)

reported in one small uncontrolled series to be effective in reducing disinhibition, compulsions, impulsivity and irritability.⁶⁹ This effectiveness may be related to the serotonergic deficit in the frontal and temporal lobes in FTD.⁶⁹

CONCLUSIONS

The frontal dementias are clinically, pathologically and genetically heterogeneous, and each of these aspects must be addressed in reaching a complete formulation. Neither neuropsychological nor neuroimaging studies can be relied on entirely in reaching the diagnosis, though each may make important contributions. The neuropsychiatric features are particularly important, and can be detected readily by the neurologist attuned to their nature and salience. Although no specific pharmacological treatments have been proven to influence the natural history of the disease(s), the neurologist retains an important role in education and advocacy.

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